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CATALYSED REACTIONS

PART 1

THE CATALYTIC HYDROGENATION OF CYCLIC IMIDES

AND ANHYDRIDES

CONTENTS

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THE CATALYTIC HYDROGENATION OF COMPOUNDS CONTAINING THE CARBONYL FUNCTION

CATALYTIC HYDROGENATION OF CYCLIC IMIDES AND ANHYDRIDES

This investigation was prompted by the work of McCrindle, Overton and Raphael[1a,b] on the catalytic hydrogenation of cyclic anhydrides, using Adams' platinum oxide catalyst at room temperature and atmospheric pressure. The results obtained in the present investigation indicate that the relative ease of hydrogenation of a carbonyl function depends, in a qualitatively predictable manner, on its electronic environment. This observation, in conjunction with the constitution and stereochemistry of the products, has permitted the discussion of possible mechanisms for the reaction.

Conditions and Mechanisms for the Catalytic Hydrogenation of Carbonyl Compounds

In the following summary, the different classes of carbonyl compounds are discussed in order of their susceptibility to hydrogenation, except that imides and anhydrides are dealt with last, when their position with respect to the remainder of the series is considered.

I. ACID CHLORIDES.

These are the most readily hydrogenated of all carbonyl compounds, this reactivity being the basis of the Rosenmund reaction for the preparation of aldehydes.[2] The most widely used catalyst for this reaction is palladium on barium sulphate, the reaction usually being carried out by bubbling hydrogen through a solution of the acid chloride in hot toluene or xylene. As the resulting aldehydes are often themselves readily hydrogenated further to alcohols, addition of a poison to the reaction may improve yields by retarding or even eliminating this subsequent step. A procedure which permits the use of much lower temperatures than are normally used for the Rosenmund reduction has been developed.[3] Hydrogenation is carried out in benzene solution over unpoisoned 10% palladium on carbon at 30-35°, the system being maintained at reduced pressure so as to maintain refluxing, and assist in the removal of hydrogen chloride as it is formed. In a paper on selective poisoning of the catalyst in the Rosenmund reaction,[4] tetramethylthiourea was found to be the most effective of a range of sulphur-containing poisons in preventing the hydrogenation of benzoyl chloride beyond the aldehyde stage. The efficacity of this technique was suggested to derive from the requirement of four neighbouring co-ordination sites on the catalyst for hydrogenation of an aldehyde (two for adsorption of the aldehyde, and two for hydrogen), whereas an acid chloride requires only two, chlor-

ine being replaced by active hydrogen from the catalyst surface without adsorption of the acid chloride. As catalyst sites are occupied by molecules of poison, the probability of there being four neighbouring sites vacant drops much more rapidly than the probability for two such sites, so that the hydrogenation rate for the aldehyde is affected to a greater extent, than that for the acid chloride.

Other products which can arise in the course of the Rosenmund reaction[2,4] are:-

(i) ester; by reaction of alcohol with original acid chloride.

$$RCH_2OH + RCOCl \longrightarrow RCH_2OCOR + HCl.$$

(ii) hydrocarbon and acid; by hydrogenolysis of alcohol or ester, if activated by an aromatic ring.

$$ArCH_2OH \xrightarrow{H_2} ArCH_3 + H_2O \xrightarrow{ArCOCl} ArCO_2H + HCl.$$

$$ArCH_2OCOAr \xrightarrow{H_2} ArCH_3 + ArCO_2H.$$

Hydrocarbon may arise from unactivated acid chlorides by direct hydrogenolysis of the intermediate aldehyde without formation of free alcohol, by a mechanism similar to that suggested for the formation of propane from acetone (see p.30)

(iii) acid anhydride; by reaction of acid with the original acid chloride.

$$RCOCl + RCO_2H \longrightarrow RCO_2COR.$$

II. ALDEHYDES AND KETONES.

The ease of hydrogenation of aldehydes and ketones is greatly dependent on the environment of the carbonyl group. Those compounds in which the aldehydo or keto function is α to an activating function such as a second carbonyl group. a trifluoromethyl group, or an aromatic ring, are more readily hydrogenated than are their unactivated aliphatic or alicyclic analogues.(5) The usual product of hydrogenation is an alcohol, but hydrogenolysis to the hydrocarbon may occur, either as a side reaction, or, in certain cases, as the major reaction.

The most commonly used catalysts for the conversion of aldehydes and ketones to alcohols are platinum and nickel. More recently, ruthenium has been found to be a useful catalyst for this reaction at low temperatures and pressures.(6) Copper-chromium oxide catalysts may be employed, but are generally less convenient, elevated temperatures and pressures being necessary to promote reaction. Palladium is almost completely ineffective as a catalyst for the reduction of aliphatic aldehydes and ketones, but will catalyse the hydrogenation of activated carbonyl compounds, being particularly useful for aromatic ketones. This latter reaction is often accompanied by hydrogenolysis of the initially formed alcohol, particularly in acid medium, to give the methylene compound. A study of the relative effectiveness of the platinum metals, Pt, Pd, Rh and Ru, supported on carbon, for the hydrogenation

of representative aliphatic, aromatic and α,β-unsaturated ketones in a variety of solvents has been reported.[7] Hydrogenation of the carbonyl group is promoted by certain additives, notably ferrous ions.[8,9] Thus, α,β-unsaturated aldehydes or ketones may be hydrogenated to the allyl alcohols over platinum in presence of ferrous sulphate and zinc acetate, the presence of zinc ions serving to prevent saturation of the double bond, which normally occurs more readily than carbonyl reduction.

Most suggestions on the mechanism of the catalytic hydrogenation of this group of carbonyl compounds are based on the stereochemistry of the products obtained on hydrogenation of cyclic ketones. The earliest work in this field is due to Skita, who found that in hydrogenation of a number of methyl substituted cyclohexanones to cyclohexanols, and of their corresponding oximes to cyclohexylamines, products in which the resulting hydroxyl or amino function was cis to the alkyl substituents were preferred when hydrogenation was carried out in acetic acid solution, whereas hydrogenation in neutral or basic medium led to a greater proportion of trans isomers. Addition of concentrated hydrochloric acid to the acetic acid medium further increased the proportion of cis isomers in the products. The configurational assignments were based on rules formulated by von Auwers[10] for differentiating cis and trans isomers by comparison of their physical properties, e.g. boiling point, density and refractive index, and on the assumption

that the trans isomer was the more stable isomer in all cases.* Thus, Skita found his generalisation to apply in the cases of 2,4,5-trimethylcyclohexanone and its oxime,[11] 2,4-dimethylcyclohexanone and its oxime,[12] 2-methylcyclohexanone,[13] the oximes of 2,-3,- and 4-methylcyclohexanone,[14] and 2,5-dimethylcyclohexanone and its oxime.[15] Hydrogenation of phenols and aromatic amines to cyclohexanols and cyclohexylamines was also found to follow the rule. By hydrogenation of the cresols at 70° with a colloidal platinum catalyst, the corresponding cyclohexanones could be isolated, from which it was deduced that hydrogenation of phenols proceeded via the cyclohexanones.[13] In these publications, no quantitative measurement of isomer content of product mixtures was attempted, the product simply being stated to be rich in one particular isomer, or, in some cases, to consist of a single isomer. In a later publication,[16] on the hydrogenation of 2,3-and 4-methylcyclohexanone, in which they confirmed the preferred formation of cis alcohol in each case in acetic acid/hydrochloric acid medium, Skita and Faust reported a more detailed investigation of the hydrogenation of 2-methylcyclohexanone. From the results of analysis of mixtures obtained on hydrogenation of the last in different solvents, under various conditions of temperature and pressure, and using different batches of catalyst, they concluded that formation

*These criteria led to the assignment of the wrong configurations to 1,3-disubstituted cyclohexanes. These original assignments were later reversed.(p.24)

of cis isomer is favoured by a rapid rate of hydrogenation, which in turn is favoured by

(i) increase in temperature,

(ii) increase in pressure,

(iii) high activity of the catalyst preparation employed, and

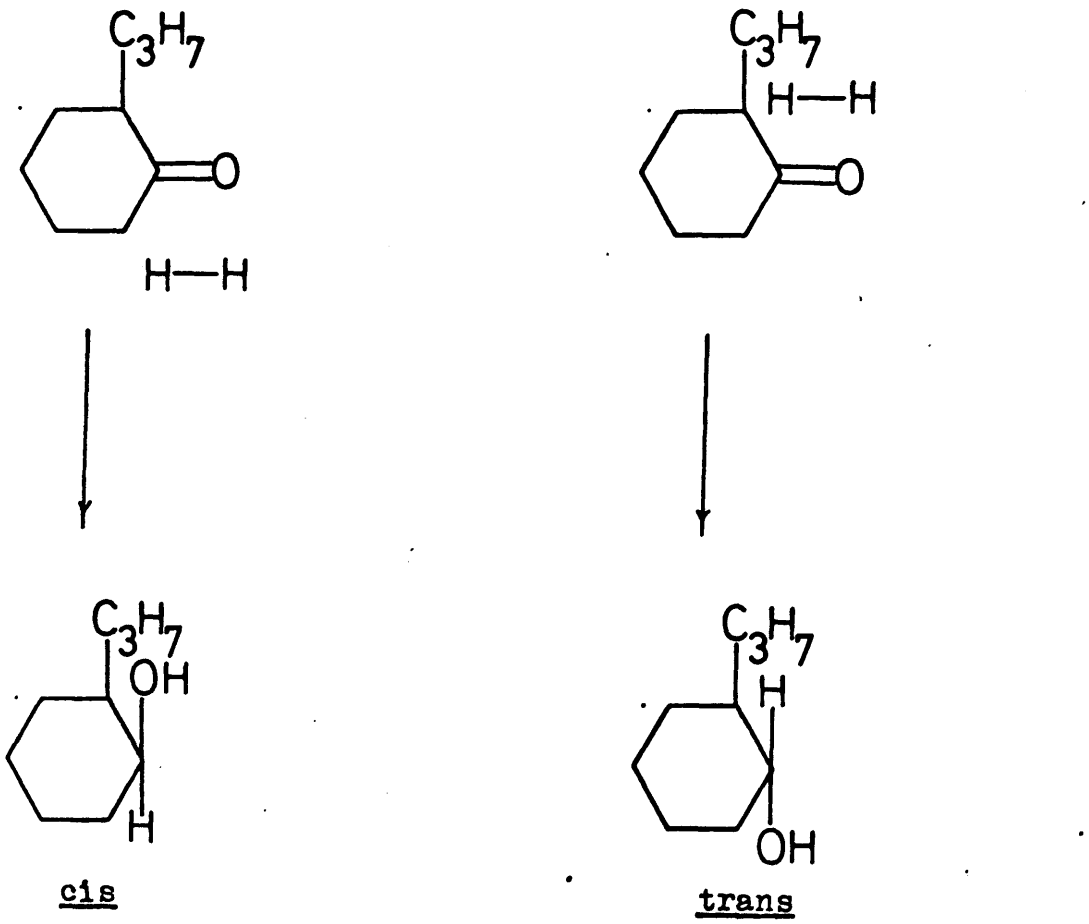
(iv) use of an acid medium.

At about this period, a series of papers, concerned with the relationship between steric hindrance and cis-trans isomerism, and involving hydrogenation of a series of cyclic ketones (mainly 2-substituted cyclohexanones) was published by Vavon and co-workers. Vavon considered that steric hindrance was an important factor in determining the stereochemistry of hydrogenation of cyclic ketones. Thus, in a summary of some of his early results,[17] in which it was noted that hydrogenation is more difficult the greater the number of alkyl substituents in the neighbourhood of the function being hydrogenated, and the greater the bulk of the substituents, he considered the specific case of 2-n-proplycyclohexanone. The carbonyl group in this molecule was considered to be bound by two bonds in a plane perpendicular to the plane of the cyclohexane ring, one below and one above the plane of the ring. One of these bonds would then be cis with respect to the substituent, and the other trans, approach to the former bond being more hindered. He reasoned that addition of hydrogen would be expected to occur preferentially at the less hindered trans bond, so that the hydroxyl function in the product would become cis to the

FIGURE 1

(17)

Hydrogenation of 2-n-propylcyclohexanone after Vavon.



propyl substituent. The less favoured addition to the other bond would result in formation of the trans alcohol. This argument was illustrated by Vavon as shown in fig. 1, and supported by the observed preferential formation of cis isomer in hydrogenation of 2-cyclohexylcyclohexanone,[18] methone[17] and o-propylphenol.[19] Hydrogenation of phenols was assumed, from the results of previous work,[20] to proceed via the cyclohexanone. (Similar observations by Skita have already been referred to.[13]) Support came from further work on substituted cyclohexanones; 2-isopropyl,[21] 2-ethyl;[22] phenols; o-isopropyl,[23] 2,6-dipropyl,[24] which gave cis,cis-2,6-dipropylcyclohexanol; and cyclopentanones; 2-n-propyl,[25] 2-isopropyl[26] and cis-2,5-dipropyl,[27] which gave cis,cis-2,5-dipropylcyclopentanol. This work was further reviewed by Vavon,[28] and the following conclusions were drawn.

(a) Steric hindrance, and accordingly, the tendency to give cis isomers on hydrogenation is greater in compounds with a branched alkyl substituent next to the carbonyl function, or in cis α,α'-dialkyl ketones.

(b) Placing the substituent at a position further removed from the carbonyl function leads to an increase in the proportion of trans isomer formed, since the substituent is less favourably orientated for blocking access to the carbonyl group. In support of this, hydrogenation of 4-isopropylcyclohexanone, in ether or acetic acid,[21] gave a mixture containing similar proportions of cis and trans-4-isopropylcyclohexanol.

(c) For highly hindered ketones, cis products are favoured, no matter what medium is used, i.e. acid is not necessary as implied by Skita. When steric hindrance is less, a considerable proportion of trans isomer may be formed even in acetic acid solution. However, addition of concentrated hydrochloric acid results in production of mixtures rich in cis isomer in all cases.' Thus for ketones where steric hindrance is low, the nature of the medium in which hydrogenation is carried out becomes the dominating factor in determining the nature of the products. In the case of 4-isopropylcyclohexanone referred to above, use of acetic acid/hydrochloric acid as solvent results in formation of cis-4-isopropylcyclohexanol as the major product.

(d) On comparing the cis/trans ratio of alcohols obtained in the hydrogenation of 2-isopropylcyclopentanone,[26] with the ratio obtained on hydrogenation of 2-isopropylcyclohexanone, Vavon concluded that the steric directing effect of the isopropyl in the cyclopentanone is less than that of the same group in the cyclohexanone.[26]

(e) The proportion of cis isomer formed is lower when a catalyst of low activity is used. This effect, as has been mentioned above, was also noted by Skita.[17] Vavon offered the following explanation.

Formation of the cis alcohol requires more energy than formation of its trans isomer. An active catalyst is able to promote reaction with ketone so orientated as to produce either

the cis or trans alcohol, but since the preferred direction of attack is that which results in formation of the cis alcohol, the latter will be the main product. With a catalyst of low activity, only a portion of the molecules in position to give the cis product have high enough energy to react, whereas reaction with those molecules which could give trans product proceeds more readily, resulting in a greater proportion of trans alcohol in the product mixture.

In his work, Vavon differentiated pairs of cis and trans isomers by comparing their rates of esterification, and the rates of saponification of their esters, these reactions being expected to occur more rapidly with the less hindered trans isomers. However, little effort was directed to the quantitative determination of the isomer content of mixtures. Only in the case of the hydrogenation of menthone,[17] where measurement of optical activity of the product was possible, was such a determination made.

Both Skita and Vavon generally used platinum catalysts in acid medium in their investigations. Later investigators repeated some of this work, and extended it by more frequent use of Raney nickel catalysts, and a wider range of solvents. Attempts were made to determine isomer ratios for the alcohol mixtures obtained by measurement of physical properties of the mixtures, such as density, refractive index and mixed melting point of derivatives, and comparing the values obtained with measurements made on synthetic mixtures of known composition.

Considerable interest was shown in the methylcyclohexanones. Thus, it was confirmed that hydrogenation with platinum black in acetic acid/hydrochloric acid gave mainly the cis isomer from 2-[29] and 4-[30] methylcyclohexanone, and the trans* alcohol from 3-methylcyclohexanone.[30] Hydrogenation of 2- and 4-methylcyclohexanones over Raney nickel[31] in the absence of solvent still gave cis isomers as the major products, but in lower proportions than had been obtained over platinum. 3-methylcyclohexanone on hydrogenation over Raney nickel in acetic acid gave mainly the trans isomer,[32] although again in lower proportion than had been obtained over platinum in acetic acid/hydrochloric acid, but in higher proportion than was obtained over platinum in acetic acid alone.[32] A study of the hydrogenation of 2-methylcyclohexanone over platinum black in a range of solvents[29] led to the observation that the cis alcohol was the main product in all solvents, including neutral and basic media, but that the proportion of cis alcohol formed was greatest in acetic acid/hydrochloric acid. The rate of hydrogenation varied greatly from one solvent to another, but could not be related to the isomer content of the product. cis alcohol was also the main product in hydrogenation over Raney nickel in neutral or basic solvents. Similar conclusions were reached in a further investigation of a series of 2-substituted cyclohexanones,[33] hydrogenation over platinum in

*Believed, at the time, to be cis alcohol.
See footnote on p.5.

acetic acid/hydrochloric acid giving very largely the cis isomer, whereas although this latter was also the main product over Raney nickel, the proportion obtained was lower.

The methods of analysis used by these workers have however been criticised by Hückel,[34] who has shown that the margin of error in the percentages quoted was considerable. He has repeated a number of hydrogenations using both platinum and nickel catalysts, and determined isomer ratios using improved analytical techniques. His results, in general, appear to confirm the conclusions of earlier workers, but the results obtained with 2-isopropyl-[35] and 2-cyclopentylcyclopentanone[36] are notable in that hydrogenation over Raney nickel gave a higher proportion of cis isomer than hydrogenation over platinum black in acetic acid/hydrochloric acid.

The work cited up to now has concerned only monocyclic ketones, for which the Skita Rule, and Vavon's concept of determination of the preferred product by steric hindrance seem to apply generally, at least in the case of α-substituted ketones. A series of publications, by Hückel and co-workers, involving the hydrogenation of bicyclic ketones of the decalin and hydrindane series appeared at around the same period as the work of Skita and Vavon. Thus, hydrogenation of cis-α-decalone (I) in acetic acid solution over platinum black was reported[37] to give a single readily-crystallised product (II) whereas trans- -decalone (III) similarly gave a mixture of isomers (IV and V) in which one isomer (IV) predominated.

The configurations of these products were established in a later publication.[38] Further, cis-α-decalone (VI) gave a single product (VII), whereas trans-α-decalone (VIII) gave a mixture of isomers (IX and X) from which one isomer (IX) could be isolated in crystalline form. By performing this latter hydrogenation in acetic acid/hydrochloric acid, according to the method of Skita, a mixture was obtained in which the main product was the isomer X.[39] In the hydrindane series, cis-1-hydrindanone (XI) was initially reported to yield almost a single isomer,[40] but in later work this could not be duplicated,[41] some of the other isomer always being present in the product obtained under various conditions. The major product was the all-cis isomer (XII), and the minor product the cis-trans isomer (XIII). cis-2-hydrindanone (XIV) gave a mixture of the two possible isomers[42] (XV and XVI) of which the main product was suggested[43] to be the all-cis isomer (XV) by analogy with the formation of all-cis isomer (II) in the hydrogenation of cis-β-decalone (I). In a summary of this work,[44] Hückel draws the following conclusions:-

(a) Hydrogenation of cis-fused decalones and hydrindanones in acetic acid solution gives products consisting largely of one isomer.

(b) The reaction is less selective in the case of trans-fused ketones, but in the α-series, it is possible to favour production of one isomer by carrying out the hydrogenation in strongly acid medium.

(c) As to the configuration of the products, prediction of which isomer would be preferred was difficult. A tentative suggestion could be made that in the α-series, the resulting hydroxyl function would become cis to the neighbouring ring junction in the preferred product.[37] One difficulty was that the Skita Rule, and Vavon's method of distinguishing between cis and trans isomers led to conflicting predictions, as is pointed out by Hückel in a further publication.[45]

In a recent publication[46] on the stereochemistry of the products of reduction of ketones of the decahydroisoquinoline series, by various methods, including catalytic hydrogenation, a close parallel was observed between the results in this series and the decalone series. Hydrogenations were carried out in acetic acid solution over platinum oxide catalyst.[47] The proportions of isomers in mixtures were determined from yields obtained on chromatographic separation, and in assigning their structures, it was assumed the conformations adopted by the decahydroisoquinolines are similar to those of the corresponding decalins. The results obtained are summarised, along with those of Hückel in the decalin series, in table 1.

The ketones considered so far have conformational mobility (apart from the trans-fused decalones and decahydroisoquinolones), so that reaction in more than one conformation is possible. Since configurational isomers may arise from reaction of different conformers, it is of interest to ascertain what happens in conformationally rigid systems, where steric

hindrance effects should be more readily predictable. Two classes of compounds of this type will be discussed, namely bridged bicyclic ketones and steroidal ketones.

In the former class of compounds, the earliest assignment of configuration to a hydrogenation product was made by Alder and Stein,[48] who studied the hydrogenation of the norbornan--2-one-trans-5,6-dicarboxylic acid (XVII) with colloidal platinum in acetic acid/hydrochloric acid, and platinum oxide in acetic acid. The product obtained in both was the lactone (XVIII), none of the alternative product (XIX) being detected. From this it was concluded that addition of hydrogen to the norbornane system takes place preferentially from the exo side, and that the single product obtained by earlier workers[49] on hydrogenation of norbornanone itself was the endo alcohol. It was also noted that if the Skita Rule were to apply, the norbornane system had to be regarded as a substituted cyclopentane rather than as a substituted cyclohexane. In a further paper by the same authors,[50] the investigation was extended to substituted members of the norbornanone series, and their oximes. Hydrogenation of camphor (XX) was known from previous work[51] to give a product containing >90% isoborneol (XXI) and only about 5% of the isomeric alcohol, borneol (XXII). Fenchone (XXIII) was resistant to hydrogenation over platinum, but the oxime could be hydrogenated over this catalyst. Later workers also found that fenchone could not be hydrogenated over platinum oxide, or colloidal platinum,[52] but use of an active Raney

nickel catalyst at elevated temperatures and pressures resulted in a mixture containing α-(XXIV) and β-(XXV) fenchols in the ratio 1:2, this proportion being little affected by reaction conditions, including presence or absence of solvent. From isofenchone (XXVI), using platinum oxide in acetic acid, Alder and Stein obtained a mixture of α-(XXVII) and β-(XXIII) isofenchols in which the former predominated. At the time at at which this work was done, the authors were unable to assign configurations to the products since it was not known whether or not steric hindrance from the methyl substituents would cause reversal of the rule of exo addition found previously. In an investigation of the hydrogenation of camphor (XX), epicamphor (XXIX) and cyclocamphanone (XXX) over platinum sponge at 40-45 atm.,[53] only one alcohol was isolated in each case. The product from camphor was, as before, isoborneol (XXI), and the other products were considered to have the same configuration as isoborneol, i.e. the exo alcohols XXXI and XXXII. A more recent paper by Hückel[54] on the hydrogenation of epicamphor (XXIX) gives figures for percentage of exo and endo products derived from certain of the above ketones, and from 1-methylnorcamphor (XXXIII) which gives largely the endo alcohol (XXXIV). The results of hydrogenation of these bicylcic ketones are summarised in table 2.

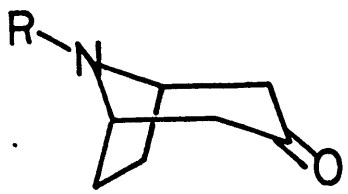
The nature of the products obtained on hydrogenation of bridged bicyclic ketones can be rationalised if steric hindrance is considered to be the main controlling factor. Thus,

in norbornanone, the exo side is less hindered than the endo side, and would be expected to be the preferred direction of addition of hydrogen, as is found to be the case. Substitution of the bridge carbon atom as in camphor, epicamphor and cyclocamphanone introduces considerable steric hindrance on the exo side, so that the preferred direction of addition of hydrogen is from the endo side. Further, hydrogenation of the substituted ketones occurs more slowly than hydrogenation of norbornanone itself. The stereochemistry of hydrogen addition to the bridge-substituted norbornane derivatives is consistent with the observed preference for endo attack by lithium aluminium hydride[55] and lithium tri-t-butoxy aluminium hydride[56] in the reduction of camphor, the principal product in both cases being isoborneol. In the case of fenchone, the carbonyl function is highly hindered by two neighbouring methyl groups, so that rigorous conditions are required to accomplish hydrogenation. Hindrance in this case occurs on both exo and endo sides, but formation of mainly β-(exo) alcohol indicates that the effect is greater on the former. For isofenchone, where the methyl substitution is in such a position as to cause no hindrance to exo addition, and little, if any, to endo addition, the preferred product is, as expected, the endo alcohol. Finally, a bridgehead methyl group has little or no effect on the direction of hydrogenation, as indicated by comparison of the results obtained with norbornanone and 1-methylnorcamphor (table 2). This is consistent

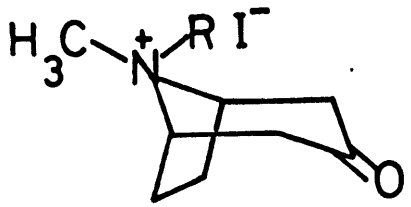
TABLE 3

Catalytic hydrogenation of the bicyclic ketones XXXVIII and XXXIX over platinum oxide.

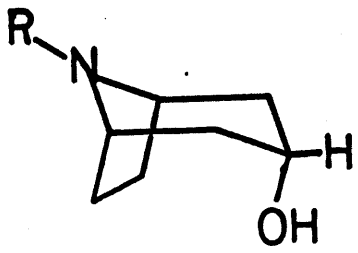
	n	Solvent	%β alcohol	%α alcohol
XXXVIII	1	iPrOH	98	2
		AcOH	81	19
	2	iPrOH	38	62
		AcOH	4	96
	3	iPrOH	1	99
		AcOH	3	97
XXXIX	1	AcOH	85	15
	2	AcOH	44	56
	3	AcOH	<1	>99



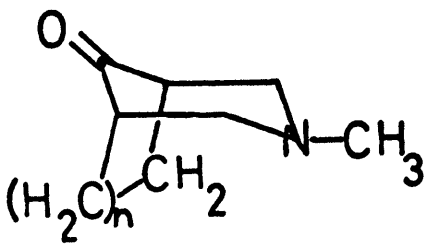
XXXV



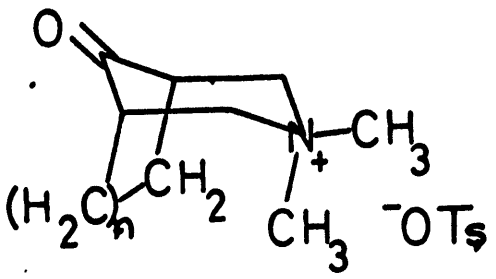
XXXVI



XXXVII
(and methiodide)



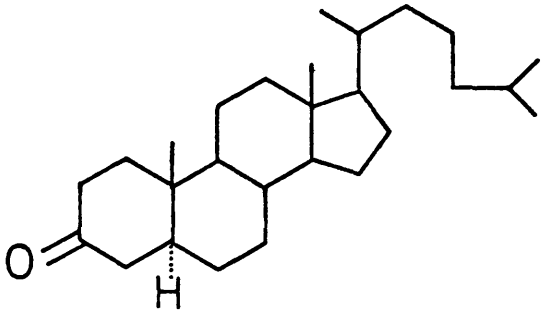
XXXVIII



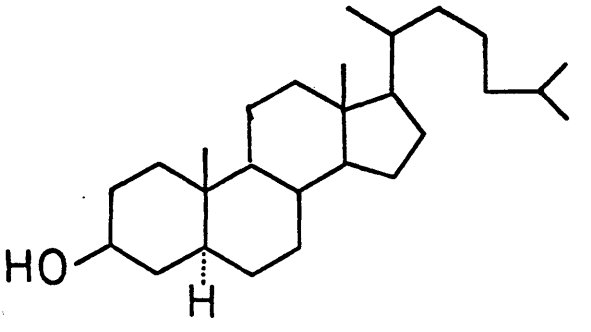
XXXIX

with the expectation that a bridgehead methyl should have little effect on approach from either the exo or the endo side.

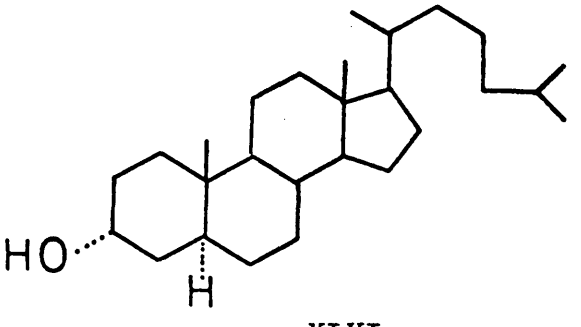
Further confirmation of the overriding importance of steric hindrance in determining the direction of addition of hydrogen in bridged bicyclic systems comes from two more recent publications. In the first of these,[57] hydrogenation of a series of N-substituted 3-nortropanones (XXXV; R=CH_3, CH_2CH_2OH, CH_2CO_2Et) and their methiodides (XXXVI) over W-5 Raney nickel at 40-50° and 60kg./cm.^{2} led to products in which only 3α-ol (XXXVII), but none of the corresponding 3β-ol, could be detected. With the methiodides, the yield of 3α-ol decreased with increasing bulk of the N-substituent, some starting material being recovered from the hydrogenation of XXXVI, R=CH_2CO_2Et, and an oil, thought to be the tertiary amine XXXV, R=CH_3, being recovered from XXXVI, R=CH_2CH_2OH, consistent with increased steric hindrance of approach to the carbonyl function. The solubility of the methiodides precluded quantitative separation of the reaction products, so that the possibility of formation of the 3β-ol methiodides could not be ruled out entirely. However, the preferred exo addition of hydrogen, even when the largest substituents were present, indicates that steric hindrance on the endo side is very high, even higher than that on the endo side of the norbornane system, as would be expected. In the second paper,[58] a series of azabicyclic bridge ketones (XXXVIII; n=1,2,3.) and their quat-



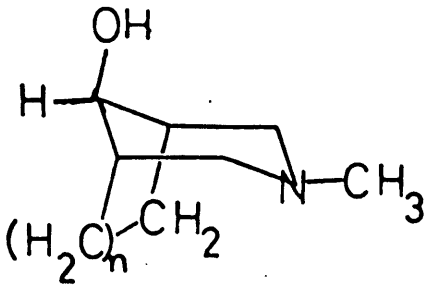
XLIV



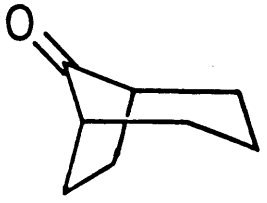
XLV



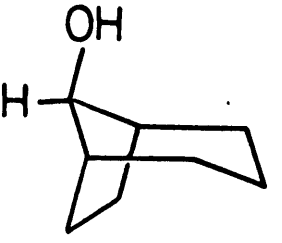
XLVI



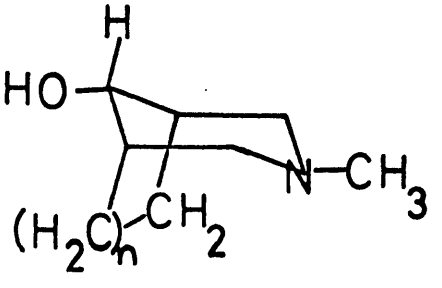
XL
(and quaternary salt)



XLI



XLII



XLIII

ernary ammonium salts (XXXIX) was hydrogenated over platinum. The percentages of products obtained are shown in table 3. With n=1, the less hindered side is that on which the five-membered ring lies, and as can be seen from the figures given in table 3, addition of hydrogen took place preferentially from this side, giving the β-alcohol (XL). An analogous observation was made by other authors for the carbocyclic analogue (XLI), which gave exclusively the alcohol XLII.[59] When n=3, giving a seven-membered ring, hindrance is lower on the side of the six-membered ring, so that hydrogenation took place preferentially on that side to give the α-alcohol (XLIII; n=3). When n=2, hindrance on both sides is of the same order and a mixture of intermediate composition was obtained. Product ratio, it is noted, may be affected to some extent by the possibility of adoption of more than one conformation by the larger rings (when n=2 or 3). In this same paper, earlier results on the hydrogenation of azabicyclic ketones are summarised. These support the same conclusion, that hydrogen is added preferentially to the less hindered side of the carbonyl function.

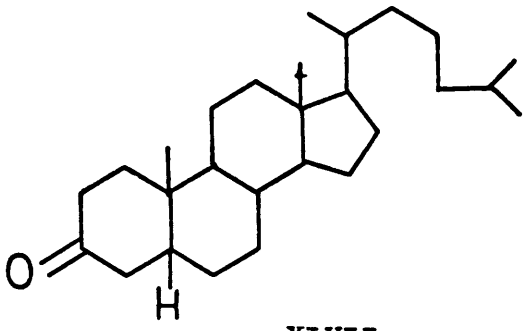
Among the earliest investigations of the hydrogenation of steroidal ketones is the work of Vavon and Jakubowicz on cholestanone (XLIV).[60] These authors found that in the hydrogenation of this ketone over platinum black, formation of cholestanol (XLV) was most favoured in neutral solvents, and that the proportion of epicholestanol (XLVI) formed could be

TABLE 4

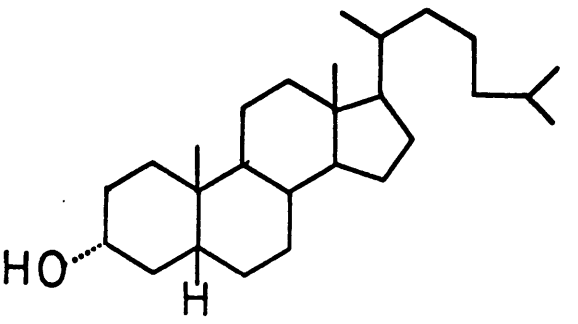
Hydrogenation of steroidal ketones of the 5α series over platinum in acetic acid. Dauben.[62]

Position of keto group	Product composition %	
	α	β
1	0	100
2	0	100
3	75	25
4	0	100
6 (MeOH solvent)	0	100
7	40	60
11	0	100
12 (ether solvent)	0	100[124]*

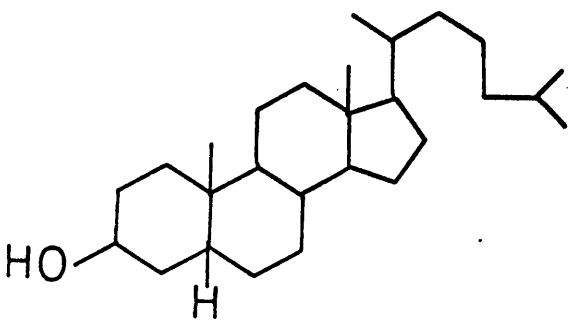
* The reference quoted for this example in Dauben's table is incorrect.



XLVII



XLVIII



XLIX

increased by addition of hydrochloric acid to the reaction medium. Hydrobromic acid was even more effective in promoting formation of epicholestanol. In a publication by Ruzicka and co-workers,[61] a similar, but more striking dependence of product formed on the medium employed is recorded. Coprostanone (XLVII) on hydrogenation in neutral medium (ether/ethanol) over platinum oxide gave almost entirely the α-alcohol, epicoprostanol (XLVIII), whereas hydrogenation in acetic acid/hydrobromic acid gave almost entirely the β-isomer, coprostanol (XLIX). These 3-keto steroids of the 5α (L) and 5β (LI) series have the keto function in that position in the perhydrocyclopentenophenanthrene skeleton which is least subject to steric hindrance, and, as was found for unhindered cyclohexanones (p.9), the nature of the products obtained on hydrogenation is critically dependent on the medium in which the reaction is carried out. In the 5α series, when the keto function is at positions other than C_3 in the steroid nucleus, attack on the β-face of the molecule is hindered by the angular methyl groups at C_{10} and C_{13}, resulting in a general preference for the formation of β-alcohols by hydrogenation from the α-side. This is reflected in the summary of the results of hydrogenation of ketones of the 5α series recorded by Dauben,[62] and shown in table 4. Most of these hydrogenations were carried out in acetic acid, and all over platinum catalysts. (On the table drawn up by Dauben the reference given for the hydrogenation of the 12-ketone in

TABLE 5

Hydrogenation of steroidal ketones of the 5β series over platinum.

Postition of keto group	Solvent	Products obtained
3	ether/ethanol	Mainly α alcohol
	acetic acid/ hydrobromic acid	Mainly β alcohol
6	acetic acid	6α alcohol (also obtained with Raney Ni in methanol)(127)
11	acetic acid	11α alcohol(128)
12	acetic acid	12α alcohol (regarded as at the time)(129) 12-oxime gave 12α-amine(130)

fact contains no mention of this reaction. The correct reference for this hydrogenation should have been No. 22). It may be noted that formation of a significant proportion of α-alcohol occurs with the 7-ketone in which the angular methyl groups are furthest removed from the keto function, and thus exert less control over the direction of reaction than in the case of the isomeric ketones. In the 5β steroid ketone series, the configuration and conformation of ring A are such as to cause steric hindrance to approach from the α-side of the molecule for all but the 3-ketone. This is reflected in the preferred formation of the α-alcohols in the examples collected in table 5. No examples of hydrogenation of the 1,2, 4 or 7-ketones of this series could be found in the literature. The effect of change of solvent on product composition has not been investigated for these two series, but steric effects probably play the dominant role in determining the preferred products. The hydrogenation of certain steroidal ketones over Urishibara nickel, in alcoholic or aqueous alcoholic medium at r.t.p., have been reported.(63) Cholestanone (XLIV) gave 90% cholestanol (XLV) and 10% epicholestanol (XLVI), a result which indicates that this is the best method of obtaining the 3β-alcohol. Coprostanone (XLVII) gave a mixture of 42% copostranol (XLIX) and 58% epicoprostanol (XLVIII), in contrast to the almost exclusive formation of the latter over platinum in neutral medium. 6-ketocholestanol gave cholestan-3β,6β-diol, and 7-ketocholestanol

gave a mixture of the 7α and 7β-alcohols in similar amounts, results similar to those obtained over platinum.

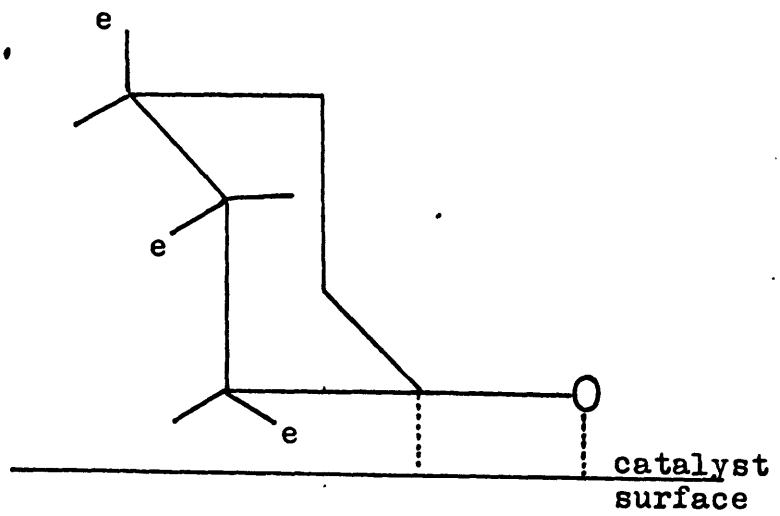
Although steric factors appear in general to exert fairly predictable control over the products of hydrogenation of steroidal ketones, anomalous results have recently been reported[64] for the keto acids (LII;R=H or Me). Hydrogenation of LII (R=H, X=OH) over platinum oxide in acetic acid gave mainly trans lactone (LIII), whereas LII (R=Me, X=C_8H_{17}) under the same conditions gave more of the cis lactone (LIV). Since addition of hydrogen from the β-side of the molecule should be more hindered by the presence of an angular methyl group than by a hydrogen atom, this result is the reverse of what would be expected. The authors were unable to account for this discrepancy, and discounted an explanation involving a boat form of ring B in the keto acid LII, (R=H, X=OH). The corresponding acetate, LII (R=H, X=OAc) however gave cis-lactone in proportion similar to LII (R=Me, X=C_8H_{17}), so it was concluded that the 17β-OH function exerts some control over the products obtained. Addition of hydrochloric acid to the reaction medium increased the amount of cis-lactone formed, and at appropriate concentrations of added acid, the latter was the main product in all cases. In the same paper, the results of a study of the effect of different acids on the products and rate of hydrogenation of cholestanone, lanost-8-ene-3-one and the keto acids LII (R=Me, X=C_8H_{17} and OCOPh; R=H, X=OH and OAc) are reported. The

rate of hydrogenation, and extent of formation of α-(axial) alcohol (or cis-lactone) increased generally on addition of either perchloric or hydrochloric acid to the reaction medium, but perchloric acid was much less effective in promoting formation of α-alcohols than hydrochloric acid. It is suggested that this casts doubt on a proposal made by Brewster (discussed below, p.25), that axial alcohols are formed by transfer of hydride ion from the catalyst to protonated ketone, since perchloric acid in acetic acid should be more acidic than hydrochloric acid in acetic acid. Dry hydrogen chloride was found to be particularly effective in enhancing hydrogenation rates and increasing the yield of axial alcohol. Use of trifluoroacetic acid as solvent led to an increase in both the rate of hydrogenation, and in the amount of axial alcohol formed, but like perchloric acid, trifluoroacetic acid was less effective than hydrochloric acid for the latter. It was concluded that although the preference for formation of axial alcohol is definitely related to solvent acidity, specific effects of different acids are also involved, since the mechanism of hydrogenation could not be related to the rate of reaction. The failure to relate the rate of hydrogenation to the isomer content of the product from 2-cyclohexanone has already been noted.(p.11).

The earliest attempt to rationalise the results observed on hydrogenation of cyclic ketones was that of Vavon, which has already been described.(p. 7). Following the work of

FIGURE 2

Hydrogenation of cyclohexanones after Siegel.[68]



Substituents prefer to adopt equatorial (e) conformation.

Hassel[65] and Pitzer[66] on the conformation of the cyclohexane ring, and of substituted cyclohexanes, Barton[67] proposed the following generalisations for predicting the stereochemistry of the products obtained.

(a) Catalytic hydrogenation of both hindered and unhindered keto groups in strongly acid media (rapid hydrogenation) affords axial alcohols.

(b) Similar reduction in neutral media (slow hydrogenation) gives equatorial alcohol if the keto group is unhindered, and axial alcohol if it is strongly hindered.

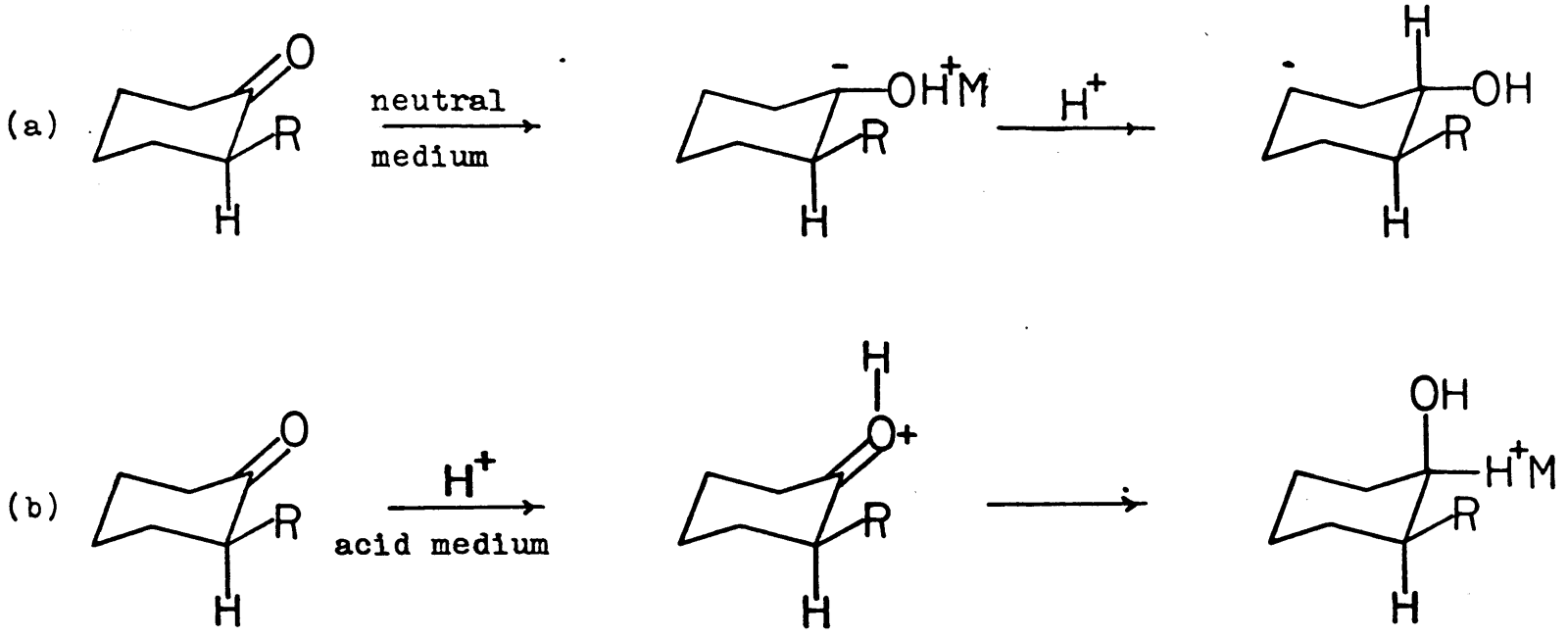
The work of Hassell and Pitzer (which showed that cis-1,3-disubstituted cyclohexanes are more stable than the trans isomers), combined with chemical evidence, also led to the reassignment of the configurations of the 3-methylcyclohexanols by Siegel.[68] Thus, hydrogenation of 3-methylcyclohexanone in acid solution must give mainly trans-3-methylcyclohexanol, and not the cis isomer, as had been previously assumed.[16,30] This result, as well as the formation of cis alcohols from α-substituted cyclohexanones, could be readily accounted for, if it was assumed that the stable conformation of a monosubstituted cyclohexanone was one in which the substituent was equatorial, and that the molecule was adsorbed on the catalyst without change in conformation. The carbonyl group was assumed to become attached at two points, carbon and oxygen, in the least hindered arrangement, in which the ring tilts away from the catalyst, as illustrated in fig. 2. Add-

ition of hydrogen from the direction of the catalyst leads to the formation of an axial hydroxyl function, i.e. cis to a substituent in the 2 or 4-position, or trans to a substituent in the 3-position. At the time of this publication, 3-methylcyclohexanone was the only monosubstituted cyclohexanone with a substituent in the 3-position to have been hydrogenated to a cyclohexanol whose configuration was adequately defined. Siegel, however, refers to the examples of cholestanone (XLIV) and coprostanone (XLVII), which are hydrogenated under acidic conditions to epicholestanol (XLVI) and coprostanol (XLIX) respectively, in which the 3-OH group and the arm of ring B attached to C-5 are trans to each other, as supporting his proposal. Hydrogenation of 3-isopropylcyclohexanone, with platinum black in acetic acid/hydrochloric acid, has been found to give mainly the trans alcohol.(69)

These explanations of the stereochemistry of the products obtained in hydrogenation of cyclic ketones do not account for the effect of solvent. Indeed, if steric hindrance were the only factor involved, similar products should be obtained no matter what solvent is employed. In order to explain the difference in results obtained in acid and neutral media, Brewster(70) proposed that the catalyst might be able to supply the equivalent of hydride ion to the ketone while the solvent supplied a proton, in two distinct steps, the stereochemistry of the product depending on whether protonation preceded or followed hydride abstraction. In neutral medium, reaction was

FIGURE 3

Hydrogenation of 2-alkylcyclohexanones after Brewster.[70]



pictured (fig.3a) as proceeding via formation of a "resonance stabilised complex", (of substrate with catalyst) in which the bulky metal assumed an equatorial conformation, followed by proton abstraction from the solvent, the proton entering the axial position to give equatorial alcohol. Reduction in acid solution was pictured (fig.3b) as proceeding via initial protonation of the ketone followed by formation of a different "resonance stabilised complex", the bulky metal again assuming the equatorial conformation leading, after hydride transfer from the metal, to axial alcohol.

A different explanation for the dependence of isomer ratio on solvent employed is suggested by Wicker,[71] who found that substituted cyclohexanols could be isomerised by heating with nickel or platinum catalysts in an atmosphere of hydrogen, if alkali was present. Raney nickel as normally prepared contains alkali, and Adams' platinum oxide has also been shown to contain alkali.[72] The use of sufficient quantities of catalyst enabled isomerisation to proceed at room temperature, the isomerisation being presumed to lead finally to an equilibrium mixture of alcohols. This suggested that the less stable isomer might be produced preferentially in both acid and neutral (or basic) media, but that in the latter, subsequent isomerisation occurred to give more of the stable isomer. A number of hydrogenations of substituted cyclohexanones were carried out at room temperature under conditions in which it was thought that the extent of isomerisation would be small.

TABLE 6

Hydrogenation of 2-methylcyclohexanone after Wicker.[71]

Conformation	Product expected on hydrogenation
Chair, equatorial-CH_3	cis
Chair, axial-CH_3	Similar amounts of cis and trans alcohols. (Larger alkyl groups favour more cis isomer.)
1:2 enol	cis only
5:6 enol	Similar amounts of cis and trans alcohols.

It was found that in the cases of 3-methylcyclohexanone, dihydroisophrone (3,3,5-trimethylcyclohexanone) and 4-cyclohexylcyclohexanone, a greater proportion of the more stable isomer resulted from hydrogenation in acetic acid than in alkaline media, which is contrary to the Skita Rule. Change of medium had little effect on the isomer ratio with 2-methylcyclohexanone, while for 4-methylcyclohexanone, the results conformed to the Skita Rule for platinum but not for nickel. These observations indicated that the effect of the medium on the products obtained on hydrogenation of cyclic ketones is not so simple as suggested by the rule. To account for his results, Wicker has suggested that the chair form of the cyclohexanone with equatorial alkyl substituents is not the only form which may be adsorbed on the catalyst surface, but that contributions may also arise from forms with substituents in the axial conformation, and from enol forms of the ketone. Acid and alkali would affect the proportions of keto and enol forms, thus changing the proportion of stereoisomers produced in hydrogenation. The possible forms, and the products predicted to arise from them are given in table 6 for the case of 2-methylcyclohexanone. Superimposed on this is the possibility of isomerisation of the initial products, the rate of which increases with increasing temperature, catalyst quantity and catalyst activity. Since hydrogenation catalysts can also catalyse dehydrogenation, the following equilibrium is proposed to account for isomerisation:-

<u>cis</u> alcohol $\rightleftharpoons$ ketone (equatorial alkyl) $\overset{(i)}{\rightleftharpoons}$ ketone (axial alkyl) $\overset{(ii)}{\rightleftharpoons}$ <u>trans</u> alcohol.

(2-and 4-substituted ketones. For 3-substituted ketones, (i) and (ii) are interchanged). The effect of alkali in isomerisation is illustrated by the observation that whereas Adams' platinum is an effective catalyst for dehydrogenation, acid-washed platinum is very inefficient for this reaction.

In a later publication,[36] Hückel also discusses the stereochemistry of catalytic hydrogenation of cyclic ketones, emphasising the importance of the exact nature of the catalyst employed, variations in the ratios of stereoisomers produced being observed from one experiment to another, even when an attempt was made to reproduce exactly the experimental conditions and procedure of catalyst preparation. The Skita Rule, and Vavon's concept of steric control are concluded to apply generally to 2-substituted cyclohexanones, but with the corresponding cyclopentanones, exceptions to the Skita Rule have been found.(p.12) 3-methylcyclohexanone is of course an exception to the Skita Rule, but the few 4-substituted cyclohexanones which have been examined appear to obey the rule, as long as acetic acid/hydrochloric acid is used as the solvent rather than acetic acid alone. Several exceptions to Barton's Rules are pointed out. Thus, <u>cis</u>-α and <u>cis</u>-β-decalone, and certain steroidal ketones (the latter previously pointed out by Dauben[62]), give mainly equatorial rather than axial alcohols in acid solution. Further,

with regard to Brewster's explanations, the envisaged route in neutral medium, predicting formation of equatorial-OH gives no indication of the effect of neighbouring groups, which favour formation of axial-OH. Hückel considers that two factors may contribute to the formation of trans isomers in hydrogenation of 2-substituted cyclic ketones:-

(a) The 2-substituent does not completely prevent adsorption of the carbonyl function on that side on which it lies. This is particularly the case with the cyclopentanones.

(b) Desorption of the hydrogenation product does not occur sufficiently rapidly to remove all of the cis alcohol from the catalyst surface, thus permitting the establishment of an equilibrium favouring the trans isomer.

i.e. cis alcohol $\rightleftharpoons$ ketone + H_2 $\rightleftharpoons$ trans alcohol.

Once desorbed, the cis isomer does not react further unless it is able to return to the catalyst surface. These views are similar to those of Wicker, but in this case, the intervention of enols is not considered. The effect of hydrochloric acid in promoting rapid hydrogenation and formation of cis isomers is seen as resulting from an increased rate of desorption of the product.

Up to now, the principal mode of hydrogenation of ketones has been assumed to involve direct addition of hydrogen across the carbonyl double bond. Support for this view comes from deuteration experiments, (summarised by Bond[73]) which indicate that in hydrogenation, ketones react in the

keto rather than the enol form at temperatures below about 150°. Thus, the principal product from deuteration of acetone is $CH_3CDODCH_3$. The steps proposed by Bond for the hydrogenation of acetone are as follows:-

$$D_2 + 2* \longrightarrow 2D.$$
$$\quad *$$

$$(CH_3)_2CO + 2* \longrightarrow (CH_3)_2\underset{*}{C}\text{-}\underset{*}{O}.$$

$$(CH_3)_2\underset{*}{C}\text{-}\underset{*}{O} + \underset{*}{D} \longrightarrow (CH_3)_2\underset{*}{C}\text{-}OD + 2*.$$

$$(CH_3)_2\underset{*}{C}\text{-}OD + \underset{*}{D} \longrightarrow (CH_3)_2CD\text{-}OD + 2*.$$

* denotes an adsorption site on the catalyst surface. The accompanying reaction of hydrogenolysis is pictured as follows:-

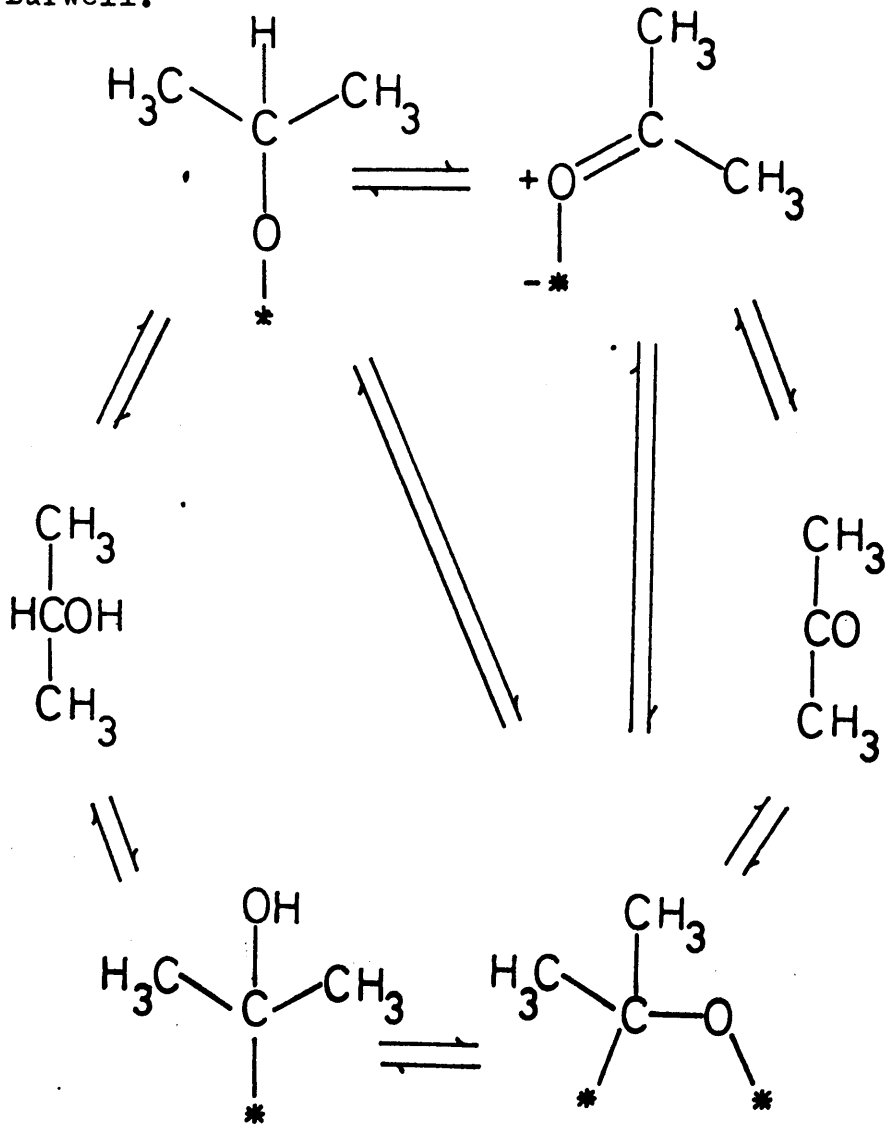
$$(CH_3)_2\underset{*}{C}\text{-}OD \longrightarrow H_2C=\underset{*}{C}\text{-}CH_2 + HDO$$

$$H_2C=\underset{*}{C}\text{-}CH_3 + \underset{*}{D} \longrightarrow H_2\underset{*}{C}\text{-}\underset{*}{C}D\text{-}CH_3 \longrightarrow \text{hydrocarbon.}$$

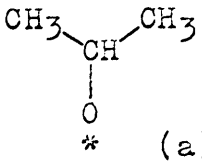
Different intermediates have however been proposed more recently by Newham and Burwell[74] based on work on the hydrogenation of 2-butanone, and hydrogen exchange between isopropyl alcohol and 2-butanone over a copper catalyst. (Some work was also done over nickel and palladium catalysts.) From the facts that -OH/-OD exchange in alcohols occurred very rapidly over hydrogenation catalysts, and that during the dehydrogenation of optically active 2-butanol, extensive racemisation of the alcohol was observed in the early stages of reaction, the species (a) rather than (b) was proposed to be a principal

FIGURE 4

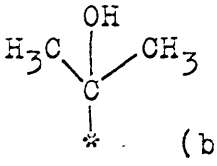
Adsorbed species in the hydrogenation of acetone, and dehydrogenation of isopropyl alcohol, after Newham and Burwell.[74]



intermediate in dehydrogenation of alcohols, and the reverse reaction, hydrogenation of ketones.

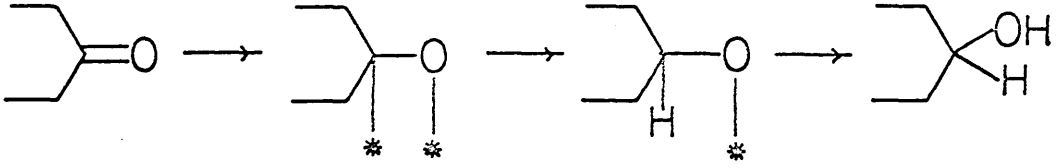


(a)



(b)

From their experimental observations, Newham and Burwell pictured these reactions as proceeding via the species shown in fig. 4. The oxygen adsorbed intermediate is also preferred by Acke and Anteunis,[75] who propose the sequence



for the reduction of cyclohexanone in neutral medium. For the side reaction of alkane formation, and for hydrogenation in acidic alcohol solution, these authors favour reduction via the enol form. Thus, in hydrogenation of 4-t-butylcyclohexanone in methanol/hydrogen chloride over platinum oxide at r.t.p., a mixture of 4-t-butylcyclohexanone, 4-t-butylcyclohexanol and 4-t-butylcyclohexyl methyl ether was obtained in proportions which varied with the HCl concentration. The t-butylcyclohexanol obtained consisted mainly of the trans isomer, whereas the methyl ether consisted mainly of the cis isomer. Formation of the trans alcohol was considered to arise by hydrogenation of the enol form of the ketone in a manner similar to the formation of trans-4-methyl-t-butylcyclohexane from 1-methyl-4-t-butylcyclohexene.[76]

FIGURE 6

Hydrogenation of cyclohexanones in methanol/HCl, after Acke & Anteunis.[75]

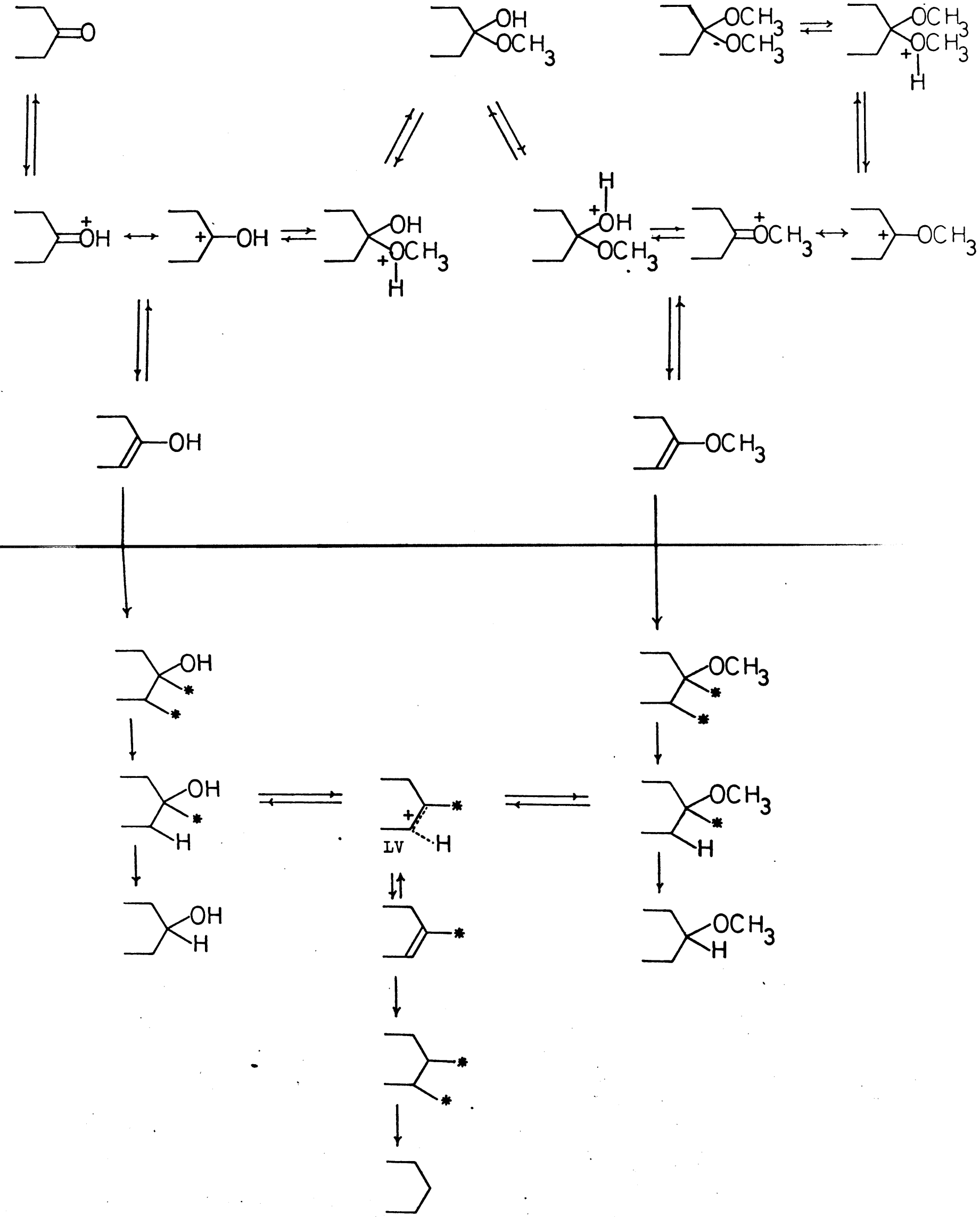
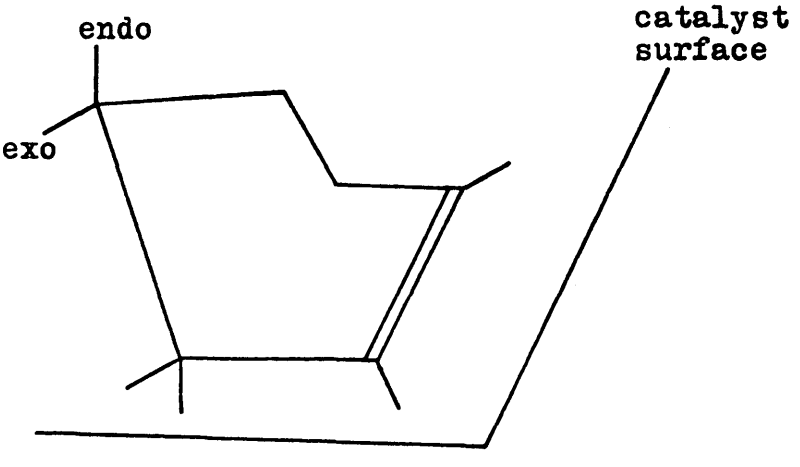


FIGURE 5

The adsorbed intermediate in hydrogenation of alkylcyclohexenes after Sauvage, Baker and Hussey.[76]



A t-butyl group is forced into the exo conformation. Smaller groups (Me, Et) adopt the endo conformation.

(To account for the cis/trans isomer ratios obtained in hydrogenation of the latter, and other alkyl-substituted cyclohexenes, adsorption on the catalyst surface in a boat conformation was proposed, as illustrated in fig. 5.) Formation of cis ether was considered to arise by axial attack of solvent methanol on a "half-hydrogenated carbonium ion" intermediate, [(LV), fig. 6.] in which the bulky metal catalyst would prefer to adopt the equatorial configuration, and which itself was formed either from enol, or from enol methyl ether as illustrated in fig. 6. The preference for formation of trans alcohol under these conditions may be contrasted with the preferred formation of cis alcohol on hydrogenation of 4-t-butylcyclohexanone in acetic acid/hydrogen chloride over platinum oxide at room temperature and 57 p.s.i.(77)

From the preceding summary, it is evident that while a preferred product may be predicted with reasonable safety when important steric factors control the direction of hydrogenation, the observation of Vavon that the products obtained from unhindered ketones depend on the medium employed still applies, and in a manner not yet sufficiently well understood to be completely explained in mechanistic terms. The dependence of the stereochemistry of the alcohols obtained on hydrogenation of ketones on other species present in the reaction medium is strikingly illustrated in a publication by Japanese workers, who have found that addition of optically active α-amino or α-hydroxy acids to the medium in hydrogenation of

methylacetoacetate over Raney nickel results in formation of optically active methyl-β-hydroxybutyrate.[78a] The effectiveness of the additives varied widely from one example to another, and was dependent on pH and temperature. The effect of these factors, and of particular structural variations of the additives has been studied in later publications[78b,c] in an attempt to elucidate the mechanism by which this effect operates.

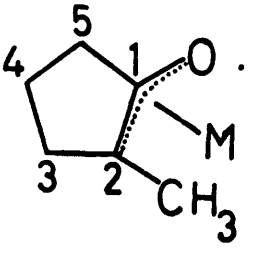
Very recently, Cornet and Gault have reported a study of the hydrogenation of 2-methyl cyclopentanone, in both the gas and the liquid phase, over a variety of catalysts and in the absence of solvent to avoid the complications introduced by its presence, and also of the cis-trans isomerisation of the 2-methylcyclopentanols.[79] The following observations were made:-

(a) In the temperature range considered (80-160°), a fast cis-trans isomerisation of the 2-methylcyclopentanols took place, which did not proceed via dehydrogenation to the ketone, as suggested by Wicker[71] and Hückel.[36]

(b) Hydrogenation of the ketone, when this was rigorously purified by gas-liquid chromatography, was unselective, the amounts of cis and trans alcohols formed initially (prior to subsequent isomerisation) being similar, and nearly independent of the catalyst and temperature. A high cis selectivity only appeared on a poisoned catalyst, or when the reacting ketone had not been rigorously purified. Further, in hydro-

FIGURE 7

The triadsorbed intermediate in hydrogenation of 2-methylcyclopentanone, and the isomerisation of the 2-methylcyclopentanols, after Cornet and Gault.[79]



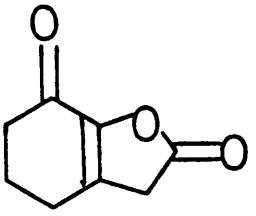
genations carried out on unpurified ketone, subsequent isomerisation of the initially formed alcohols was suppressed. (c) In deuteration experiments, the deuterium distributions of both the cis and the trans alcohol were very similar. Since these results could not be accounted for by a mechanism involving the cis addition of hydrogen to a diadsorbed ketonic species, the authors proposed the intermediacy of a triadsorbed species (see fig. 7) in which either carbon atom α to the carbonyl function may be involved, this intermediate being comparable with hydrocarbon π-allylic species. It was suggested that this intermediate could react both with atomic hydrogen on that side of the ring adjacent to the catalyst surface, and with molecular hydrogen from the top at both C_1 and C_2 (or C_5). Suppression of one mode of attack, as in hydrogenations carried out with the unpurified 2-methylcyclopentanone, would simultaneously prevent the formation of trans alcohol by hydrogenation of the ketone, or by isomerisation of the cis alcohol.

III. ESTERS AND LACTONES.

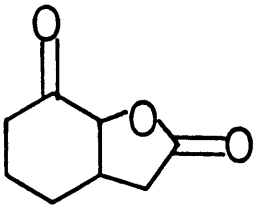
Work done on this class of compounds up to the end of 1949 has been reviewed by Adkins.[80] Catalytic hydrogenation of an ester to an alcohol usually requires elevated temperatures and pressures, branched aliphatic members being more resistant than the straight chain analogues. In general, aromatic esters, α-hydroxy and α-amino esters can be hydrogenated satisfactorily under milder conditions than their simple aliphatic analogues. Lactones may be hydrogenated under similar conditions to give glycols, or may yield acids by hydrogenolysis.

The most widely used catalyst for this reaction is copper-chromium oxide at temperatures in the range 100-250° and pressures of 150-300 atm. Zinc-chromium oxide has also been used, but requires higher temperatures, being less active. An interesting property of this catalyst is its relative inactivity in the saturation of carbon-carbon double bonds, unsaturated alcohol having been obtained, e.g. from ethyl oleate.[81] However, the unsaturated alcohol is generally accompanied by saturated alcohol, and separation is difficult. Raney nickel catalysts have also been employed for the hydrogenation of esters, highly active preparations being effective for the hydrogenation of α-hydroxy and α-amino esters, even at room temperature.[82a,b]

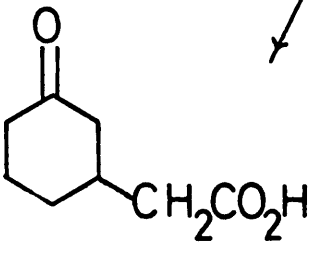
A number of lactones have been hydrogenated under milder conditions than are normally required for esters. Adams' platinum oxide has been used for the hydrogenation of sugar

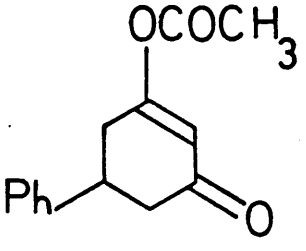


LVI

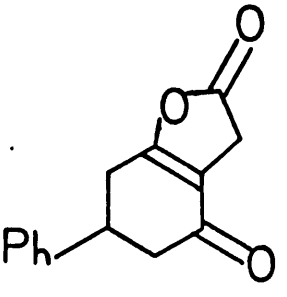


LVII

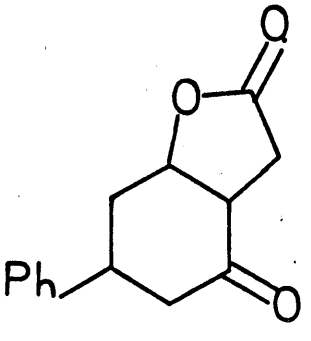




LVIII

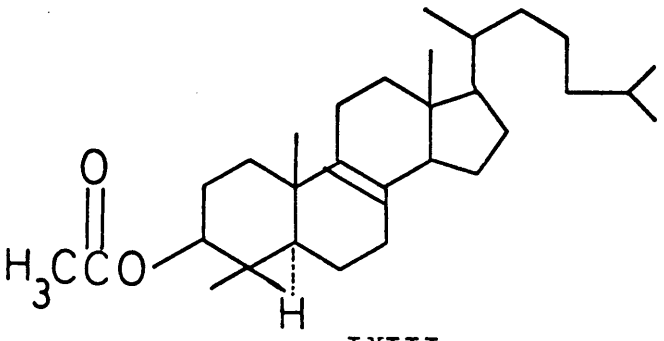


LIX

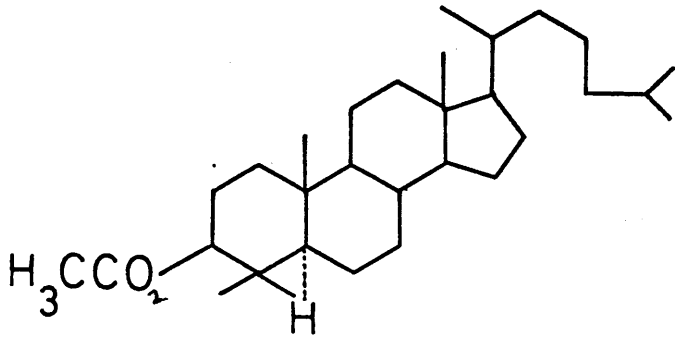


LX

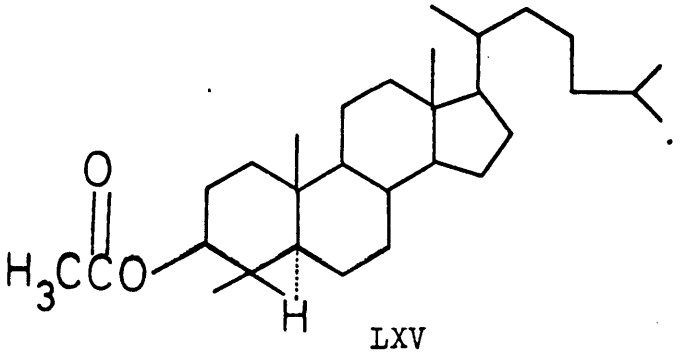
lactones in aqueous solution at room temperature and 2-3 atm.[83,84] In an investigation of the hydrogenation of both γ and δ sugar lactones, it was concluded that γ-lactones generally yielded a sugar which was more readily reduced further to the alcohol than the δ analogues. Indeed good yields of sugar could be obtained from the latter. Hydrogenolysis of certain enol lactones to saturated acids, and enol acetates to the methylene compound and acetic acid can occur under mild conditions. Thus, enol lactones activated by an α carbonyl or phenyl group, e.g. LVI, are hydrogenolysed over palladium on barium sulphate at r.t.p.[85,86] Cleavage of the saturated analogue (LVII) also occurred under these conditions. The presence of the lactone ring appears to be necessary for this hydrogenolysis to occur, since the enol acetate derived from cyclohexane-1,2-dione yielded only α-acetoxycyclohexanone on hydrogenation under the same conditions. In contrast to this, hydrogenolysis of both the enol lactone and enol acetate derived from β-diketones was observed,[87] e.g. with 5-phenyl-cyclohexan-1,3-dione enol acetate (LVIII) and 2,6-diketo-5-phenyl-cyclohexylacetic acid enol lactone (LIX). The saturated lactone (LX) was not hydrogenolysed, indicating that it is not an intermediate in the hydrogenolysis of LIX. Unactivated enol acetates derived from cyclohexanones have been hydrogenolysed over platinum oxide,[87] but over palladium on calcium carbonate these compounds were either resistant, or were hydrogenated to the saturated acetate. Enol acetates



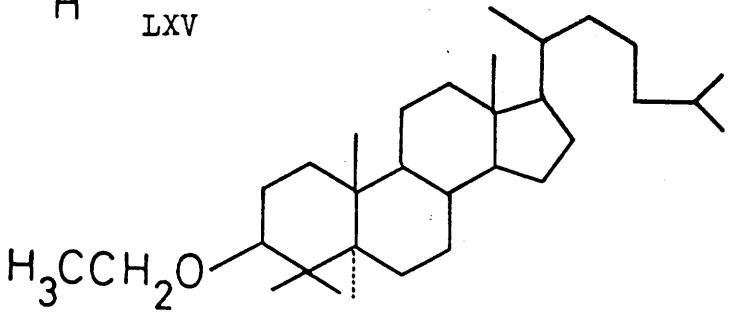
LXIII



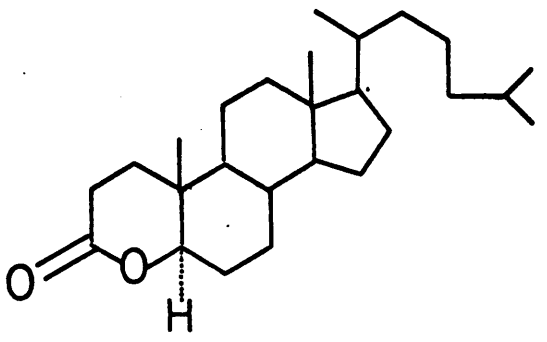
LXIV



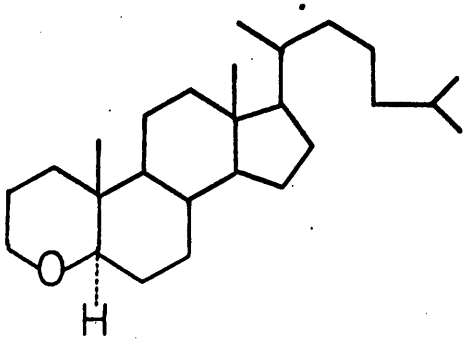
LXV



LXVI



LXI



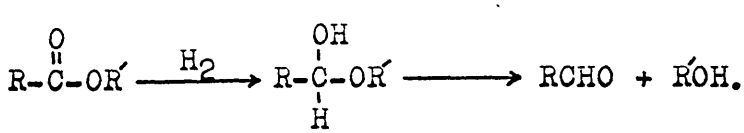
LXII

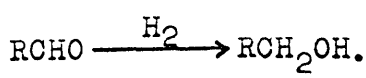
derived from cyclopentanones gave only the saturated acetate with both catalysts.

In more recent work,[88] a series of δ-lactones have been hydrogenolysed to the cyclic ethers in high yield over platinum oxide in acetic acid. e.g. 4-oxa-3-oxo-5 -cholestane (LXI) gave the ether (LXII) in 92% yield in 9 hr. The addition of 70% perchloric acid in regulated amounts resulted in a dramatic increase in the rate of hydrogenation without detriment to the yields obtained. Thus, under these conditions, hydrogenation of LXI was complete in 15 minutes. No measurable hydrogen uptake was observed in the case of γ or ε-lactones under these conditions over a period of 12 hr. A similar type of hydrogenolysis has been observed to occur on prolonged hydrogenation of dihydrolanosteryl acetate (LXIII) and dihydroagnosteryl acetate (LXIV) over relatively large amounts of platinum oxide in acetic acid containing perchloric acid.[89] In addition to the expected product (LXV), the ethyl ether (LXVI) was obtained in about 24% yield in both cases.

Two routes may be envisaged for the conversion of esters to alcohols.

(a) Initial hydrogenation.





(b) Initial hydrogenolysis.

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OR' \xrightarrow{H_2} RCHO + R'OH.$$

$$RCHO \xrightarrow{H_2} RCH_2OH.$$

As Adkins points out, the distinction between these routes may not be significant, since the intermediate may remain attached to the catalyst, and so have no independent existence before it is converted to the final product.(80)

IV. CARBOXYLIC ACIDS.

Since hydrogenation of this class of compounds requires very rigorous conditions, it has generally been found more convenient to convert the acids to esters which will hydrogenate more readily. The main products of hydrogenation of carboxylic acids, as for the corresponding esters, are alcohols, hydrocarbons being the principal by-products. Formation of the latter as the main product may be favoured by suitable choice of catalyst and reaction conditions. This may be illustrated by the preparation of dodecane and octadecane from lauric and stearic acids, or octyl and octadecyl alcohols from caprylic and stearic acids.(90) A further important side-product which may be obtained is the ester derived from the original acid, and the alcohol formed from it on hydrogenation.

Investigations of the hydrogenation of monocarboxylic(91) and α,ω-dicarboxylic(92) acids, to alcohols and polymethylene glycols respectively, over copper-barium chromite and copper oxide catalysts have been reported. It was found, in both series, that decrease in hydrocarbon chain length led to increasing difficulty in hydrogenation, little or no alcohol or glycol, but rather some ester. or polyester being obtained with the lower homologues (C_2-C_6), but that copper oxide was the more effective catalyst for acids with shorter chains (C_7-C_{10} for the monocarboxylic and C_7-C_{13} for the dicarboxylic acids). Hydrogenations were carried out at 280-300° under a pressure of ~250 atm. generally in the absence of solvent.

Hydrogenation of the dicarboxylic acids over copper-barium chromite could be accomplished more efficiently in dioxan, use of latter solvent resulting in high yields of glycols from adipic acid (C_6) and higher homologues. The resistance of the lower homologues to hydrogenation was ascribed to their reaction with the catalyst, which dissolved in the acids.

Ruthenium catalysts have also been used for the hydrogenation of carboxylic acids to alcohols at temperatures around 150°(93) Notably, hydroxyacetic acid could be hydrogenated to ethylene glycol in fair yields at pressures below 100 atm., but pressures in excess of 500 atm. are required for the hydrogenation of isolated carboxyl groups.

The most effective catalysts yet reported for this hydrogenation are the rhenium blacks. The earliest report on these catalysts concerns the catalyst obtained by in situ reduction of rhenium heptoxide.(94) This permits hydrogenations of monocarboxylic acids to be carried out at temperatures of 150-170°, and of dicarboxylic acids at 200-250° under 135-270 atm. pressure. Thus, high yields of alcohols were obtained in the homologous series, starting with acetic acid, particularly when water was used as solvent, this latter causing marked reduction in the side reaction of ester formation found when hydrogenations were run on the anhydrous acids. Branched acids were more difficult to hydrogenate, e.g. pivalic (trimethylacetic) acid was resistant. Di- and trichloroacetic acids were not successfully reduced but tri-

fluoroacetic acid and heptafluorobutyric acid gave the corresponding alcohols in high yields. The fluoro derivatives required significantly higher temperatures and pressures for hydrogenation than the parent acids. The amino acids, glycine and β-alanine also required more rigorous conditions for hydrogenation, and were deaminated in the process, yielding ethanol and n-propanol respectively. Hydrogenation of the carboxyl function to the alcohol has been achieved under similar conditions using the oxides of rhenium IV,[95] rhenium VI[96] and rhenium II,[97] the last two being particularly efficient. It was observed with rhenium VI oxide that esters required more strenuous conditions for reduction than the corresponding acids, the reverse of what has been found for all other catalysts. Further, benzoic acid was reduced to the carbinol without further hydrogenolysis to toluene. As with rhenium VII oxide, side reactions could be minimised or eliminated by conducting hydrogenations catalysed by the VI and II oxides in aqueous medium.

It has been reported that in certain hydrogenations carried out in acetic acid/perchloric acid over platinum oxide at r.t.p., the hydrogen uptake was significantly greater than the calculated amount. To explain this, the authors claim that some hydrogenation of the acetic acid solvent has also taken place. (Ref.89, footnote 17).

V. AMIDES AND LACTAMS.

Amides are the most difficult of the carboxylic acid derivatives to hydrogenate, pressures of 200-400 atm. and temperatures of 250-300° having been employed with the most commonly used copper-chromium oxide catalysts, in dioxan as solvent. The main products of hydrogenation of amides unsubstituted on the N-atom are, under favourable conditions, primary amines. Yields are however often greatly reduced by the occurrence of a wide variety of side reactions. Much of the published work in this field is due to Adkins and co-workers. Thus, in an early paper,(98) the types of reaction which occur in hydrogenation of amides over copper-chromium oxide are summarised. In the hydrogenation of amides of the type $RCONH_2$, the most important side reaction is formation of secondary amine, $(RCH_2)_2NH$. Further alkylation to tertiary amine may occur, but is much less important. Other side reactions which may occur are as follows:-

(a) Cleavage of nitrogen-carbon bonds in N-mono- or disubstituted amides, in addition to hydrogenolysis of the oxygen function.

$$RCONHR' \xrightarrow{3H_2} RCH_2NH_2 + R'H + H_2O.$$

$$RCONHR' \xrightarrow{3H_2} RCH_3 + R'NH_2 + H_2O.$$

(b) Hydrogenolysis of the carbon-nitrogen bond rather than of the carbonyl group to give the alcohol

$$RCONR'_2 \xrightarrow{2H_2} RCH_2OH + HNR'_2.$$

(c) Alkylation of amine by alcohol.

$$RNH_2 + \acute{R}OH \longrightarrow R\acute{R}NH + H_2O.$$

(d) Hydrolysis, alcoholysis, ammonolysis or amminolysis of the original amide by the products formed in the aforementioned reactions. Dioxan was used as solvent since it acts as a diluent for water formed in the course of hydrogenation, and contained in the catalyst, thereby inhibiting hydrolysis of the amide before hydrogenation can take place.

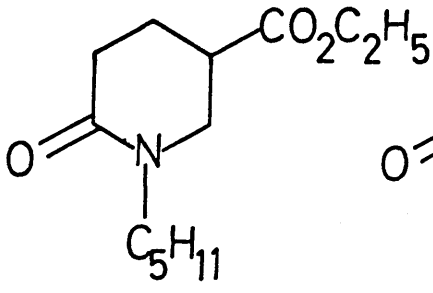
(e) Diamides from succinic,[98] glutaric[99] and adipic[99] acids gave the cyclised products having pyrrolidine, piperidine and hexahydroazepine rings respectively. Cyclisation either of the diamine, or of any one of several partially hydrogenated intermediates could conceivably lead to these products. However, the reaction does not appear to proceed via initial ring closure of diamide to imide.[99]

In hydrogenations of monocarboxylic acid amides, yields of 40-70% primary and 25-60% of the corresponding secondary amines were claimed. However, in a later publication,[100] such yields could not be duplicated under apparently the same conditions. In this case, hydrogenation of laurylamide ($nC_{11}H_{23}CONH_2$) gave dodecan-1-ol as a major product, and an amine fraction which consisted mainly of the secondary amine. In a more recent investigation of the hydrogenation of decanoic acid amide[101] over copper-chromium oxide, almost complete reduction to amine was obtained, but this consisted

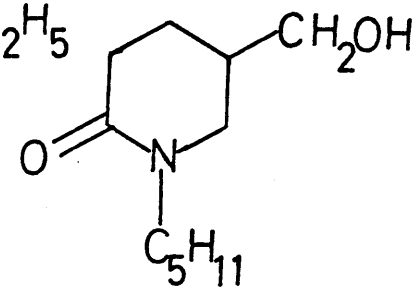
mainly of the secondary amine. Hydrogenation of amides of shorter chain length was incomplete, and hydrogenolysis to the hydrocarbon arose as a side reaction. High yields of primary amine could however be obtained from decanoic acid amide by carrying out the hydrogenation in the presence of ammonia.

Other catalysts which have been used in hydrogenation of amides are Raney nickel,[101,102] Raney cobalt[101] and the rhenium blacks from rhenium VII[94] and rhenium VI[96] oxides. Raney nickel was not much used by Adkins, who does report, however, the occurrence of a violent reaction in the course of a hydrogenation attempted with this catalyst in dioxan at 250°.[102] At 225°, at which temperature no violent reaction was observed, Raney nickel was relatively inactive for the hydrogenation of amides. Raney nickel and cobalt gave similar yields of amine in hydrogenation of amides in presence of ammonia,[101] although the cobalt catalyst was effective at temperatures 40-50° lower (230°) than nickel. Complete reduction to hydrocarbon was obtained with nickel at 330°.

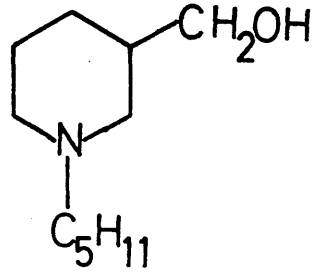
Hydrogenation of lactams proceeds with less interference from side reactions than the hydrogenation of amides. This is illustrated by the hydrogenation of 1-β-cyclohexylethylpyrrolidone-2 and 1-n-amylpyrrolidone-2 to the pyrrolidines, and of 1-β-cyclohexylethyl-4-methylpiperidone-2 to the piperidine in high yields.[99] The rate of hydrogenation of lactam carbonyl groups has been compared with the rate of hydrogenation of esters.[103] Thus, hydrogenation of 5-



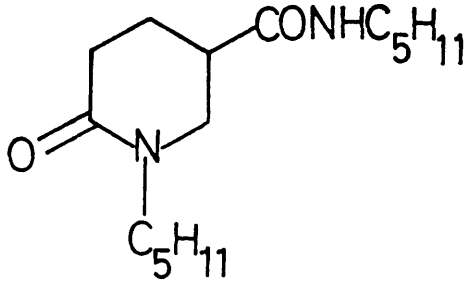
LXXIII



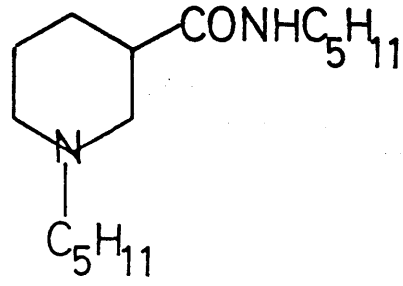
LXXIV



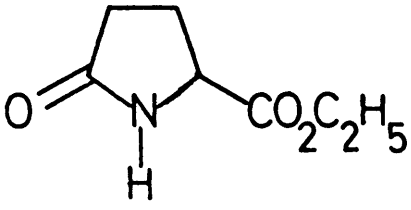
LXXV



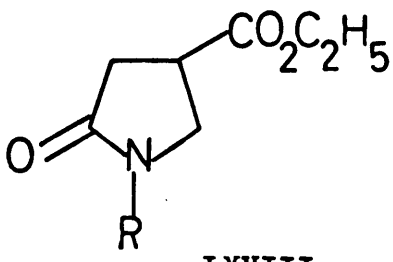
LXXVI



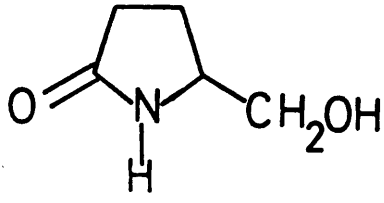
LXXVII



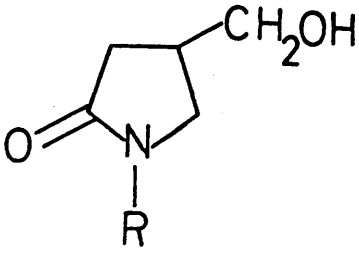
LXVII



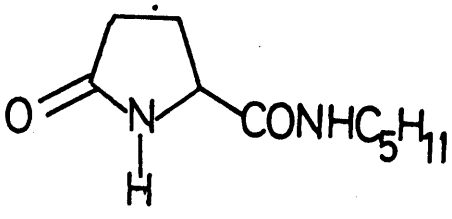
LXVIII



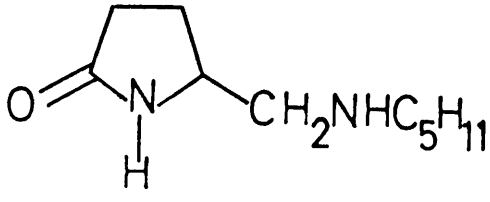
LXIX



LXX



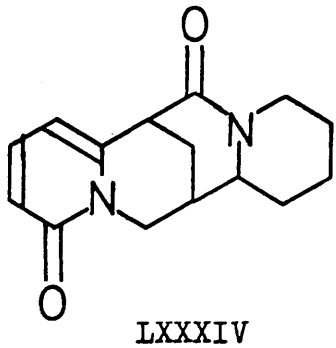
LXXI



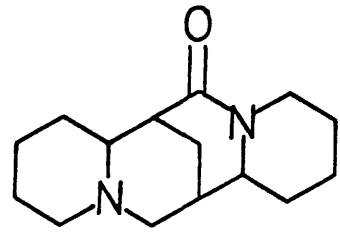
LXXII

carboethoxy-2-pyrrolidone (LXVII), or the 4-carboethoxy-2-pyrrolidones (LXVIII; R=n-amyl or β-phenethyl), gave mainly the carbinols LXIX and LXX, resulting from selective reduction of the ester groups. Further hydrogenation, at lactam carbonyl group, occurred more readily in the 4- than in the 5-carboethoxy derivative. Hydrogenation of 5-amylcarbamoyl-2-pyrrolidone (LXXI) resulted in preferential reduction of the side chain amide group, the principal product being 5-amylamino-2-pyrrolidone (LXXII). 1-n-amyl-5-carboethoxy-2-piperidone (LXXIII) gave the carbinol (LXXIV) as the main product, but this was accompanied by a significant amount of the piperidine, LXXV, even when reduction of the ester was incomplete. The main product from hydrogenation of the amide, LXXVI, was however the piperidine, LXXVII, reduction having occurred preferentially in the ring. These observations indicate that piperidones are more readily hydrogenated than pyrrolidones. This may be compared with the more ready hydrogenation of cyclohexanone than of cyclopentanone.(104)

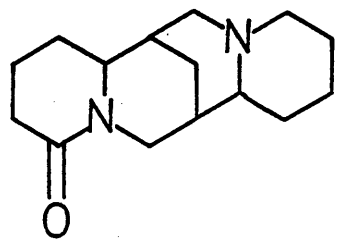
Certain lactams have been hydrogenated over platinum in dilute hydrochloric acid at r.t.p. by Galinovsky and coworkers. Thus, α-norlupinone (LXXVIII) gave the amine norlupinane (LXXIX) in practically quantitative yield.(105) Hydrogenation in acetic acid was very much slower, and still incomplete after reactivation of the catalyst, indeed, even after the addition of fresh catalyst. N-methyl and N-n-butyl-2-pyridone were similarly hydrogenated to N-methyl and



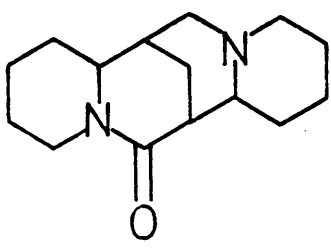
LXXXIV



LXXXV



LXXXVI



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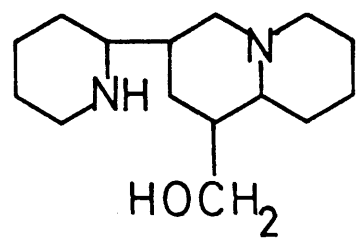

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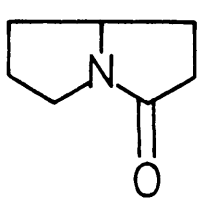

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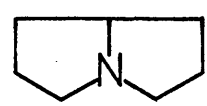
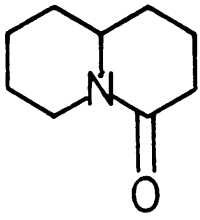


XC



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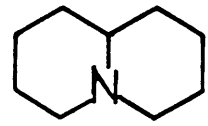

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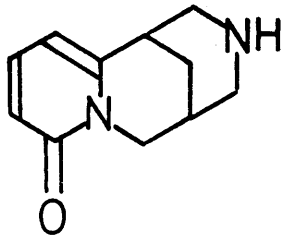
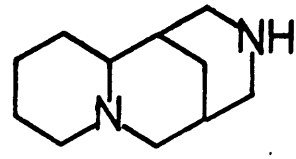
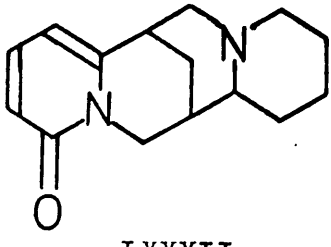


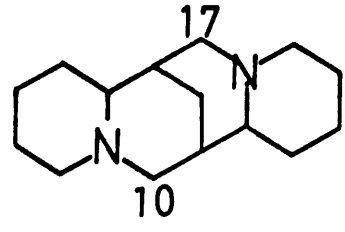
LXXX



LXXXI



LXXXII



LXXXIII

N-n-butyl piperidine.[106] N-methyl-2-piperidone was also hydrogenated, the rate being slower than with the pyridone. 2-pyrrolidone and 2-piperidone were, however, resistant to hydrogenation under these conditions. Hydrogenation of several alkaloids of the spartein group having a pyridone or piperidone ring was also accomplished under these conditions.[106] Thus cytisine (LXXX) gave tetrahydrodesoxycytisine (LXXXI), anagyrine (LXXXII) gave sparteine (LXXXIII) in quantitative yield, and oxyanagyrine (LXXXIV) gave oxysparteine (LXXXV), also in quantitative yield. In the piperidone-type series, hydrogenations occurred more slowly, but lupanine (LXXXVI) gave sparteine (LXXXIII) in quantitative yield. Aphyllidine (LXXXVII) gave sparteine as the major product, along with a minor product later characterised as the alcohol, LXXXVIII,[107] resulting from hydrogenolysis of the lactam ring. Oxysparteine (LXXXV) was however resistant to hydrogenation under these conditions. The difference in behaviour of aphyllidine and oxysparteine was ascribed to the difference in conformations of rings B and C. Indeed, examination of models of the spartein skeleton does indicate that approach to C-17 is highly hindered, whereas approach to C-10 from the β-side is relatively unhindered. The conformation of spartein has been discussed recently in the literature.[108] In a further publication,[109] hydrogenation of α-pyrrolizidone (LXXXIX) was reported to proceed very slowly under the same conditions to give the base, pyrrolizidine (XC) in low yield.

From these observations, the following conclusions may be drawn:-

(a) Hydrogenation of δ-lactams occurs more readily than that of γ-lactams, in agreement with the observations of Adkins on hydrogenation of pyrrolidone and piperidone carboxylic acid derivatives referred to above (p.44).

(b) Hydrogenation is facilitated by complete substitution of the nitrogen atom. (This effect is not confined to lactams. See, for example the more ready hydrogenation of N-substituted pyrroles than of their N-unsubstituted analogues. See ref. 5, p.107.)

The mechanism of the conversion of amides to amines has been discussed by Adkins.[99] The reaction may proceed either through hydrogenolysis of the carbon-oxygen bond,

$$RCONHR' \xrightarrow{2H_2} RCH_2NHR' + H_2O,$$

or through hydrogenolysis of the carbon-nitrogen bond, followed by alkylation of the amine with the alcohol so formed.

$$RCONHR' \xrightarrow{2H_2} RCH_2OH + R'NH_2 \longrightarrow RCH_2NHR' + H_2O.$$

In support of the intermediacy of alcohol in the formation of amine, Adkins presents the following evidence:-

(a) Both alcohols of the type RCH_2OH, and amines of the type $R'NH_2$ are obtained on hydrogenation of amides.

(b) Alcohols or glycols and amines react under the hydrogenation conditions to give yields of amines similar to those obtained directly from amides. Alcohols had been found previously to alkylate amines over nickel catalysts,[110] and by reaction of butane-1,4-diol, pentane-1,5-diol and hexane-1,6-

diol with primary amines over copper-chromium oxide, pyrrolidines, piperidines and hexahydroazepines were obtained.[99]

(c) Benzoyl piperidine was cleaved completely to toluene, piperidine and water far more rapidly than benzylpiperidine was hydrogenolysed, indicating that the primary cleavage in the former was at the carbon-nitrogen rather than at the carbon-oxygen bond.

Against the intermediacy of alcohol is the fact that ammonia did not react with glycols to give good yields of the corresponding amines. It is concluded that since carbon-nitrogen and carbon-oxygen bond hydrogenolyses take place under similar conditions, both types of reaction probably occur.

The catalytic hydrogenation of amides may be envisaged as proceeding, like the hydrogenation of esters, either through initial hydrogen addition to the carbonyl function,

$$R\text{-}CONHR' \xrightarrow{H_2} R\text{-}\underset{\displaystyle NHR'}{\overset{\displaystyle OH}{\underset{|}{\overset{|}{C}}}}H \longrightarrow RCHO + NH_2R'.$$

$$\downarrow$$

$$RCH{=}NR' + H_2O.$$

or by initial hydrogenolysis,

$$RCONHR' \xrightarrow{H_2} RCHO + R'NH_2.$$

Again, as in the case of esters, the intermediates probably are not released as such from the catalyst surface before further hydrogenation to final products takes place, so that distinction between the alternatives will be very difficult.

VI. IMIDES AND ANHYDRIDES.

On consideration of the conditions so far outlined for the hydrogenation of carbonyl compounds, the order of reactivity observed leads one to the conclusion that an important factor in determining the reactivity of a particular carbonyl compound is the susceptibility of the carbonyl carbon atom to nucleophilic attack. The intervention of a step involving nucleophilic attack in the hydrogenation of carbonyl compounds can be visualised in at least two ways.

(a) Formation of a chemisorbed intermediate by electron pair donation from catalyst to substrate giving a metal-carbon bond which is subsequently cleaved by hydrogen.

(b) Transfer of a hydride ion, or equivalent, from the catalyst to the adsorbed carbonyl function.

If imides and anhydrides have reactivities in accord with this scheme, then their position with respect to the other carbonyl compounds as to susceptibility to catalytic hydrogenation, may be summarised as follows:-

$RCOCl > RCOR > (RCO)_2O > (RCO)_2NR > RCO_2R > RCO_2H > RCONH_2$.

The order of reactivity, ester > free acid > amide > sodium salt, has been recently confirmed for hydrogenation of hexanoic acid and its derivatives over copper-barium chromite.[111] (The authors report successful hydrogenations over this catalyst at significantly lower pressures than had previously been employed.) As anhydrides are expected to be more reactive than imides, the former will be discussed first.

The literature records little work on the hydrogenation of aliphatic acid anhydrides, apart from several patents for the production of alcohols. Among the earliest references to such hydrogenations is one concerning the production of esters by hydrogenation of aliphatic anhydrides in the vapour phase over a nickel catalyst according to the method of Sabatier.[112] Aldehydes can also be prepared by such hydrogenations. The hydrogenation of acetic anhydride over palladium black has been investigated.[113] In the absence of solvent, at 40° and $3\frac{3}{4}$ atm. very slow hydrogenation took place, only 16 mole% hydrogen being absorbed in 7 hr. to give a mixture from which acetaldehyde and a little ethyl acetate was recovered. However, in presence of 2% by weight of dry hydrogen chloride, hydrogenation proceeded more readily, 93 mole% hydrogen being absorbed in 8 hr. Fractionation of the product gave largely acetaldehyde, a little ethyl acetate, and some paraldehyde. The authors believe that the promotion of reaction by HCl is due to reaction of the latter with the anhydride to give acetyl chloride, which is the species which actually undergoes hydrogenation. The hydrogenation of propionic anhydride was reported to proceed similarly, but no details were given. Lauric anhydride was hydrogenated in decalin solution, 44 mole% hydrogen being absorbed in $6\frac{1}{2}$ hr. at 120° in absence of HCl. From the resulting mixture, lauraldehyde, lauric acid, dilauryl ether, and a further product which could not be identified, were isolated. Hydrogenation in presence of HCl

led to greater hydrogen absorption (77 mole%), but the product contained much less aldehyde than before, dilauryl ether being present in much greater amount. Some of the previously obtained unidentified product was also present. More recently, the hydrogenation of acetic anhydride over palladium and platinum, and of propionic anhydride over palladium, at r.t.p., has been reported,[114] the products being analysed by gas liquid chromatography. Hydrogenation was slow and incomplete, giving mainly aldehyde and acid, but only a little alcohol over palladium, whilst over platinum, mainly alcohol and acid, but also a little acetaldehyde, were obtained.

Rather more work is recorded on cyclic anhydrides. The above-mentioned method of Sabatier (p.50) has been applied to the preparation of lactones from phthalic anhydride,[115] camphoric and succinic anhydrides,[116] and the anhydrides of Δ^2-tetrahydrophthalic,[117] $\Delta^{2,6}$-dihydrophthalic[118] and Δ^1-tetrahydrophthalic acids.[119] In the case of Δ^2-tetrahydrophthalic anhydride, the product obtained (XCI) is that in which the carbonyl group not conjugated with the double bond is reduced. Hydrogenation of cyclooctene-1,2-dicarboxylic acid anhydride, over platinum oxide in dioxan at r.t.p., has been reported to give the lactone (XCII, while hydrogenation of cycloheptene-1,2-dicarboxylic acid anhydride gave only the expected saturated anhydride.[120] As noted in this latter publication, no lactone formation was reported on hydrogenation of 3-methylcyclopentene-1,2-dicarboxylic acid anhydride

over 10% palladium on carbon, only saturated anhydride being obtained.[121]

The most recent work on the hydrogenation of cyclic anhydrides is that of McCrindle, Overton and Raphael already referred to.[1a,b] Hydrogenations were carried out in ethyl acetate or acetic acid over platinum oxide at r.t.p. Three types of product were obtained corresponding to reaction of the anhydride function with one, two or three moles of hydrogen, namely hydroxylactone ($-CO_2CHOH-$), lactone ($-CO_2CH_2-$; or corresponding hydroxy acid, $-CO_2H\ HOCH_2-$.) and methyl acid ($-CO_2H\ CH_3-$) respectively. In ethyl acetate solution, the Diels-Alder adducts XCIII and XCIV gave the hydroxylactones XCV and XCVI as the major products at completion of reaction, whereas the adducts XCVII and XCVIII gave the lactones XCIX and C (or corresponding hydroxy acids). The hydroxylactones (CI and CII) were obtained from these adducts by stopping the reaction when the appropriate volume of hydrogen had been absorbed. Cantharidin (CIII) gave mainly the lactone (CIV) and a little hydroxylactone (CV), and camphoric anhydride (CVI) gave a mixture of hydroxy acids, (CVII and CVIII) corresponding to α and β-campholides, the former being in excess. In acetic acid, the adducts XCIII and XCVII gave a mixture of lactone (CIX, XCIX) and acid (CX, CXI) in ratios of 1:1 and 5:2 respectively. Hydrogenation of the intermediate hydroxylactone XCV gave the lactone (CIX) and acid (CX) in the ratio 2:1. Hydrogenolysis to the methyl acid in addition to lactone

formation was also observed in hydrogenation of hexahydrophthalic anhydride in acetic acid, and succinic anhydride in acetic acid or ethyl acetate. Lactones did not appear to be intermediates in the formation of methyl acids since CIX and XCIX did not react further when shaken with fresh catalyst in acetic acid under hydrogen.

In this work, the configurations of the hydroxylactones obtained were not assigned. In a more recent publication, the structure CXII has been assigned to the hydroxylactone obtained from adduct XCIV, the assignment being based upon n.m.r. studies.(122)

Few publications dealing with the hydrogenation of imides appear in the literature. The earliest of these concerns the hydrogenation of phthalimide over a nickel catalyst at 200° and 200-300 atm., under which conditions the lactam, phthalimidine, was obtained in good yield.(123) Succinimide, however, could not be hydrogenated under these conditions. N-alkyl substituted imides appear to be more susceptible to hydrogenation. (c.f. lactams and pyrroles, p.47). Thus, N-amyl and N-β-phenethyl succinimide have been hydrogenated to the pyrrolidones over Raney nickel in dioxan at 200-220° and 200-400 atm.,(98) and to the pyrrolidines over copper-chromium oxide in dioxan at 250° and 200-300 atm.(99) N-amyl and N-β-phenethylphthalimide were hydrogenated to the octahydroisoindolines. Only the phthalimide benzene ring was saturated in the latter example, copper-chromium oxide being

generally inactive in hydrogenation of unactivated benzene rings. Some alkyl cleavage was observed in these two reactions, particularly with the N-β-phenethyl derivative, octahydroisoindoline being isolated as a by-product. A number of N-alkyl glutarimides have also been hydrogenated under the above conditions, giving the piperidones over Raney nickel, and piperidines over copper-chromium oxide,[98] some cleavage of the N-alkyl groups being observed over the latter catalyst. This side reaction was used in the preparation of hexahydroazepine from the N-benzyl derivative. Notably, the N-unsubstituted derivatives, β-methyl and β-phenyl glutarimide could be hydrogenated over copper-chromium oxide to the piperidines, although yields were poor, indicating that hydrogenation of six-membered ring imides occurs more readily than that of their five-membered ring analogues. A similar finding has already been noted in the hydrogenation of lactams (p.47) and lactones (p.37).

Hydrogenation of phthalimide over a number of copper-chromium oxide catalysts has been investigated more recently as a means of preparing octahydroisoindoline.[124] The product in all cases was, however, phthalimidine. The authors do not seem to have taken account of the facilitation of hydrogenation by N-substitution.

CATALYTIC HYDROGENATION OF CYCLIC IMIDES AND ANHYDRIDES

RESULTS AND DISCUSSION

As can be seen from the introduction, the catalytic hydrogenation of imides has been attempted only under conditions of elevated temperature and pressure. It has been noted that substitution of the imide nitrogen atom with an alkyl group appears to facilitate hydrogenation of such compounds, this effect possibly arising from a readier desorption of products from the catalyst surface. In addition, an apparent correlation between the susceptibility of a carbonyl function to (a) hydrogenation and (b) nucleophilic attack at the carbonyl carbon atom has been emphasised. This latter consideration suggested that the ease of hydrogenation of imides could be further enhanced by substitution of the imide nitrogen atom with an electron-withdrawing group, which would effectively reduce the delocalisation of the nitrogen lone-pair electrons towards the imide carbonyl carbon atoms. In order to test this suggestion, the hydrogenation, at room temperature and atmospheric pressure, of phthalimide, succinimide, and a series of N-substituted derivatives has been studied. The majority of these hydrogenations were carried out in ethyl acetate solution over either Adams' platinum oxide, or 10% palladium on carbon catalysts. Two different batches of platinum oxide, one supplied by Engelhard Industries Ltd, and the other by Johnson Matthey & Co. Ltd, were used and found to differ considerably in their activity. The former cata-

lyst is referred to in the following discussion simply as platinum oxide, and the latter as Johnson Matthey platinum oxide.

The Hydrogenation of Phthalimide, N-methyl Phthalimide and Succinimide.

The earliest reference to the hydrogenation of phthalimide under mild conditions is contained in work by Willstätter and Jaquet,[131] who obtained hexahydrophthalimide, m.p. 132°, as the sole product of hydrogenation in acetic acid over platinum black. The lack of reaction in the imide ring was contrasted with the results obtained by the same authors on hydrogenation of phthalic anhydride, where reaction in the anhydride ring occurred more rapidly than saturation of the benzene ring, the products in this case being hexahydrophthalide, hexahydro-o-toluic acid, and cis-hexahydrophthalic acid, the last resulting from hydrolysis of anhydride by water generated in formation of the first two products. In the present work, the hydrogenation of phthalimide over platinum oxide in ethyl acetate was found to be complete in 10-12 hr, no further uptake of hydrogen occurring on prolonging the reaction time to 24 hr. Hexahydrophthalimide (m.p. 135-136°) was obtained as the sole product of hydrogenation, the absence of by-products being confirmed by thin layer chromatography (t.l.c.). Succinimide, as expected, was not affected under these conditions, and was recovered quantitatively. That simple alkyl substitution of the imide

nitrogen atom was not sufficient to promote hydrogenation was shown by the formation, in almost quantitative yield, of the hexahydro derivative from N-methyl phthalimide. T.l.c. of this product did however indicate the presence of two very minor components of greater polarity than the principal product, but as these constituted only a minute percentage of the total, and since their proportion in the mixture could not be increased by prolonging the time of hydrogenation, even after the addition of fresh catalyst, they were not examined further. It is likely that these minor products were formed by a slow reduction in the imide ring which has to occur before saturation of the benzene ring. Such promotion of hydrogenation by a neighbouring benzene ring is well known, an example being the observation of Willstätter (131) in the work referred to above, that some hydrogenolysis to hexahydro-o-toluic acid occurs in the hydrogenation of phthalide, but that hexahydrophthalide is not hydrogenolysed under the same conditions.

The Hydrogenation of N-acyl Imides.

(1) Variation of the electronic nature of the acyl substituent.

The resistance of five-membered cyclic imides and their N-alkyl derivatives to hydrogenation under the chosen conditions, led us to investigate the hydrogenation of a series of N-acyl phthalimides and succinimides, the acyl substituent serving as an electron-withdrawing species. N-acetyl phthal-

imide (CXIII; R=CH_3) prepared by acetylation of phthalimide with acetic anhydride, was hydrogenated in ethyl acetate solution over platinum oxide. Hydrogenation was virtually complete in about 8 hr, after which time the equivalent of 4-4½ moles of hydrogen had been taken up, little or no further absorption of hydrogen occurring when the reaction was left for an additional 24 hr. On removal of the catalyst and solvent, the product was obtained as a viscous, cloudy oil which solidified on standing. T.l.c. indicated the presence of one major and a second less abundant component, and two very minor, polar products. The i.r. spectrum of the mixture showed that saturation of the benzene ring had occurred, as expected, but a broad-based peak at 3370cm.$^{-1}$ (hydroxyl) and a strong doublet in the carbonyl region at 1730 and 1680cm.$^{-1}$ suggested that, in addition, the desired reduction in the imide ring had taken place. The two main products were separated by column chromatography on silica gel, but only a very small quantity of a mixture containing the two minor products was obtained. These minor products were not examined further, but their identity is discussed later in the light of other results (p.103). The less abundant of the two main products could be crystallised from ethyl acetate (m.p. 136°) and was identified as hexahydrophthalimide by direct comparison (i.r. and mixed m.p.) with an authentic sample. The fate of the acetyl group cleaved in the course of formation of hexahydrophthalimide was not

determined by isolation of the resulting product, but this last was presumably ethanol. (The alcohol was isolated from cleavage of other acyl groups. See p.74)

The major product crystallised from light petroleum (b.p. 60-80°) as clumps of white needles (m.p. 81°) which were converted to clear prisms on standing under solvent. Both forms, however, gave identical physical data. The i.r. spectrum of this compound accords with its formulation as the hydroxylactam (CXIV; R=CH_3) hexahydro-N-acetylhydroxyphthalimidine, showing strong maxima at 3450, 1748 and 1693cm.$^{-1}$ (nujol), and no aromatic absorption, a product which is the analogue of the hydroxylactones obtained by McCrindle, Overton and Raphael[1a,b] by hydrogenation of cyclic anhydrides under similar conditions. Further support for this structural assignment came from the n.m.r. spectrum (shown in fig.8) which showed the following features:-

7.45τ(s., 3H.) —— -CH_3 of N-acetyl group.

6.92 (m., 1H.) —— proton α to lactam carbonyl group.

6.01 (d., J=3c/s., 1H; lost on D_2O equil.) —— CHO<u>H</u>.

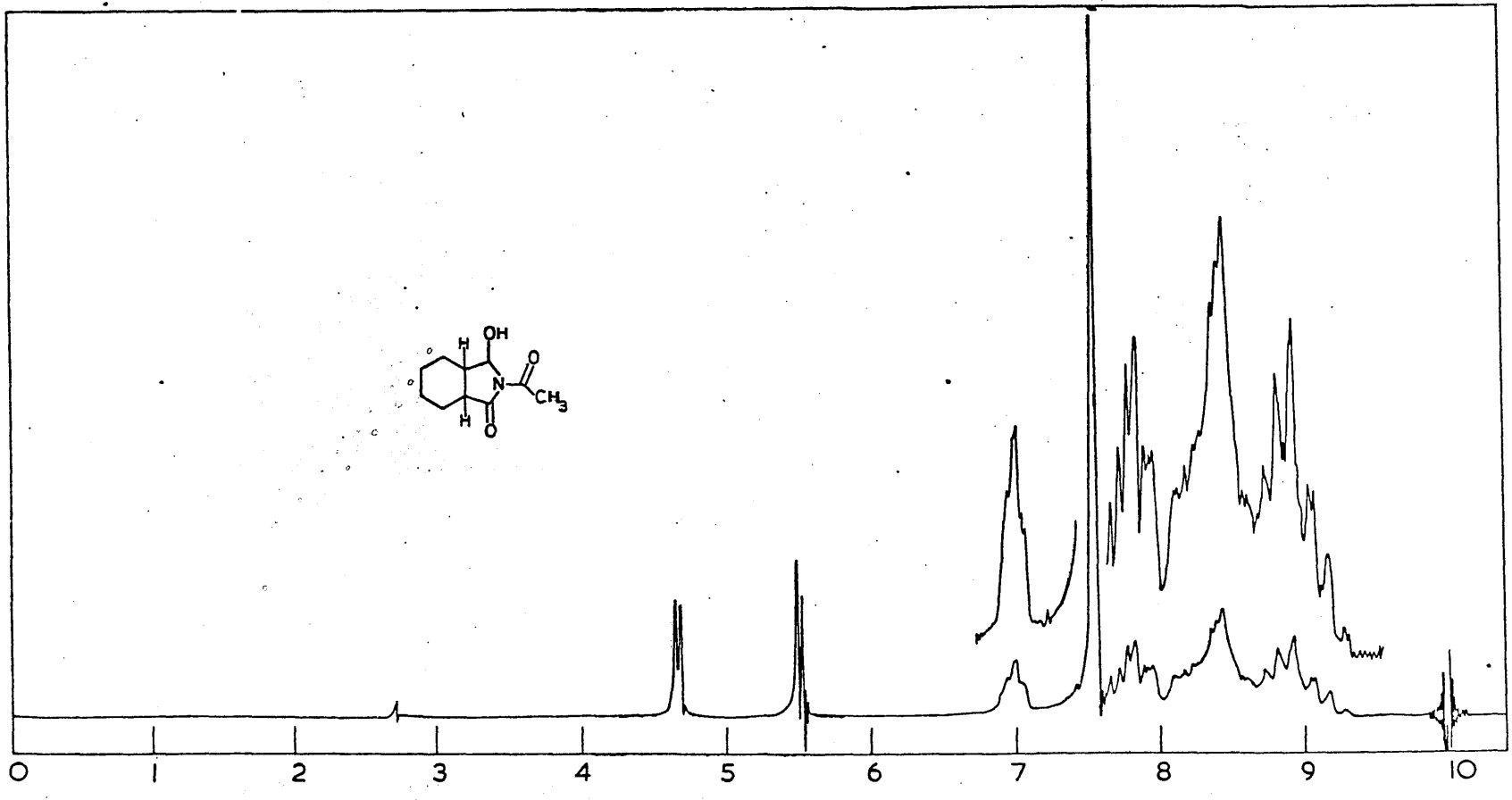
7.5-9.1 (m., 9H.) —— cyclohexane ring protons.

This compound (CXIV; R=CH_3) underwent ready acetylation with acetic anhydride-pyridine to give a product m.p. 106° on crystallisation from light petroleum (b.p. 60-80°). That this was the expected acetate (CXV; R=CH_3) followed from its analysis, i.r. spectrum (no absorption in the hydroxyl region, and overlapping peaks, centred at 1722cm.$^{-1}$, in the carbonyl

region) and n.m.r. spectrum, in which the O-acetate methyl group appeared as a singlet at 7.93 , and the proton on the carbon atom carrying the acetate group as a singlet at 3.60 . In the n.m.r. spectra of CXIV and CXV, the absence of observable coupling between the proton on the carbon atom bearing the hydroxyl or acetoxyl substituent (C_3) and the proton on the neighbouring ring junction carbon atom (C_9) indicated a dihedral angle between them of about 90°.[132] The examination of models suggested that this requirement is best met if the hydroxyl or acetate function is cis with respect to the neighbouring ring junction proton, as indicated in formulae CXIV and CXV. The stereochemistry of the ring junction was assumed to be cis by analogy with the formation of cis-hexahydrophthalimide in the hydrogenation of phthalimide. This assumption is supported by further investigations (p.77), and also by the fact that the dihedral angle of approximately 90° referred to above could not be accommodated in a trans-fused system. Two conformations (CXIVa,b and CXVa,b) can be envisaged for these products, assuming the cyclohexane ring adopts a distorted chair conformation, by analogy with cis-1-hydrindanone.[133] The energy difference between the two conformers would be expected to be small, the suggestion having been made that the conformation of hydrindanone corresponding to CXIVa (CXVa) is destabilised relative to that corresponding to CXIVb (CXVb) by a 2-alkyl ketone effect,[133] but CXIVb (CXVb) appears from models to display a non-

FIGURE 8

100 Mc/s. n.m.r. spectrum



bonded interaction between the C_3 hydrogen and the axial proton at C_5 in the cyclohexane ring somewhat greater than any such interaction in CXIVa (CXVa). The requirement of a dihedral angle of about 90° is however satisfied only in the conformation CXIVa (CXVa). There are two further indications that this is the conformation adopted:-

(a) the band shape and width ($W^{\frac{1}{2}}$ = 15cs) of the signal in the n.m.r. spectrum due to the C_8 ring junction proton (see fig. 8) which suggests the absence of axial-axial coupling, and therefore that this proton is equatorial;

(b) the presence of absorption, in the n.m.r. spectra of CXIV and CXV, arising from two protons in the region 7.5-8.0τ, one of these probably being H_9, a methine proton which in addition will be deshielded by the inductive effect of the electronegative substituents at C_3. The second proton of this pair could be the C_7-equatorial proton, which lies directly in the plane of the carbonyl group in CXIVa (CXVa), and hence in the deshielding zone of that function.[134]

Since the initial suggestion that the catalytic hydrogenation of imide carbonyl groups might be facilitated by increasing the susceptibility of the carbonyl carbon atoms to nucleophilic attack appears to be borne out by the results obtained with N-acetyl phthalimide, the next step was to test an acyl group with a weaker inductive effect. For this purpose, the compound N-carboethoxy phthalimide (CXIII; R=OEt) was prepared by reaction of ethyl chloroformate with potassium

phthalimide in refluxing benzene. In addition to being more weakly electron-withdrawing than the acetyl group, the carboethoxy group should not be susceptible to attack in the hydrogenation reaction, so that reduction, if any, might be expected to be confined to a carbonyl group in the imide ring. Hydrogenation of the imide (CXIII; R=OEt) under the conditions used for N-acetyl phthalimide resulted in the absorption of the equivalent of four moles of hydrogen per mole of CXIII (R=OEt) in about 12 hr, the product being obtained as a viscous, cloudy oil on removal of solvent and catalyst. T.l.c. indicated the presence of essentially a single component with only a trace of a polar by-product. The i.r. spectrum of the oil showed a strong, broad peak in the hydroxyl region indicating that the desired hydrogenation of an imide carbonyl group had again taken place. The major product, when freed from traces of the minor by chromatography on silica gel, was a clear, colourless oil which could not be persuaded to solidify. An attempt was made to purify this material by distillation at $85^{\circ}/0.05$ m.m. on the sublimation block, but t.l.c. of the resulting oil indicated the presence of small quantities of decomposition products in addition to the starting material, so the product obtained by chromatography was submitted for analysis. Although the figures obtained for percentage of hydrogen were in agreement with the value for the expected product, hexahydro-N-carboethoxyhydroxyphthalimidine (CXIV; R=OEt), the figures obtained for carbon were consistently

about 1% low. The structure (CXIV; R=OEt) for this product is however supported by i.r. and n.m.r. spectroscopic evidence, and by its conversion, with refluxing acetic anhydride-pyridine, into the acetate (CXV; R=OEt), which readily crystallised (m.p. 115° from light petroleum, b.p. 60-80°), and for which satisfactory analytical figures were obtained. Thus, the i.r. spectrum of CXIV(R=OEt) showed strong maxima at 3490 (hydroxyl group), 2950 and 2870 (aliphatic CH str.), and 1785 and 1725cm.$^{-1}$ (broad, overlapping peaks; lactam and carboethoxy carbonyl groups). The n.m.r. spectrum showed the following features:-

7.5-9.1τ(m., 9H.) —— cyclohexane protons.

8.65 (t., J=7c/s., 3H.) —— $-CH_3$ of carboethoxy group.

7.01 (m., 1H.) —— proton to lactam carbonyl group.

5.71 (quartet, J=7c/s., 2H.) —— $-CH_2-$ of carboethoxy group.

5.09 (d., J=3c/s., 1H; lost on D_2O equil.) —— CHO<u>H</u>.

4.72 (d., J=3c/s., 1H; s. on D_2O equil.) —— C<u>H</u>OH.

The derived acetate (CXV; R=OEt) lacked hydroxyl absorption in the i.r. and showed two sharp, cleanly separated peaks in the carbonyl region at 1788 and 1736cm.$^{-1}$. In the n.m.r. spectrum, the acetate methyl group appeared as a singlet at 7.93τ, and the low field signal for the proton on the carbon atom carrying the acetate group also appeared as a singlet, at 3.60τ. The lack of observable coupling of the low field proton in CXIV and CXV(R=OEt) with the neighbouring ring junction proton indicated that the stereochemistry of these

compounds is similar to that of the products (CXIV and CXV; R=CH_3) from N-acetyl phthalimide, i.e. the hydroxyl or acetate function is cis with respect to the ring junction protons.

Column chromatography of the product from the hydrogenation of N-carboethoxy phthalimide yielded, in addition to the major component, a small quantity of the minor component, the amount obtained suggesting that the latter constituted only about 3% of the total reaction product. This compound was not obtained in a high state of purity, but from the i.r. and n.m.r. spectral data obtained on the material isolated by chromatography, the structure (CXVI; R=OEt), in which opening of the imide ring occurred, is suggested for this product. It was also found that this material reacted when the total hydrogenation product from N-carboethoxy phthalimide was acetylated with acetic anhydride-pyridine, to give apparently two products for which the structures CXVII and CXVIII are suggested. This conclusion is however based solely on the n.m.r. spectrum of a crude mixture of these two products, obtained by column chromatography, so that these assignments can only be tentative. (For spectral details see the experimental section.) Some support for these conclusions was obtained in subsequent experiments. (see p.103) That the minor component was not formed by further hydrogenation of the major was shown by the fact that no further absorption of hydrogen was observed on shaking the latter with fresh cata-

lyst under hydrogen for a further 24 hr. T.l.c. confirmed the presence of starting material only.

Since the main product from the hydrogenation of N-carboethoxy phthalimide was an oil which did not give satisfactory analyses, hydrogenation of the N-carbomethoxy derivative (CXIII; R=OMe) was carried out, in the expectation that the corresponding product, hexahydro-N-carbomethoxyhydroxyphthalimidine (CXIV; R=OMe) should be amenable to purification by crystallisation. The hydrogenation of CXIII(R=OMe) proceeded as expected, with the uptake of four moles of hydrogen to give a mixture containing one major and two very minor products, one more polar and one less polar than the major product, which was indeed readily purified by crystallisation from ethyl acetate, and had m.p. 105°. The analysis, i.r. and n.m.r. spectra of this material were in agreement with expectation for the product (CXIV; R=OMe). The n.m.r. spectrum was run at 100Mc/s, and showed very clearly absorption due to two protons in the region 7.5-8.0τ as has been noted for the N-acetyl analogue. (p.61)

As an N-carboalkoxy substituent has been shown to be sufficiently electron-withdrawing to promote hydrogenation at imide carbonyl functions, it was of interest to ascertain whether hydrogenation would still take place if this property of the imide nitrogen substituent were further reduced. The compound envisaged to be ideally suited to test this was N-dimethylcarbamoyl phthalimide (CXIII; R=$N(CH_3)_2$), which does

not appear to be recorded in the literature. This compound (m.p. 158° from ethyl acetate) was prepared by reaction of equimolar quantities of phthaloyl chloride and asymmetric dimethylurea in pyridine. Its structure was confirmed by analysis, i.r. which showed a weak doublet at 1794 and 1767cm.$^{-1}$ and a strong doublet at 1736 and 1675cm.$^{-1}$ in the carbonyl region, and n.m.r., which showed the following features:-

6.95τ(s., 3H.) —— N-methyl group.

6.82 (s., 3H.) —— N-methyl group.

2.08 (sym. m. of AA'BB' system, 4H.) —— aromatic protons.

Hydrogenation of CXIII(R=N$(CH_3)_2$) was noticeably slower than that of the N-acetyl and N-carboalkoxy analogues. After 24 hr, in which time rather less than four moles of hydrogen were taken up, t.l.c. of the reaction mixture indicated the presence of two principal products, and only a trace of one (or possibly two) polar by-product. The main products were separated by column chromatography over silica gel, the less abundant (and less polar) being purified by crystallisation from benzene/light petroleum (b.p. 60-80°), whence it had m.p. 114-114.5°. That this was simply the product of saturation of the benzene ring of CXIII(R=N$(CH_3)_2$), hexahydro-N-dimethylcarbamoyl phthalimide (CXIX; R=N$(CH_3)_2$) was indicated by analysis, i.r., which showed a doublet in the carbonyl region at 1725 and 1701cm.$^{-1}$, with some weaker absorption at higher frequencies, and the absence of aromatic

bands, and n.m.r., which showed the following peaks:-

8.48τ(m., 4H.) —— axial protons of cyclohexane ring.

8.15 (m., 4H.) —— equatorial protons of cyclohexane ring.

7.07 (s., 3H.) —— N-methyl group.

6.90 (s., 3H.) —— N-methyl group.

The last two peaks were superimposed on absorption arising from a further two protons, those α to the imide carbonyl groups.

The major product was obtained as a viscous oil which, after a considerable time, was finally induced to solidify and a little of the solid was then used to promote crystallisation from light petroleum (b.p. 60-80°), from which solvent the purified material had m.p. 95-97°. The i.r. spectrum of this product showed a peak in the hydroxyl region at 3545cm.$^{-1}$, and a doublet in the carbonyl region at 1728 and 1675cm.$^{-1}$, indicating that once again hydrogenation had occurred in the imide ring, and that the product was hexahydro-N-dimethylcarbamoylhydroxyphthalimidine (CXIV; R=N$(CH_3)_2$). This conclusion was supported by analysis, and the n.m.r. spectrum, which showed the following features:-

7.5-9.2τ(m., 9H.) —— cyclohexane methylene protons.

7.0 (s., 6H.) —— methyl groups of -N$(CH_3)_2$.

This latter peak was superimposed on absorption due to the single proton α to the lactam carbonyl group.

5.21 (s., 1H; lost on D_2O equil.) —— CHO<u>H</u>.

4.84 (s., 1H.) —— C<u>H</u>OH.

The n.m.r. data indicate the same configuration for the hy-

droxyl group in CXIV($R=N(CH_3)_2$) as has been assigned to its N-acetyl and N-carboalkoxy analogues.

From the results thus far obtained on the hydrogenation of N-acyl phthalimides, three points of interest emerge.

(1) The relative effectiveness of acyl substituents in enhancing the rate of imide carbonyl group hydrogenation, as judged qualitatively from the times required to hydrogenate the N-acyl phthalimides, is in the order

acetyl > carboalkoxy > dimethylcarbamoyl,

although the rate difference for the first two substituents was not nearly as marked as that between the last two. Two factors may account for this observation:-

(a) A stage in the course of hydrogenation which involves nucleophilic attack will be accelerated to the greatest extent by the most powerful electron-withdrawing group, i.e. the acetyl group.

(b) The rate of hydrogenation will depend upon the relative strength of adsorption of the starting material, intermediates and product on the catalyst surface. The dimethylcarbamoyl group would be expected to be the most strongly adsorbed of the series of acyl groups employed, so that such a substituent should most effectively retard the rate of hydrogenation, both by competition with other groups in the substrate, and with hydrogen, for catalyst sites, and by retarding the rate of desorption of products.

(2) There is competition between hydrogenation in the imide

ring and cleavage of the acetyl group in the case of N-acetyl phthalimide, where the susceptibility to nucleophilic attack should be of a similar order for all three possible sites. The quantities of products isolated indicated that hydrogenation in the imide ring is a somewhat more favoured reaction, even allowing for the statistical factor of 2:1 in favour of reaction at this site, so that it was of interest to attempt to estimate how much difference a neighbouring benzene ring made to the ease of hydrogenation of the carbonyl group, and also to determine whether other acyl groups with different steric requirements would compete more or less favourably as the site of reaction. It is well known that palladium catalysts are effective for the hydrogenation of aromatic, but not of aliphatic ketones, but other catalysts appear to be much less selective, and in some cases, are apparently even less active in the hydrogenation of aromatic than of aliphatic ketones.(7)

(3) The stereochemistry of the hexahydro-N-acylhydroxyphthalimidines (CXIV) obtained requires explanation. Two intermediates could be involved in formation of these products.

(a) Reduction at an imide carbonyl group, to give the N-acyl hydroxyphthalimidines (CXX), might occur prior to saturation of the benzene ring. The latter reaction would then have to involve specific addition of hydrogen to that side of the benzene ring on which the hydroxyl group lay, to account for the stereochemistry of the products.

(b) Initial saturation of the benzene ring may occur to give the hexahydro-N-acyl phthalimides (CXIX). It would then be required that the subsequent step of carbonyl reduction should be stereospecific. If this were a simple addition of hydrogen across the less hindered side of the carbonyl group, then the main product would be expected to be that in which the resulting hydroxyl group is cis to the cyclohexane ring (CXXI), by analogy with the formation of cis-cis-hydrindan-1-ol (XII) as the main product of hydrogenation of cis-hydrindan-1-one. The products obtained in all cases, however, have the opposite stereochemistry from that predicted by such a route, none of the isomer (CXXI) being detected.

The stereochemistry suggested for the hexahydro-N-acylhydroxyphthalimidines is in line with that deduced by Brown, Sternhell and Warrener[122] for the lactols (XCIV and CI) obtained by hydrogenation of the Diels-Alder adducts (XCIV and XCVII respectively),[1a,b] i.e. in both cases, the hydroxyl group lies on the less hindered side of the molecule, cis to the neighbouring ring junction hydrogen. In the n.m.r. spectra of XCIV and XCVII the low field, lactol protons are reported to resonate at 4.37 and 4.26τ respectively, and further, no coupling was observed in either case between the lactol proton and the neighbouring ring junction proton, from which it was deduced that the dihedral angle between the planes described by these protons and the two intervening carbon atoms was about 90°, a finding entirely analogous to

that in the present work.

At this point, it appeared desirable to compare the behaviour of derivatives of the succinimide series with those in the phthalimide series. Only a single example of the catalytic hydrogenation of an N-acyl succinimide under mild conditions could be found in the literature. Hydrogenation of N-stearoyl succinimide in ether over 10% palladium on barium sulphate took place at room temperature, reaction being complete within 20 hr,[135] after which time, 93% of the theoretical quantity of succinimide was recovered. The products arising from the stearoyl substituent were, in order of the amounts obtained, stearaldehyde, octadecanol, dioctadecyl ether, and a small quantity of hydrocarbon, presumed to be octadecane. This result is in direct contrast with that obtained with N-acetyl phthalimide, where hydrogenation occurred preferentially in the imide ring. This difference between the two series was however confirmed in the present work by the results obtained with N-acetyl succinimide. Hydrogenation of this compound in ethyl acetate over platinum oxide proceeded with the uptake of two moles of hydrogen to give a mixture from which succinimide was recovered as the major product. T.l.c. indicated the presence of a small quantity of a product less polar than succinimide, and at least three more polar components, two of which were however present only in very minor amount. Column chromatography of the material remaining after crystallisation of most of the succinimide gave fractions

in which the less polar component, and the principal polar product were concentrated. These compounds were not present in sufficient quantity to permit purification, but n.m.r. spectra were run on the crude fractions obtained by chromatography. The spectra clearly showed that these by-products must have arisen from hydrogenation in the imide ring. Thus, the less polar fraction showed absorption at 4.10τ(double doublet; J_1=5.6c/s., J_2= 2.8c/s.), 7.48τ(singlet;-CH_3 of acetyl group) and 7-8τ(multiplet in which absorptions due to individual protons, or groups of protons, could not be distinguished), indicating the presence of the hydroxylactam (CXXII). This spectrum also showed absorption due to succinimide (s. at 7.25τ), and a weak triplet at 5.63τ(J=7c/s.) which may arise from the -$C\underline{H}_2O$- protons of butyrolactone. The polar fraction showed a triplet at 5.61τ(J=7c/s.) and a singlet at 7.98τ indicating the $CH_3CO_2CH_2CH_2$-system, a triplet at 6.28τ(J=6c/s.) indicating the $HOCH_2CH_2$-system, a singlet at 7.64τ(-CH_3 of N-acetyl group?), a very broad band at 4τ (amide NH_2?), a further broad band at 0.25τ(imide NH?), and further absorption between 7.1 and 8.2τ in which the signals due to individual protons could not be distinguished. This suggested that the polar fraction in fact contained two principal products, probably $AcOCH_2CH_2CH_2CONH_2$ and $HOCH_2CH_2CH_2CONH$-$COCH_3$.

The feasability of hydrogenation of N-acyl succinimides under the chosen conditions having now been demonstrated, an

attempt was made to promote hydrogenation in the succinimide ring by substitution of the imide nitrogen with an acyl group which would not itself be susceptible to reduction. Such a group, as has been found for phthalimide, is the carboalkoxy group. Thus, N-carboethoxy succinimide (CXXIII; R=OEt), prepared by reaction of ethyl chloroformate with potassium succinimide in refluxing benzene, on hydrogenation in ethyl acetate solution over platinum oxide absorbed two moles of hydrogen. T.l.c. of the resulting product indicated the presence of practically a single component with only a trace of a by-product of slightly lower polarity. Crystallisation from ethyl acetate/light petroleum (b.p. 60-80°) gave a product m.p. 71-72° which showed absorption in the i.r. at 3275, 3205, 1750 and 1690 (v.w.) $cm.^{-1}$, indicating that it was the desired product of hydrogenation in the imide ring, i.e. $HO(CH_2)_3CO$-$NHCO_2Et$. This was supported by the n.m.r. spectrum which showed the following features:-

8.70τ(t., J=7.2c/s.,3H.) —— $-CH_3$ of carboethoxy group.

8.08 (quintuplet, J=6.6c/s.,2H.) —— central-CH_2- of aliphatic chain.

7.17 (t., J=6.6c/s.,2H.) —— $-CH_2-$ α to carbonyl group, the last superimposed on absorption at 7.05 which was lost on D_2O equil., and thus arose from a hydroxyl proton.

6.29 (t., J=6.6c/s.,2H; base of peaks broad; sharpened on D_2O equil.) —— $-C\underline{H}_2OH$

5.77 (quartet, J=7.2c/s.,2H.) —— $-CH_2-$of carboethoxy group.

1.48 (broad s., 1H; lost on D_2O equil.) —— imide proton.

Comparison of the results obtained on hydrogenation of N-acetyl phthalimide and N-acetyl succinimide shows that reduction in the imide ring is more favoured in the phthalimide series than in the succinimide series. One factor contributing to this difference may be a preference for attack on a carbonyl function next to a benzene ring, as has been already discussed (p.69). This would imply that in the case of N-acetyl phthalimide, carbonyl reduction occurs more rapidly than saturation of the benzene ring. In order to obtain some idea of the ability of a benzene ring to determine the site of hydrogen attack, the hydrogenation of N-benzoyl (CXIII; R=Ph) and N-hexahydrobenzoyl phthalimide (CXIII; R=cyclohexyl) and N-benzoyl succinimide (CXXIII; R=Ph) was examined. It was expected that these derivatives would also provide the answer to the question as to the fate of the N-acyl groups on cleavage. It has been assumed that ethanol results from cleavage of the acetyl group of N-acetyl phthalimide, and, from the volume of hydrogen absorbed, this is probably also the product from N-acetyl succinimide. The phthalimide derivatives gave three principal products on hydrogenation, hexahydro-N-hexahydrobenzoylhydroxyphthalimidine (CXIV; R=cyclohexyl), hexahydrophthalimide and cyclohexylcarbinol. The first (CXIV; R=cyclohexyl) had m.p. 118-120° on crystallisation from light petroleum, and its structure was indicated by its i.r. spectrum, which showed strong absorption at 3480cm.$^{-1}$, due to the hydroxyl

group, and in the carbonyl region at 1746 and 1678cm.$^{-1}$, and n.m.r. spectrum, which showed the following features:-

7.5-9.1τ(m.,19H.) —— cyclohexane protons.

6.97 (m.,1H.) —— proton α to lactam carbonyl group.

6.50 (m.,1H.) —— proton α to carbonyl group of hexahydrobenzoyl substituent.

6.05 (d., J=3c/s.,1H; lost on D_2O equil.) —— CHO<u>H</u>.

4.60 (d., J=3c/s.,1H; s. on D_2O equil.) —— C<u>H</u>OH.

The cyclohexylcarbinol was characterised as its α-naphthylurethane, m.p. 109-110°, thus establishing that an alcohol does indeed result from cleavage of the acyl moiety of the N-acyl imides. The recovery of a somewhat greater proportion of hexahydrophthalimide from the hydrogenation of N-benzoyl phthalimide than from the hydrogenation of the N-hexahydrobenzoyl derivative did indicate some preference for reaction at a carbonyl group next to a benzene ring over the platinum catalyst, but the effect seems to be minimal. As might be anticipated from these observations, the principal products obtained on hydrogenation of N-benzoyl succinimide were succinimide and cyclohexylcarbinol. However, when the solid residue remaining after extraction of the cyclohexylcarbinol with cold light petroleum (b.p. 40-60°) was crystallised from ethyl acetate, a few crystals of a product other than succinimide were obtained, and found to be cyclohexanecarboxylic acid amide, which must have resulted from hydrogenation in the succinimide ring. This is a further indication that any ten-

dency for hydrogenation to occur preferentially at a carbonyl group with a neighbouring benzene ring is very small.

(2) Intermediate products in the hydrogenation of N-acyl phthalimides.

As has already been noted (p.69), hydrogenation of the N-acyl phthalimides to hexahydro-N-acylhydroxyphthalimidines (CXIV) might conceivably proceed through either the N-acylhydroxyphthalimidines (CXX) or the hexahydro-N-acyl phthalimides (CXIX) depending on whether hydrogenation at the carbonyl group preceded or followed saturation of the benzene ring. To allow consideration of possible mechanisms for the hydrogenation of the carbonyl group, it was necessary to determine which, if any, of these intermediates were involved. Two approaches to the solution of this problem were adopted;

(a) partial hydrogenation of the N-acyl phthalimides and attempted isolation of the intermediates, and

(b) synthesis and hydrogenation of the possible intermediates.

The substituted phthalimides examined were the N-acetyl, N-carboethoxy and N-dimethylcarbamoyl derivatives, and they are discussed below in that order.

N-acetyl phthalimide.

When hydrogenation of N-acetyl phthalimide was interrupted after about three moles of hydrogen had been absorbed, and the resulting mixture subjected to fractional crystallisation, hexahydro-N-acetylhydroxyphthalimidine (CXIV; R=CH_3), hexahydrophthalimide, and a third compound, m.p. 162° from ethyl

acetate, were obtained. The last proved to be N-acetylhydroxyphthalimidine (CXX; R=CH_3), but the other possible product, hexahydro-N-acetyl phthalimide (CXIX; R=CH_3) was not isolated, and could not be detected on t.l.c. of the reaction mixture. This result suggested that the catalytic hydrogenation of N-acetyl phthalimide to CXIV(R=CH_3) proceeded largely, or entirely through initial reduction of the imide carbonyl group, therefore, it was of interest to investigate the hydrogenation of the hexahydro derivative to determine whether or not the resulting hexahydrohydroxyphthalimidine would have the same stereochemistry as CXIV(R=CH_3). Hexahydro-N-acetyl phthalimide was prepared by refluxing hexahydrophthalimide in acetic anhydride, being obtained as long, white needles, m.p. 69°, on crystallisation from ethyl acetate/light petroleum (b.p. 60-80°). Hydrogenation of this material, in ethyl acetate over platinum oxide was complete after absorption of rather more than one mole of hydrogen, and t.l.c. of the resulting mixture indicated the presence of two principal components with only a trace of polar by-products. These two products, on separation and comparison with authentic samples, proved to be hexahydrophthalimide and hexahydro-N-acetylhydroxyphthalimidine (CXIV; R=CH_3), i.e. the latter was identical with the product obtained directly from N-acetyl phthalimide, so that the stereochemistry of the final product is apparently the same, no matter which intermediate (CXIX or CXX) is involved. The proportion of hexahydrophthalimide in the reaction mixture from this hydro-

genation was somewhat greater than that in the mixture obtained on hydrogenation of N-acetyl phthalimide, indicating, as was suggested by the results obtained with the N-benzoyl and N-hexahydrobenzoyl derivatives, that the presence of a benzene ring adjacent to a carbonyl function does facilitate the hydrogenation of the latter to a small extent.

N-carboethoxy phthalimide.

The partial hydrogenation of N-carboethoxy phthalimide in ethyl acetate over platinum oxide gave a mixture containing four principal components, which on t.l.c. appeared as two pairs of close-running spots. The mixture was separated by column chromatography on silica gel into two major fractions each containing two components. Partial crystallisation of the less polar of these two fractions gave a few crystals of a compound which, on comparison with authentic material, proved to be starting material. Partial crystallisation of the more polar fraction also gave a crystalline product which, after repeated crystallisation, had m.p. 137° (from ethyl acetate). The i.r. spectrum of this product showed a peak in the hydroxyl region at 3460cm.$^{-1}$, a very strong peak in the carbonyl region at 1772cm.$^{-1}$ and a weak peak at 1694cm.$^{-1}$ Other peaks at 1618 and 702cm.$^{-1}$ showed that a benzene ring was still present, indicating that the product was N-carboethoxyhydroxyphthalimidine (CXX; R=OEt). This assignment was supported by analysis, and by the n.m.r. spectrum, which showed the following features:-

8.61τ(t., J=7.2c/s.,3H.) —— $-CH_3$ of carboethoxy group.

5.59 (quartet, J=7.2c/s.,2H.) —— $-CH_2-$of carboethoxy group.

5.44 (d., J=4.2c/s.,1H; lost on D_2O equil.) —— CHO<u>H</u>.

3.56 (d., J=4.2c/s.,1H; s. on D_2O equil.) —— C<u>H</u>OH.

2.05-2.65 (m.,4H.) —— aromatic protons.

The material remaining after crystallisation of these two products was examined by n.m.r. The n.m.r. spectrum of the residue from the less polar fraction indicated that the second component, with similar Rf to that of the starting material, was its hexahydro derivative (CXIX; R=OEt), and the spectrum of the more polar fraction showed that the remaining component was the fully hydrogenated product, hexahydro-N-carboethoxy-hydroxyphthalimidine (CXIV; R=OEt). These results suggested that in this case, the competing primary reactions of benzene ring saturation and carbonyl reduction are occurring at comparable rates. In order to further substantiate the formation of the same final product from the two possible intermediates, these intermediates, N-carboethoxyhydroxyphthalimidine and hexahydro-N-carboethoxyphthalimide were synthesised, and subjected to catalytic hydrogenation under the same conditions. The latter compound was obtained by reaction of ethyl chloroformate with the potassium salt of hexahydrophthalimide in refluxing benzene, by analogy with the preparation of N-carboethoxyphthalimide. As to the preparation of N-carboethoxy-hydroxyphthalimide, it was thought that hydrogenation of N-carboethoxy phthalimide over a palladium catalyst should give

the required product, palladium, as has already been noted (p.69), being particularly effective for the hydrogenation of carbonyl groups adjacent to benzene rings, while being inactive in promoting saturation of the latter under mild conditions. Indeed when N-carboethoxy phthalimide in dry ethanol was shaken in a hydrogen atmosphere in presence of 10% palladium on carbon, the equivalent of one mole of hydrogen was absorbed in about 9 hr. T.l.c. of the product indicated the presence of practically a single component, and direct crystallisation from ethyl acetate gave the desired N-carboethoxyhydroxyphthalimidine, m.p. 137°, in good yield. This hydrogenation could also be carried out in ethyl acetate solution, although it appeared to proceed somewhat more slowly in that solvent. Prolonged hydrogenation over palladium resulted in the very slow uptake of more hydrogen to give a product which was less polar on t.l.c. than the initial product. Although this subsequent product was not isolated, the n.m.r. spectrum of a mixture of it and N-carboethoxyhydroxyphthalimidine indicated that it was N-carboethoxyphthalimidine (CXXIV; R=OEt), which would result from the hydrogenolysis of hydroxyphthalimidine. The generality of this hydrogenation with palladium was shown by the preparation of N-acetyl and N-carboethoxyhydroxyphthalimidine (CXX; R=CH_3 and OCH_3) from the corresponding phthalimides.

N-dimethylcarbamoyl phthalimide.

In the hydrogenation of this compound over platinum oxide

already discussed, the hexahydro derivative (CXIX; R=$N(CH_3)_2$) was found to comprise about 25% of the total reaction product. This result might be interpreted in one of two ways, either

(a) benzene ring saturation is the faster initial reaction, being followed by slow carbonyl reduction, or

(b) as with the N-carboethoxy analogue, benzene ring saturation competes with carbonyl reduction as the initial reaction, the fully hydrogenated product (CXIV; R=$N(CH_3)_2$) arising from the intermediate CXX(R=$N(CH_3)_2$) while the hexahydro derivative (CXIX; R=$N(CH_3)_2$) is either not susceptible to further hydrogenation, or undergoes very slow hydrogenation to the final product.

Accordingly, further hydrogenation of hexahydro-N-dimethylcarbamoyl phthalimide, isolated from the product of hydrogenation of N-dimethylcarbamoyl phthalimide, was investigated. This reaction was found in fact to proceed very slowly to give the expected product (CXIV; R=$N(CH_3)_2$). However, it was not possible to decide on the basis of this observation alone which of the two suggested descriptions of the course of reaction of N-dimethylcarbamoyl phthalimide was the correct one, so it was decided to examine the partial hydrogenation of this compound. If benzene ring saturation occurs before carbonyl group reduction in this case, stopping the hydrogenation when three moles of hydrogen have been absorbed should permit isolation of hexahydro-N-dimethylcarbamoyl phthalimide in good yield. At this juncture, platinum oxide from a batch

supplied by Johnson Matthey & Co. Ltd was used, and a rather surprising result obtained. Absorption of the first mole of hydrogen by N-dimethylcarbamoyl phthalimide, on hydrogenation in ethyl acetate over this platinum oxide, was markedly faster than the subsequent reaction, a phenomenon which was not observed when Engelhard catalyst was used. Further absorption of hydrogen was very slow, the equivalent of only about two moles being taken up altogether after 24 hr. Examination of the resulting product by t.l.c. indicated the presence of a principal product with an Rf similar to that of hexahydro-N-dimethylcarbamoylhydroxyphthalimidine (CXIV; R=$N(CH_3)2$). This product was isolated by crystallisation from ethyl acetate, whence it had m.p. 169-171°. The i.r. spectrum showed peaks at 3390, 1704 and 1688cm^{-1}, indicating that reduction at an imide carbonyl group had taken place, and other peaks at 1619 and 710cm^{-1} which showed that a benzene ring was present. From this it could be concluded that the product was N-dimethylcarbamoylhydroxyphthalimidine (CXX; $R=N(CH_3)_2$), an assignment supported by analysis and the n.m.r. spectrum which showed the following features:-

6.93τ(s.,6H.) —— protons of $-N(CH_3)_2$ group.

4.14 (d., J=6c/s.,1H; lost on D_2O equil.) —— CHO<u>H</u>.

3.35 (d., J=6c/s.,1H; s. on D_2O equil.) —— C<u>H</u>OH.

2.08-2.6 (m.,4H.) —— aromatic protons.

Repeating this hydrogenation, again using Johnson Matthey platinum oxide, and stopping reaction when one mole of hydro-

gen had been absorbed, permitted the isolation of this compound in good yield. Examination, by n.m.r., of the residue remaining on crystallisation of the principal product from the reaction mixture indicated the presence of only a little hexahydro-N-dimethylcarbamoyl phthalimide along with starting material and the principal product. The results obtained using the Johnson Matthey catalyst make it appear likely that in the hydrogenation of N-dimethylcarbamoyl phthalimide over Engelhard platinum oxide, there is competition between initial benzene ring saturation and reduction at a carbonyl group, but that the rate of the latter reaction compared with the former was relatively slower than in the case of the N-acetyl and N-carboethoxy analogues. Thus, for the series of N-acyl phthalimides investigated, the rates of imide carbonyl group hydrogenation relative to benzene ring saturation are in the order,

N-acetyl > N-carboethoxy > N-dimethylcarbamoyl,

which is in the same order as the electron-withdrawing ability of these substituents.

Attempted hydrogenations of N-dimethylcarbamoyl phthalimide over 10% palladium on carbon in either ethanol or ethyl acetate were unsuccessful, only starting material being recovered. This indicates an order of reactivity for the N-acyl phthalimides over palladium similar to that over platinum, although there appeared to be no significant difference in the times required for the uptake of one mole of hydrogen by the N-

acetyl and N-carboethoxy derivatives on hydrogenation under similar conditions.

In the course of repeating some of the earlier hydrogenations using the Johnson Matthey catalyst, in order to determine if the increased activity of this catalyst compared with Engelhard platinum oxide for carbonyl group reduction was general, some support for the order of reactivity of the imide carbonyl groups deduced above came from the observation that, under similar conditions, N-acetyl phthalimide absorbed one mole of hydrogen rather more rapidly than the N-carboethoxy derivative, and in about half the time required by the N-dimethylcarbamoyl derivative. (As has been already indicated (p.68), adsorption, as well as intramolecular electronic factors, may of course contribute to this difference in rate.) The corresponding N-acylhydroxyphthalimidines (CXX; R=CH_3 and OEt) could be isolated in good yield in these hydrogenations by stopping the reaction when one mole of hydrogen had been absorbed. On prolonging the reaction time, however, complete saturation of the benzene ring was accomplished only very slowly, and often came to a virtual standstill before all the intermediate products had reacted, from which it appeared that the Johnson Matthey catalyst was much less active for this particular reaction than the Engelhard catalyst. A further difference between these two batches of catalyst was noted in the hydrogenation of N-acetyl phthalimide. After shaking this material in ethyl acetate over Johnson Matthey platinum

oxide under hydrogen for 24 hr, t.l.c. indicated the presence of two products, the major one having the same Rf as hexahydro-N-acetylhydroxyphthalimidine (CXIV; R=CH_3), and the minor one having an Rf similar to hexahydrophthalimide, which was produced in the hydrogenation over Engelhard catalyst. On extraction of the reaction mixture with boiling light petroleum (b.p. 60-80°), and allowing the extract to cool, the expected major product (CXIV; R=CH_3) crystallised out. However, crystallisation of the light petroleum-insoluble residue from ethyl acetate gave a product m.p. 162°, which was shown by direct comparison with material obtained previously, to be N-acetylhydroxyphthalimidine (CXX; R=CH_3), and not the expected product, hexahydrophthalimide, from which it appeared that little or no cleavage of the acetyl group had occurred in this case.

(3) Effect of increasing bulk of the acyl substituent.

Since hydrogenation in the imide ring was found to occur only to a minor extent with the N-acetyl and N-benzoyl derivatives of succinimide, it was of interest to determine whether attack in the ring could be promoted by substitution with a bulky group. For this purpose, N-pivaloyl succinimide (CXXIII; R=$C(CH_3)_3$, m.p. 100° from methanol) was synthesised by reaction of pivaloyl chloride with succinimide in pyridine. On hydrogenation in ethyl acetate over platinum oxide, this compound absorbed two moles of hydrogen, and t.l.c. of the reaction mixture indicated the presence of a single product with the

same Rf as succinimide. Pure succinimide was indeed recovered on crystallisation of the reaction product from ethyl acetate. Only a trace of a by-product, which may have been pivalamide (see p. 90 and experimental section) was obtained, contrary to what would be expected if steric hindrance were to play an effective role in controlling the site of hydrogenation. That cleavage of the acyl group had given the expected alcohol, neopentyl alcohol, was supported by the i.r. spectrum of the product from distillation of the residual oil obtained after crystallisation of the succinimide, and careful evaporation of the solvent, the spectrum showing a strong, broad band in the hydroxyl region. The alcohol was also recognisable by its very characteristic odour.

The apparent increased rather than decreased preference for cleavage of the acyl group in N-pivaloyl succinimide, as compared with the N-acetyl and N-benzoyl analogues, made it necessary to ascertain whether a similar result would be obtained for the phthalimide series. Accordingly, N-pivaloyl phthalimide (CXIII; R=$C(CH_3)_3$, m.p. 84.5-85° from light petroleum, b.p. 60-80°) as prepared by a method analogous to that for the succinimide derivative, and hydrogenated in ethyl acetate over platinum oxide. After 24 hr, $4\frac{1}{2}$-5 moles of hydrogen had been taken up, and on t.l.c., the resulting mixture was found to contain a main product with the same Rf as hexahydrophthalimide, some less polar products, and a small amount of more polar material. Extraction of the mixture

with boiling light petroleum removed the less polar products, and crystallisation of the insoluble residue from ethyl acetate gave the main product, which did indeed prove to be hexahydrophthalimide on comparison with an authentic sample, a result which confirms the enhanced susceptibility to cleavage of the pivaloyl group when compared with the acetyl or benzoyl groups. The minor products formed in the course of hydrogenation of N-pivaloyl phthalimide were not examined in this instance, but are returned to in the following investigations.

At this stage, it seemed desirable to ascertain whether the preferred cleavage at an apparently more hindered site observed with Engelhard catalyst also applied to the Johnson Matthey catalyst. For this purpose, the hydrogenation of the series of substituted phthalimides, N-acetyl, N-isobutyryl and N-pivaloyl, in which the acyl substituents are successively more hindered α to the carbonyl function was investigated over this catalyst. As has already been found, little or no acyl group cleavage was obtained with the N-acetyl derivative when hydrogenated over the Johnson Matthey catalyst. N-isobutyryl phthalimide on hydrogenation over this catalyst absorbed less than four moles of hydrogen after 24 hr. T.l.c. of the product indicated the presence of three main components, the most polar of which had the same Rf. as hexahydrophthalimide, the other two running very close together. The polar component was separated from the less polar ones by column chromatography on silica gel, and proved, as expected,

to be hexahydrophthalimide. The less polar components were separated by fractional crystallisation from light petroleum (b.p. 60-80°). The first of these had m.p. 89-90° and its i.r. spectrum showed peaks at 3460, 1717 and 1691cm.$^{-1}$, which indicated that hydrogenation at an imide carbonyl group had occurred. Further bands at 1619, 759 and 706cm.$^{-1}$ indicated the presence of a benzene ring, from which it could be deduced that this product was N-isobutyrylhydroxyphthalimidine (CXX; R=$CH(CH_3)_2$). This conclusion was reinforced by the n.m.r. spectrum, which showed the following features:-

8.73τ(d., J=6.6c/s.,3H.) —— $-CH_3$ of isobutyryl group.

8.72 (d., J=6.6c/s.,3H.) —— $-CH_3$ of isobutyryl group.

6.08 (septet, J=6.6c/s.,1H.) —— $-C\underline{H}(CH_3)$s.

5.21 (d., J=3c/s.,1H; lost in D_2O equil.) —— CHO$\underline{H}$.

3.43 (d., J=3c/s.,1H; s. on D_2O equil.) —— C$\underline{H}$OH.

2.0-2.6 (m.,4H.) —— aromatic protons.

The non-equivalence of the methyl groups in the isobutyryl group of this compound reflects the effect of the introduction of an asymmetric centre by reduction of an imide carbonyl group, the two methyl groups in the starting material being magnetically equivalent. The second of the less polar components had m.p. 103.5-104.5°, and its i.r. spectrum showed a peak in the hydroxyl region at 3425cm.$^{-1}$ and a doublet in the carbonyl region at 1736 and 1675cm.$^{-1}$, but no aromatic bands, which suggested that it was simply the hexahydro derivative (CXIV; R=$CH(CH_3)_2$) of the first component. This was again

confirmed by the n.m.r. spectrum, which showed the following features:-

7.5-9.2τ(m.,9H.) —— cyclohexane protons.

8.85 (d., J=6.6c/s.,3H.) —— $-CH_3$ of isobutyryl group.

8.83 (d., J=6.6c/s.,3H.) —— $-CH_3$ of isobutyryl group.

6.97 (m.,1H.) —— proton α to lactam carbonyl group.

6.28 (septet, J=6.6c/s.,1H.) —— $-C\underline{H}(CH_3)2$.

6.00 (d., J=3c/s.,1H; lost on D_2O equil.) —— $CHO\underline{H}$.

4.60 (d., J=3c/s.,1H; s. on D_2O equil.) —— $C\underline{H}OH$.

The methyl groups in this compound, as might be expected, are magnetically non-equivalent, and, as has been observed for all the hexahydrohydroxyphthalimidines (CXIV) obtained, there is no detectable coupling in the n.m.r. spectrum between the low field proton and the neighbouring ring-junction proton. N-isobutyrylhydroxyphthalimidine (CXX; R=$CH(CH_3)_2$) was also obtained in good yield by hydrogenation of N-isobutyryl phthalimide in ethyl acetate over 10% palladium on carbon.

Finally, the hydrogenation of N-pivaloyl phthalimide over Johnson Matthey platinum oxide was investigated. Hydrogenation of this compound under the same conditions as were used for the N-acetyl and N-isobutyryl analogues resulted in the uptake of less than four moles of hydrogen after 24 hr. T.l.c. of the resulting mixture showed three groups of products, the principal, single product with the same Rf as hexahydrophthalimide, a complicated mixture of less polar components, and, in contrast to what was found when Engelhard catalyst was used, a

considerable quantity of polar material. These three groups of products were separated by column chromatography over silica gel, and crystallisation of the main product and comparison with an authentic sample confirmed that it was hexahydrophthalimide. Comparison of the quantity of this product obtained in the present instance with the quantities obtained from N-acetyl'and N-isobutyryl phthalimide under similar conditions showed that, with the Johnson Matthey catalyst, as with the Engelhard catalyst, the susceptibility to cleavage of the acyl substituent increases with increasing degree of substitution α to the acyl carbonyl group. Crystallisation, from ethyl acetate, of the polar fraction obtained by column chromatography gave clear plates of a compound which volatilised without melting when heated on the Kofler block. The i.r. spectrum of this material showed two well-separated peaks at 3435 and 3235cm.$^{-1}$, and a very low frequency band in the carbonyl region at 1658cm.$^{-1}$, which suggested an amide, probably pivalamide, by analogy with the formation of cyclohexane carboxylic acid amide on hydrogenation of N-benzoyl succinimide (p.75), a conclusion indeed confirmed by direct comparison of the product with an authentic sample of pivalamide. Attempts at the separation of the mixture of products less polar than hexahydrophthalimide were not successful, but the mixture was examined by n.m.r., the following conclusions being drawn:-

(a) The relatively low intensity of peaks attributable to absorption by $(CH_3)_3C$-groups suggested that a considerable pro-

portion of the mixture must have arisen by loss of the pivaloyl group as pivalamide.

(b) Benzene ring saturation was incomplete, as evidenced by the presence of considerable absorption in the range 2.0-2.6τ

(c) A prominent singlet at 4.69τ(somewhat broadened at the base) indicated that the principal component in the mixture was phthalide (CXXV).

(d) Peaks at 3.41τ(benzylic proton on carbon atom carrying hydroxyl group) and 8.58τ(N-pivaloyl group) suggested the presence of N-pivaloylhydroxyphthalimidine (CXX; R=$C(CH_3)_3$).

(e) A broad mulitplet, possibly arising from an ABX system, in the range 5.69-6.23τ may have arisen from hexahydrophthalide (CXXVI).

(f) A sharp singlet, of low intensity, at 8.78τ may have arisen from N-pivaloyl phthalimidine (VXXIV; R=$C(CH_3)_3$), the signal due to the aliphatic $-CH_2-$ not being detectable, being obscured in the base line of the spectrum.

(g) No evidence for the presence of the fully hydrogenated product, hexahydro-N-pivaloylhydroxyphthalimidine (CXIV; R=$C(CH_3)_3$), could be found.

A pure sample of N-pivaloylhydroxyphthalimidine (CXX; R=$C(CH_3)_3$) was prepared by hydrogenation of N-pivaloyl phthalimide in ethyl acetate over 10% palladium on carbon. The rate of hydrogenation was notably slower in this case than it had been for the other N-acyl phthalimides, and the yield of N-acylhydroxyphthalimidine was lower. N-pivaloylhydroxyphthal-

imidine had m.p. 82-83° (from light petroleum, b.p. 60-80°), and its structure was confirmed by its i.r. spectrum, which showed a peak due to the hydroxyl group at 3495cm.$^{-1}$, a doublet in the carbonyl region at 1736 and 1668cm.$^{-1}$, and aromatic absorption at 1619, 773 and 708cm.$^{-1}$, and n.m.r. spectrum which showed the following features:-

8.58τ(s.,9H.) —— $-C(CH_3)_3$.

5.22 (d., J=4.2c/s.,1H; lost on D_2O equil.) —— CHOH.

3.42 (d., J=4.2c/s.,1H; s. on D_2O equil.) —— CHOH.

2.0-2.6 (m.,4H.) —— aromatic protons.

Before discussion of possible mechanisms for these hydrogenations, the following conclusions with regard to the different activities of the two batches of platinum oxide catalyst used may be drawn.

(a) Hydrogenation at carbonyl groups was markedly more rapid with Johnson Matthey catalyst than with the Engelhard catalyst.

(b) Benzene ring hydrogenation, on the other hand, was slower, and generally incomplete with the former catalyst.

(c) If cleavage of acyl groups could take place, the extent of cleavage was greater with the Engelhard than with the Johnson Matthey catalyst.

In spite of these differences for which no explanation can be offered, three factors, of importance in the discussion of mechanism which follows, were the same for both catalysts.

(i) The apparent rate of hydrogenation at the imide carbonyl group fell with decreasing electron-withdrawing power of the

N-acyl substituent with both catalysts.

(ii) The stereochemistry of the hexahydro-N-acylhydroxyphthalimidines (CXIV) was the same with both catalysts.

(iii) The relative ease of cleavage of acyl groups increased as their bulk increased with both catalysts; i.e. with Engelhard catalyst, the extent of cleavage increased in the order acetyl < hexahydrobenzoyl < pivaloyl, and with Johnson Matthey catalyst, acetyl < isobutyryl < pivaloyl.

On the mechanism of the catalytic hydrogenation of cyclic imides and anhydrides.

(1) Influence of the electronic effect of N-substituents in imides.

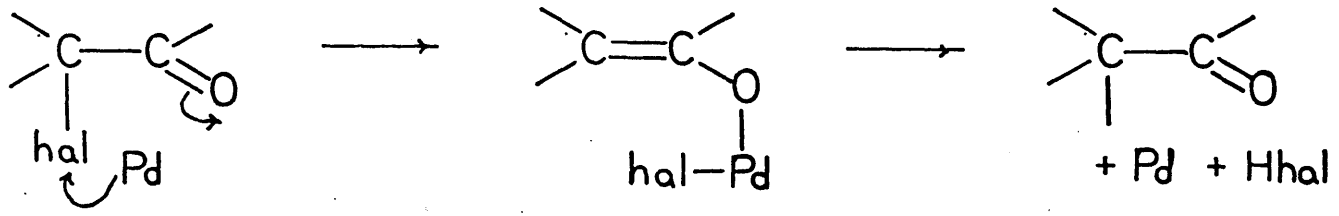
The apparent rate of hydrogenation at the carbonyl group of cyclic imides has been shown to decrease for the N-acyl phthalimides in the order

N-acetyl > N-carboethoxy > N-dimethylcarbamoyl,

over platinum oxide and 10% palladium on carbon catalysts. As has already been noted (p.68) this rate difference might be ascribed to a combination of two effects, namely the inductive effect of the acyl substituent, and the strength of adsorption of that substituent on the catalyst surface. However, since the latter effect should lead to concomitant slowing of the rate of hydrogenation of the benzene ring in these derivatives, it is considered that the decrease in the rate of carbonyl group hydrogenation relative to benzene ring hydrogenation found when Engelhard platinum oxide was used is evidence for

FIGURE 9

Hydrogenolysis of -haloketones over palladium, after Denton, McQuillin and Simpson.(136)



a significant contribution from the electron-withdrawing effect of the acyl groups. Further support for this conclusion comes from the observation that simple N-alkyl substitution of phthalimide was not sufficient to promote hydrogenation at an imide carbonyl group under the conditions employed. The influence of the nature of the acyl substituent on the rate of hydrogenation could arise, as has been outlined in the introduction (p.49) from the participation in the course of reaction of a step involving nucleophilic attack at the carbonyl function undergoing hydrogenation, by either hydride or the catalyst metal itself. Nucleophilic attack by the catalyst has been suggested by Denton, McQuillin and Simpson[136] to occur in the hydrogenolysis of certain α-halogeno ketones and lactones over palladium. Thus, hydrogenolysis of α-bromo ketones was envisaged as involving nucleophilic attack on the halogen, as illustrated in figure 9.

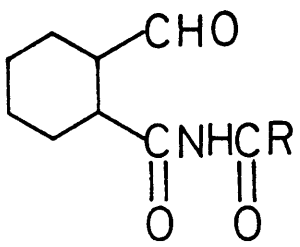
(2) Deductions from the stereochemistry of the products.

The catalytic hydrogenation of cyclic imides and anhydrides to the corresponding hydroxylactams and hydroxylactones may be envisaged as proceeding by one of two routes analogous to those considered by Adkins for the hydrogenation of esters,[80] viz.
(1) direct addition of hydrogen across a carbonyl group as may occur with ketones, or
(2) hydrogenolysis to give a free aldehydo function, followed by rapid recyclisation before further reduction of the latter function can occur.

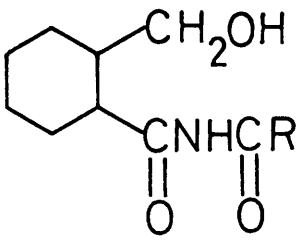
i.e. $-CO-X \longrightarrow -CHO + HX \longrightarrow -\overset{H}{\underset{OH}{C}}-X$ (X=-OCOR or RCONCOR').

If route (1) represents the correct mechanism, then the stereochemistry of the products would be expected to be subject to control by the same type of steric hindrance factors as have been considered in the introduction for ketones. Hydrogenation of the hexahydro-N-acyl phthalimides (CXIX) over platinum should then give mainly those products in which the entering hydrogen has added from the less hindered side of the molecule, namely CXXI. Similarly, hydrogenation of the anhydrides XCIV and XCVII would be expected to give the products CXXVII and CXXVIII. In fact, the only products isolated in these reactions have the hydroxyl group in the opposite configuration. If the hydrogenation proceeded by route (1), this result could however be explained in the two ways (a and b) discussed below.

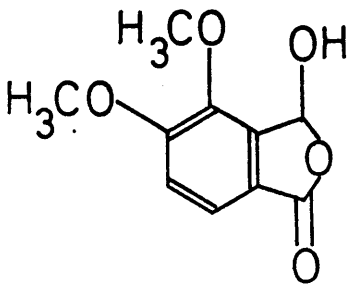
(a) The expected products (CXXI, CXXVII and CXXVIII) are indeed formed initially, but subsequent ring opening to the aldehydo forms (e.g. CXXIX) occurs, followed by reclosure to give the products in which the configuration of the hydroxyl group is reversed, and in which it is of course less hindered. Against this explanation is the fact that prolonging the time of hydrogenation of the N-acyl phthalimides, or attempted further hydrogenation of the hexahydro-N-acylhydroxyphthalimidines using fresh catalyst, results in no further uptake of hydrogen, whereas if reversible ring opening to the aldehydo form (CXXIX) occurred, hydrogenation to the ring opened alcohol (CXXX)



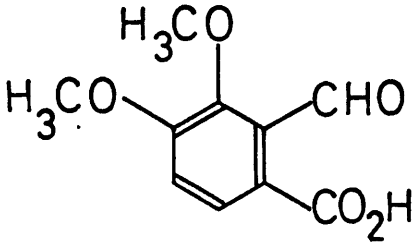
CXXIX



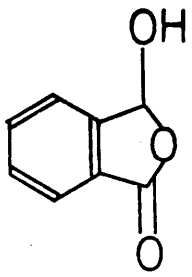
CXXX



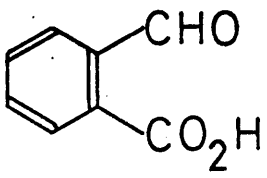
CXXXIa



CXXXIb

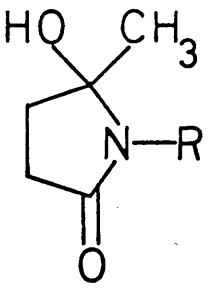


CXXXIIa

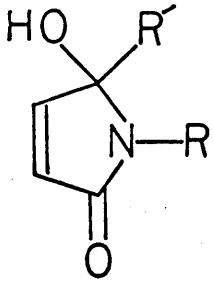


CXXXIIb

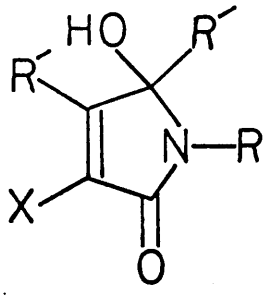
should be obtained. On the other hand, the hydroxylactone CI for example could be hydrogenated further in ethyl acetate over platinum oxide to the lactone XCIX.[1b] This may reflect a more ready ring opening for hydroxylactones than for hydroxylactams, indeed the fact that the readiness with which further hydrogenation of different hydroxylactones could be accomplished varied considerably with their structure[1b] may indicate that prior ring opening is an essential step. The equilibrium between the open and closed forms of hydroxylactones has been observed. From a study of its i.r. spectrum in aqueous solution, it has been concluded that undissociated opianic acid (CXXXIa,b) exists as an equilibrium mixture containing about 30% of the lactol form (CXXXIa), whereas when chloroform is the solvent, it is mainly in the cyclic form (CXXXIb).[137] The parent compound, phthalaldehydic acid (CXXXIIa,b) appeared from its i.r. spectrum in aqueous solution to exist only in the cyclic form (CXXXIIa), but from the fact that oxime formation took place under the slightly acidic conditions resulting when the acid and hydroxylamine hydrochloride were dissolved in water, it was suggested that an equilibrium between the open and cyclic forms does exist, but that it was strongly displaced towards the latter.[138] (In base, the anions of these acids, which exist in the open form, are of course obtained.) No observation of a similar type of equilibrium between hydroxylactams and the corresponding aldehydo (or keto-) amides appears to be recorded in the literature, but



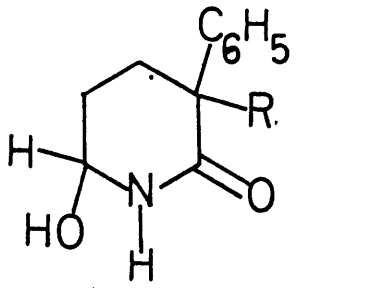
CXXXIII,



CXXXIV

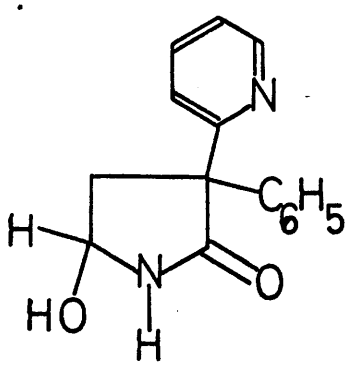


CXXXV

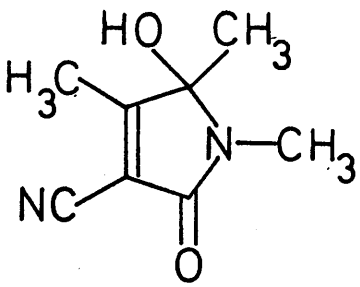


R=$-(CH_2)_2N(C_2H_5)_2$

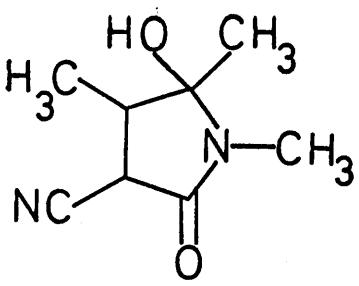
CXXXVI



CXXXVII



CXXXVIII



CXXXIX

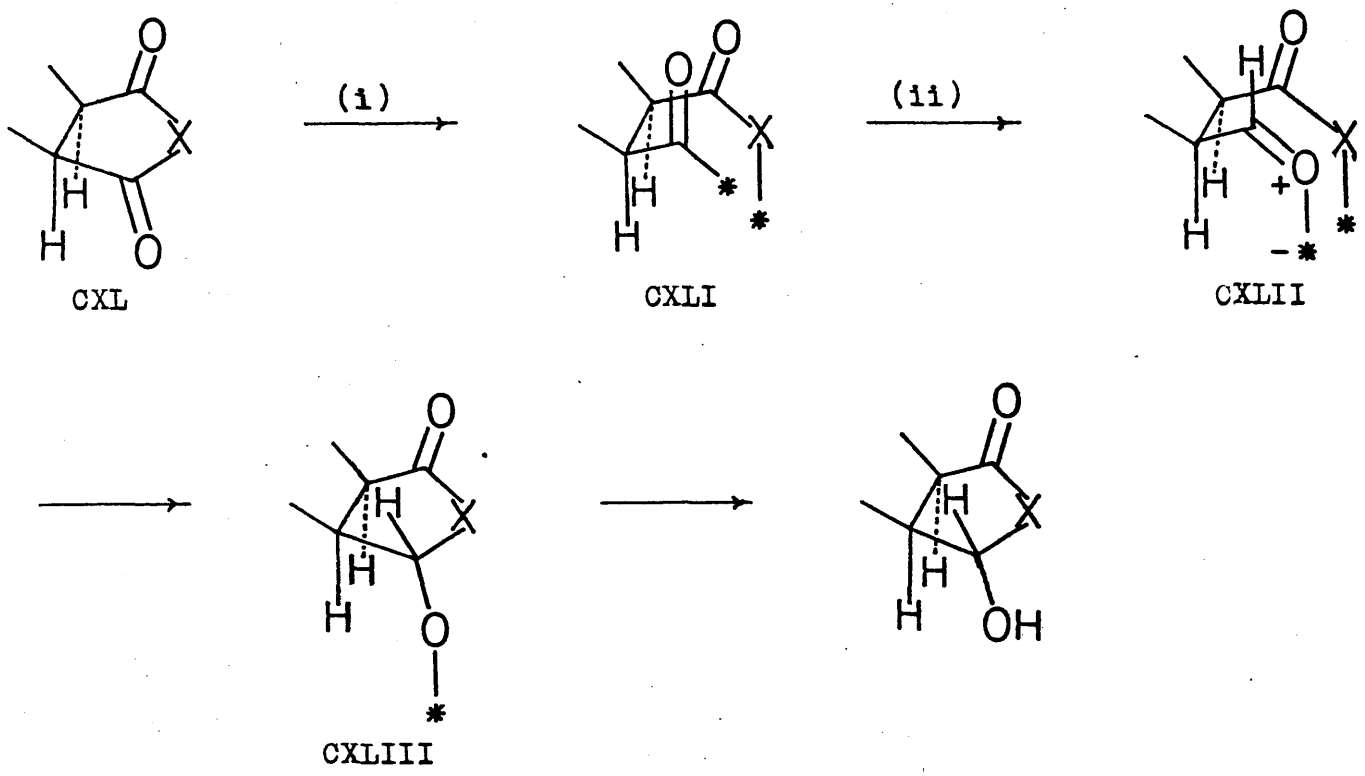
N-methyl levulinamide ($CH_3COCH_2CH_2CONHCH_3$), levulinic acid anilide ($CH_3COCH_2CH_2CONHPh$) and the corresponding hydroxylactams (CXXXIII; R=CH_3 or Ph respectively) have been prepared, so that in these examples at least, equilibrium between the open and cyclic forms does not appear to be established.[139,140,141] Products obtained by the reaction of one mole of Grignard reagent on cyclic imides,[139-143] or by condensation of 1:2-diketones, such as benzil or diacetyl, with species of the type XCH_2CONHR[144,145] (where X is a strongly electron-withdrawing group such as -CN,-CO_2Et,-$COCH_3$ etc.) have all been formulated as cyclic species. The products of reaction of Grignard reagents with N-substituted maleimides (CXXXIV) were reported to give derivatives readily with 2:4-dinitrophenylhydrazine,[143] whereas the hydroxylactams derived from 1:2-diketones (CXXXV) apparently did not react with ketonic reagents.[144,145] The 6-hydroxy piperidone (CXXXVI) and the 5-hydroxy pyrrolidone (CXXXVII), obtained by the partial reduction of the corresponding glutarimide and succinimide respectively with lithium aluminium hydride, were also concluded to exist in the cyclic rather than the open form, from the observations that no reaction was obtained with 2:4-dinitrophenylhydrazine, and that they could not be hydrogenated over palladium in ethanol at elevated temperatures.[146] (Details of the attempted hydrogenation were not given. Palladium, as has been noted in the introduction, is not an active catalyst for the hydrogenation of aliphatic aldehydes

and ketones at r.t.p. The α,β-unsaturated hydroxylactam CXXXVIII has been hydrogenated in methanol over 5% palladium on carbon at r.t. and 1500lb/in^2 to the saturated derivative CXXXIX.[145]) In conclusion, the somewhat meagre information available on hydroxylactams does however indicate that such compounds are less subject to ring opening than hydroxylactones.'

(b) The observed products could have been formed directly if hydrogen addition to the carbonyl group took place by an Eley-Rideal type of mechanism, whereby hydrogen adds to the top side of the adsorbed molecule rather than to that side attached to the catalyst. As has been discussed in the introductory section, the intervention of such a process has been proposed very recently by Cornet and Gault[79] to account for the results of a study of the hydrogenation of 2-methylcyclopentanone and the isomerisation of the 2-methylcyclopentanols. Formation of the hexahydro-N-acylhydroxyphthalimidines (CXIV) from the hexahydro-N-acyl phthalimides (CXIX) via a triadsorbed species analogous to that suggested by these authors, and illustrated in fig. 7, would require that hydrogen addition takes place specifically to the ring junction carbon atom adjacent to the carbonyl group undergoing reduction from the catalyst side, and to the carbonyl carbon atom from the free side of the molecule, assuming this to be adsorbed on its less hindered side. This possibility is however excluded by the requirement (see p.34) that either addition to both sides of

FIGURE 10

Catalytic hydrogenation of cyclic imides and anhydrides over Adams' platinum oxide.



each of the carbon atoms involved in adsorption may occur, which would give mixtures of stereoisomers, or addition to both carbon atoms must occur from the same side, which would give a product in which the hydroxyl function was trans rather than cis to the neighbouring ring junction proton. Hydrogen addition by an Eley-Rideal type of mechanism could give the observed products only if the diadsorbed species (adsorbed through the carbonyl carbon and oxygen atoms) were involved. In a recent study of the hydrogenolysis of benzyl-type alcohols and their derivatives, Khan, McQuillin and Jardine have described a model for such a process to account for the inversion of configuration observed when hydrogenolyses are carried out over palladium.(147)

The stereochemistry of the products obtained on hydrogenation of the hexahydro-N-acyl phthalimides, and of the Diels-Alder adducts of maleic anhydride, could be accounted for if reaction occurred by initial hydrogenolysis as in route (2), by a mechanism outlined in figure 10, and involving the following steps:-

(i) Nucleophilic attack of the catalyst on an imide or anhydride carbonyl carbon atom of the substrate molecule adsorbed on the catalyst surface on its less hindered side as in CXL (fig.10), with concomitant ring opening to give the species CXLI.

(ii) Hydrogenolysis of the metal-carbon bond to give the free aldehydo function followed by rotation of this function through

180° to give the species CXLII adsorbed through the aldehyde carbonyl oxygen. This mode of adsorption of the carbonyl function is analogous to that suggested by Newham and Burwell for the initial adsorbed intermediate in the hydrogenation of ketones.[74] (See fig.4)

(iii) Ring closure of the intermediate CXLII to give the oxygen-bound species CXLIII. The rate of this step compared with the rate of further hydrogenation of the aldehydo function in CXLII will determine whether products of further reduction are obtained. Thus, for the N-acyl phthalimide series, ring closure must be relatively fast, so that little or no further hydrogenation can take place. In the N-acyl succinimide series, where ring closure would be expected to be slower, the aldehydo and imide groups of the intermediate not being held in a position sterically favouring interaction as is the case with the phthalimide series, the main product of reaction is the primary alcohol. In the hydrogenation of the Diels-Alder adducts of maleic anhydride, an additional complication comes into play in that the derived hydroxylactones may be in equilibrium with the open forms, so that further hydrogenation may occur, not only of the adsorbed intermediate CXLII, formed directly from the adduct, but also of the hydroxylactone at a rate depending on how rapidly ring opening of the cyclic form occurs as the aldehydo form is removed from the equilibrium by hydrogenation.

(iv) Hydrogenolysis of the metal-oxygen bond in CXLIII, and

desorption of product.

This type of acyl group cleavage mechanism may also apply to the hydrogenation of acyl halides to aldehydes, the effectiveness of poisons discussed in the introduction (p.2) being due to selective interference with the hydrogen addition type of mechanism necessary for reduction of the aldehyde. Many homogeneous analogies for this type of reaction can be found in the recent literature which records the cleavage of acyl halides, RCOX, by four co-ordinate square planar complexes of the group VIII metals, ML_4, to give six co-ordinate octahedral complexes of the type $RCOM(X)L_4$. (For recent examples, see refs 148 and 149.)

(3) The influence of substitution α to the carbonyl group of the acyl substituent.

It has been demonstrated that the extent of cleavage of acyl groups in the hydrogenation of N-acyl phthalimides over platinum increases in the order

acetyl < isobutyryl or hexahydrobenzoyl < pivaloyl.

In the introduction, it has been noted that the hydrogenation of ketones substituted in the α-position, or of branched aliphatic esters and acids is more difficult than hydrogenation of the unsubstituted analogues, as a result of steric hindrance in the substituted derivatives, so that the above order of susceptibility to hydrogenolytic cleavage is the opposite of what would be expected if such steric factors were important in the hydrogenation of the N-acyl phthalimides. This apparent

anomaly might however be explained if the acyl groups were cleaved by initial hydrogenolysis as in step (i) of figure 10, rather than by hydrogen addition to give the intermediate CXLIV with subsequent fragmentation (CXLIV, arrows), whereas ketones, esters and acids were hydrogenated by the addition type of mechanism. This suggests that the preferred mode of hydrogenation of acid derivatives, with the general formula RCOX, depends on the leaving ability of the group X, which could either leave as an anion, or more likely, co-ordinate with the catalyst. Thus, for acid halides, where X is a good leaving group, hydrogenation should proceed via the hydrogenolysis route, (2), whereas esters and acids would react preferably by the hydrogen addition route, (1).

(4) The stereochemistry of hydrogenation of the N-acylhydroxyphthalimidines.

The hexahydro derivatives obtained on hydrogenation of N-acylhydroxyphthalimidines over platinum had the same stereochemistry as the products obtained on hydrogenation of the hexahydro-N-acyl phthalimides. In order to account for this, it is necessary to assume that the stereochemistry of addition of hydrogen to the benzene ring was controlled by adsorption of the substrate molecules on the catalyst surface through the hydroxyl function. Such control of the direction of hydrogen addition has been suggested in numerous cases to account for the stereochemistry of products obtained on saturation of double bonds having a hydroxyl function in their vicinity, but

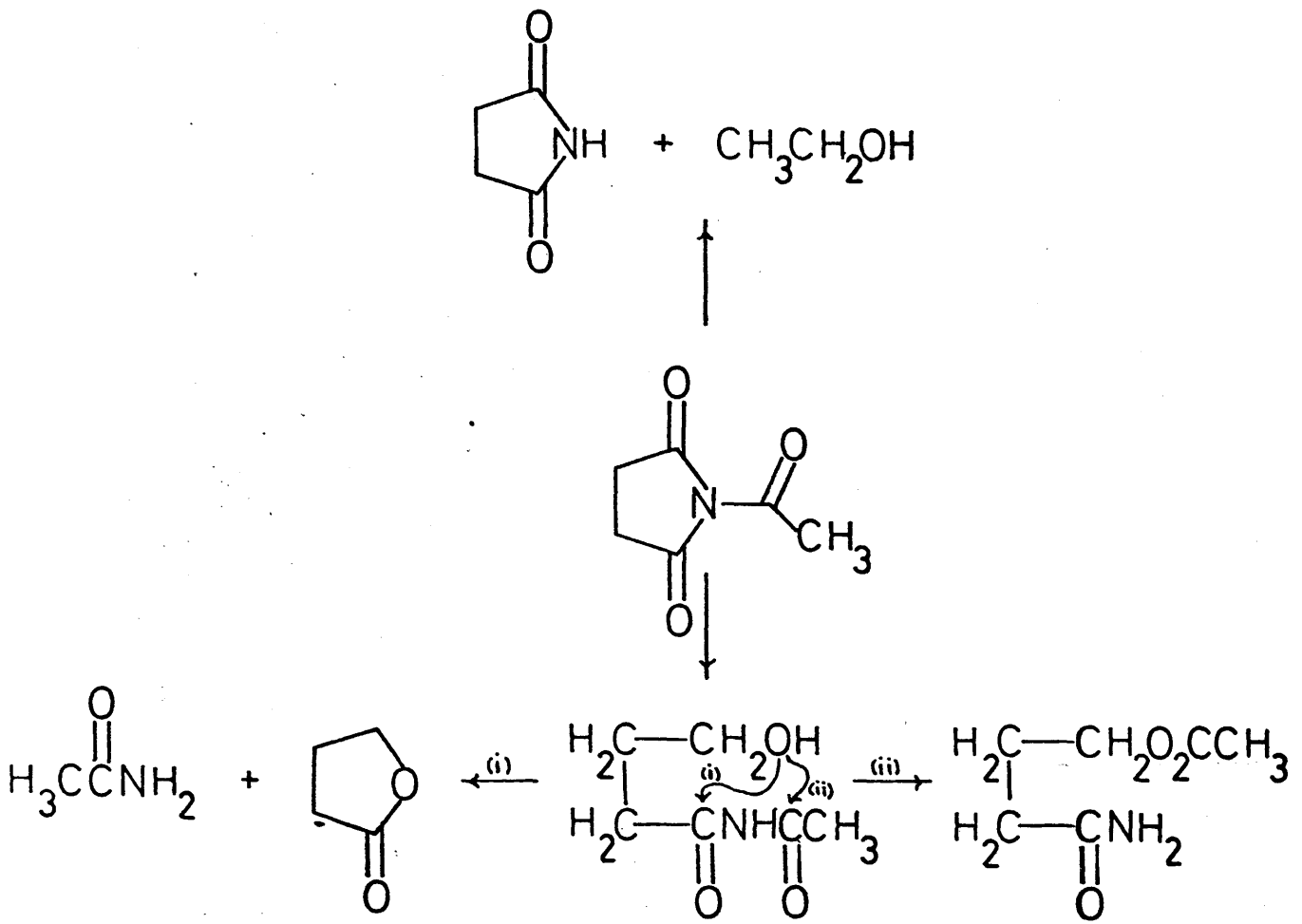
no reference could be found in the literature to such a phenomenon in the course of hydrogenation of benzene rings. Among the most striking of the examples of this effect in the hydrogenation of olefins is the exclusive formation of the 5β-cholestane on hydrogenation of cholest-4-en-3β,6β-diol over platinum oxide in ethanol,[150] and the formation of at least 96% trans-2-cyclopentylcyclopentanol, on hydrogenation of 2-cyclopentylidenecyclopentanol over Raney nickel at r.t. and 110atm.[151] A recent publication lists several other references to results of this kind.[152]

(5) Nature of the minor products in hydrogenations over platinum.

In the hydrogenations of N-acyl phthalimides over platinum, small amounts of polar products were usually observed on t.l.c. of the total reaction mixture, and in one case, on hydrogenation of N-pivaloyl phthalimide over Johnson Matthey platinum oxide, a considerable quantity of polar product, pivalamide, derived from the acyl substituent, was recovered. These polar products probably arose by hydrogenation of the intermediate aldehydo species CXLII (fig.10), to the alcohol (e.g. CXXX) which could recyclise to the lactone hexahydrophthalide (CXXVI) with ejection of the amide derived from the acyl substituent. The phthalide suggested to have formed in the hydrogenation of N-pivaloyl phthalimide over Johnson Matthey platinum oxide could have been formed in a similar manner. (p.91). The readiness with which this ring closure occurred would depend

FIGURE 11

Catalytic hydrogenation of N-acetyl succinimide over Adams' platinum oxide.



on the nature of the acyl substituent, so that the polar products from these hydrogenations may be the amides derived from the acyl substituents, and/or the alcohols of the type CXXX. That this type of reaction occurs in the succinimide series is shown by the isolation, from the hydrogenation of N-benzoyl succinimide, of cyclohexanecarboxylic acid amide, which probably results from the cyclisation of the intermediate CXLV to give butyrolactone. The product from N-carboethoxy succinimide, on the other hand, does not appear to undergo cyclisation to form butyrolactone with ejection of ethyl urethane, H_2NCO_2Et. The minor products obtained from N-acetyl succinimide may also be explained, as outlined in figure 11.

Conclusion.

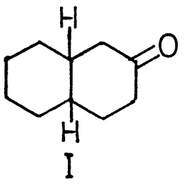
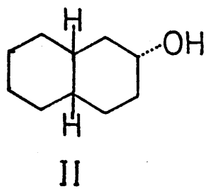
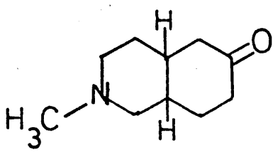
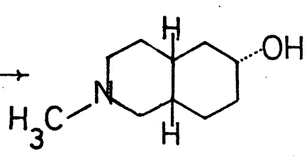
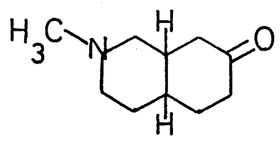
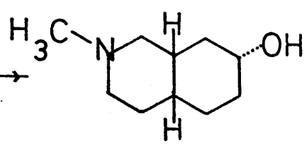
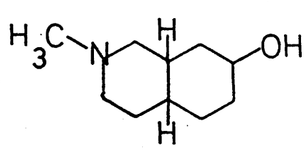
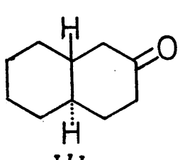
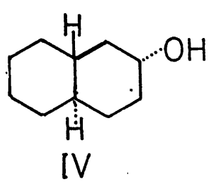
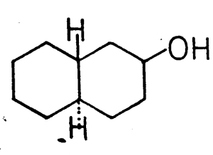
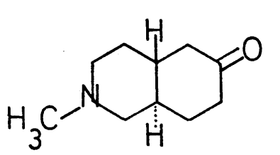
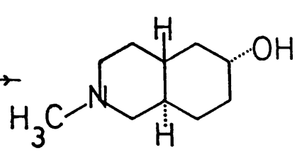
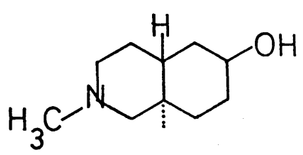
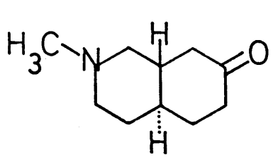
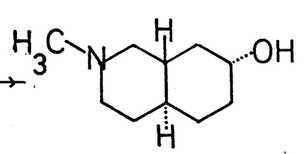
The balance of evidence suggests that the catalytic hydrogenation of N-acyl imides of the phthalimide and succinimide series over Adams' platinum oxide proceeds by a mechanism involving nucleophilic attack of the catalyst at an imide carbonyl carbon atom with concomitant opening of the imide ring rather than by direct addition of hydrogen to the carbonyl group. The same type of mechanism probably also applies to the hydrogenations carried out by McCrindle, Overton and Raphael on the Diels-Alder adducts of maleic anhydride.

Although the results obtained on hydrogenation of the N-acyl phthalimides over palladium may also suggest a step involving nucleophilic attack by the catalyst, it is not possible with the information at present available, to distin-

guish between the hydrogen addition and acyl group cleavage mechanisms for this catalyst.

TABLE 1

Hydrogenation of the decalones and decahydroisoquinolones.

	catalyst		solvent
 I	Pt black →	 II	acetic acid
	PtO_2 →		acetic acid or ethanol
	PtO_2 →	 100% 80% +  0 20%	acetic acid ethanol
 III	Pt black →	 IV +  V	acetic acid 88%V with Pt black in AcOH/hydrochloric acid (ref.125)
	PtO_2 →	 70% +  30%	acetic acid or ethanol
	PtO_2 →		acetic acid or ethanol

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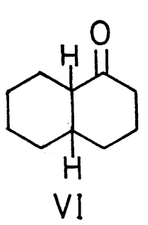
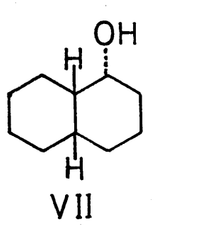
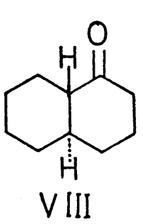
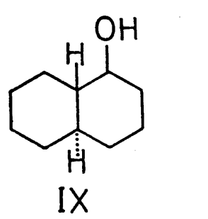
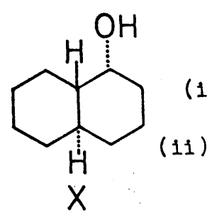
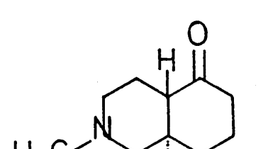
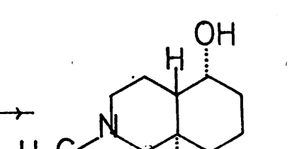
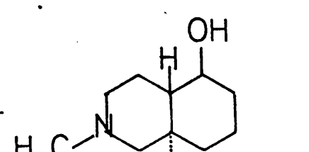
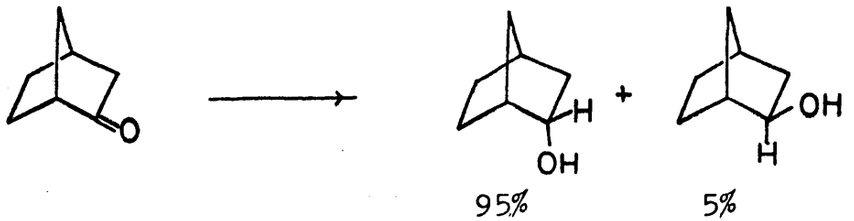
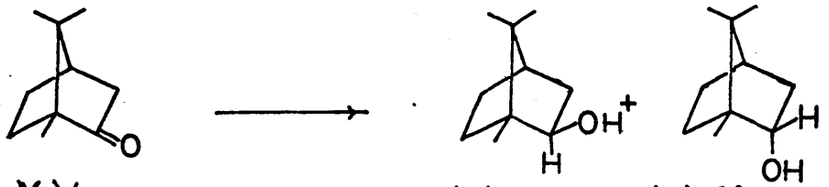
 VI	Pt black →	 VII	acetic acid
 VIII	(i)Pt black → (ii)colloidal Pt	 IX +  X	(i)acetic acid (ii)AcOH/hydrochloric acid
	PtO_2 →	 75% +  25%	acetic acid

TABLE 2

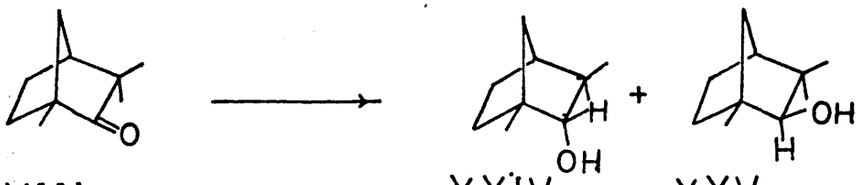
Hydrogenation of bridged bicyclic ketones. Percentages quoted are those given by Hückel for hydrogenations over Pt in acetic acid.[54]



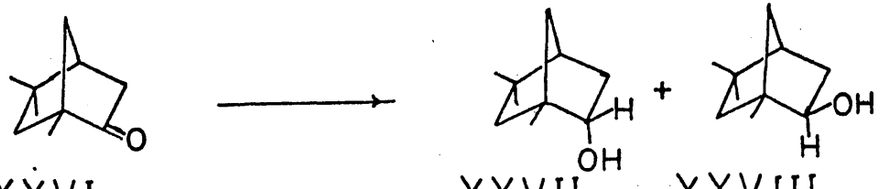
95% 5%



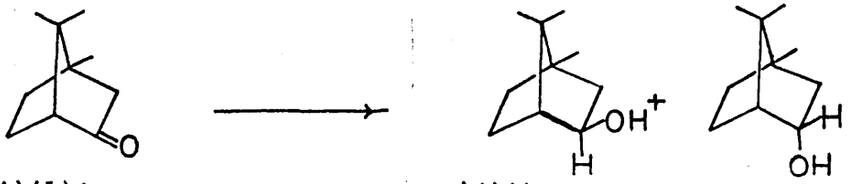
XX XXI 90% XXII 10%



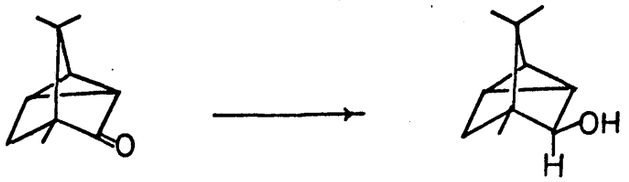
XXIII XXIV XXV



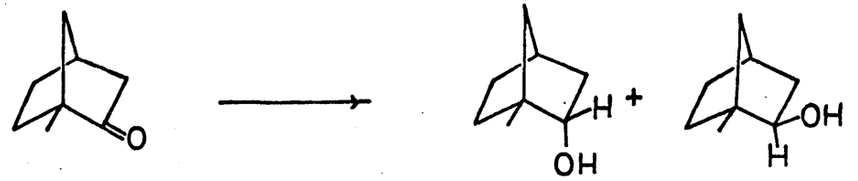
XXVI XXVII XXVIII



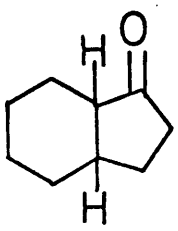
XXIX XXXI 90% 10%



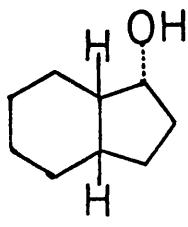
XXX XXXII



XXXIII XXXIV 95% 5%



XI



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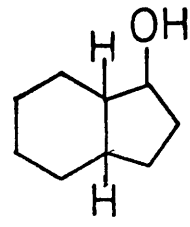

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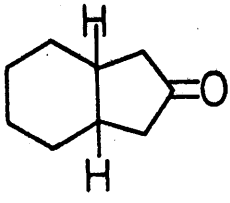

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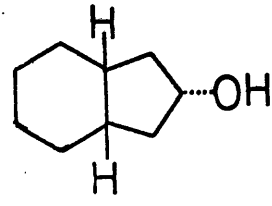
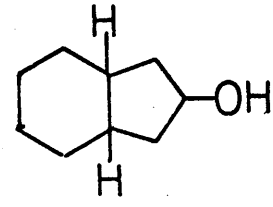


XV



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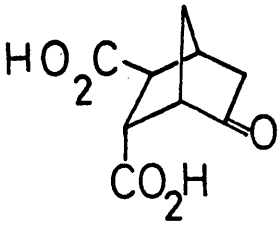
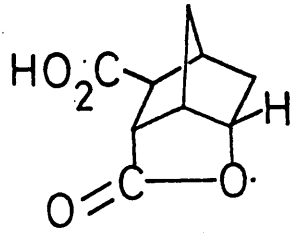
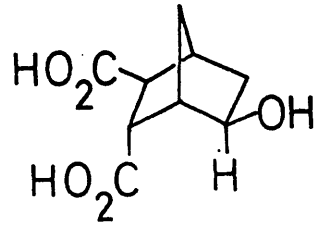


XVII



XVIII



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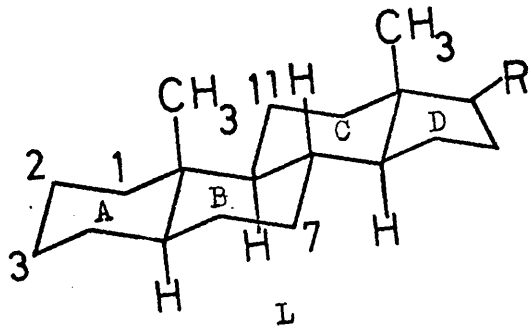

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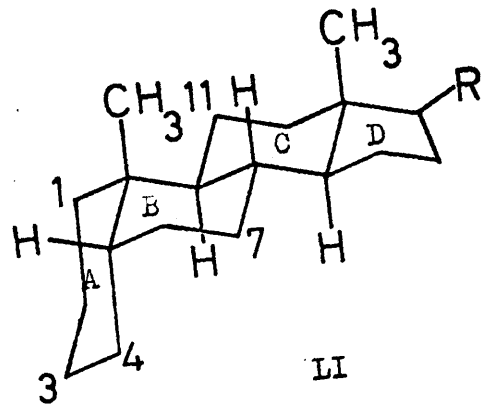

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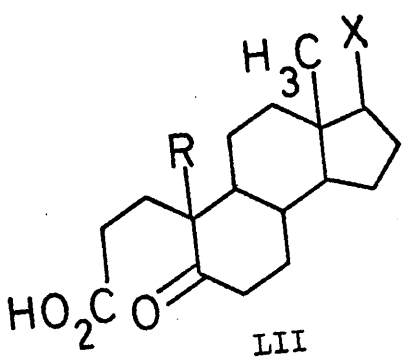

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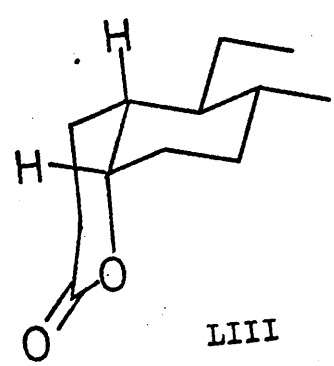

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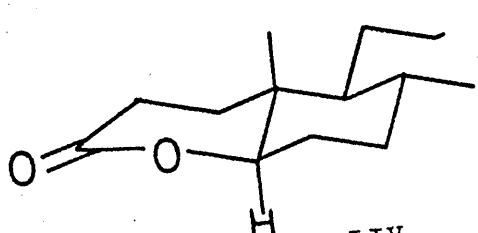

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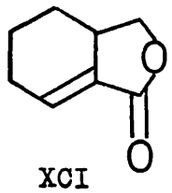

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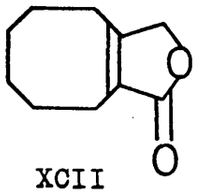

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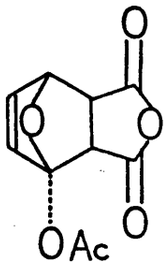

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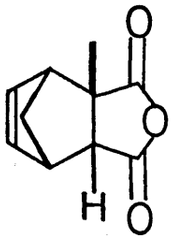

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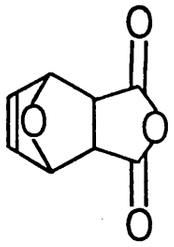

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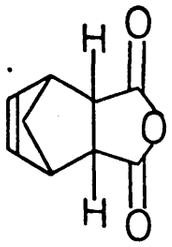

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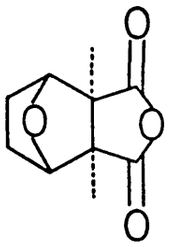

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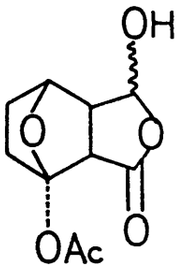

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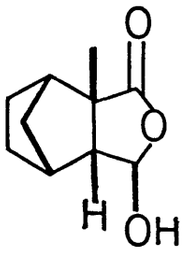

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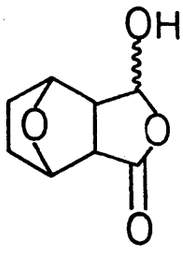

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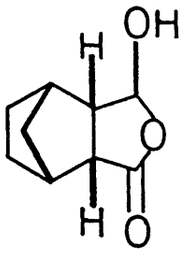

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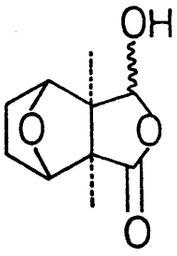

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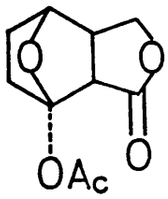

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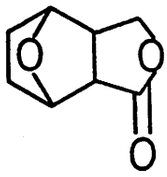

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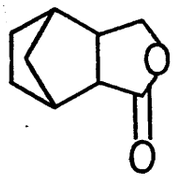

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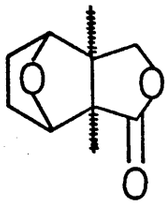

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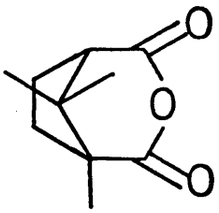

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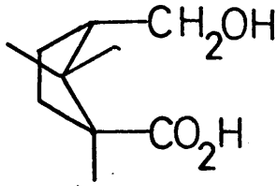

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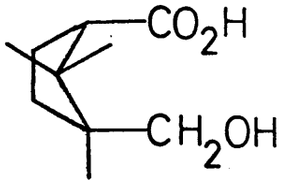

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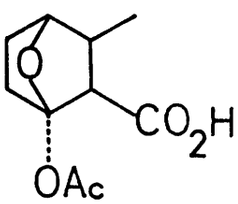

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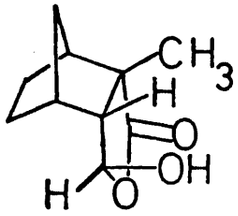

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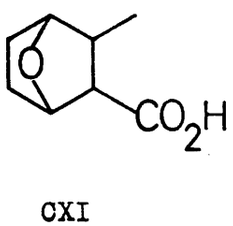

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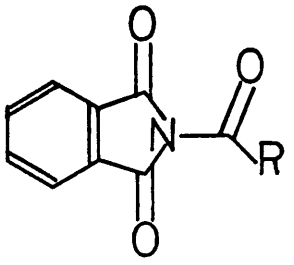

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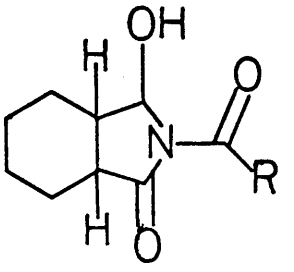

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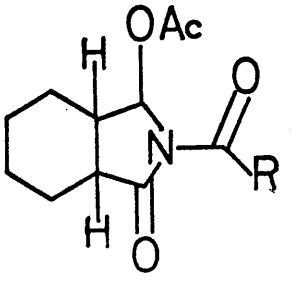

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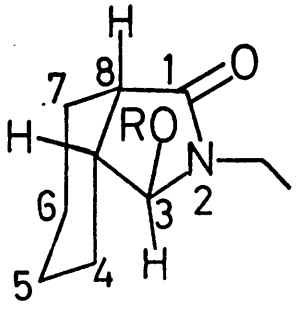

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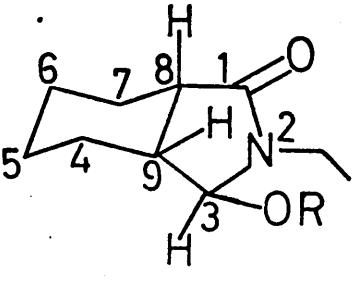

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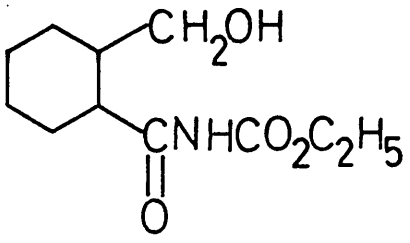
CXVb (R=Ac)



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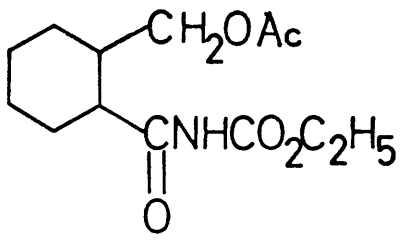

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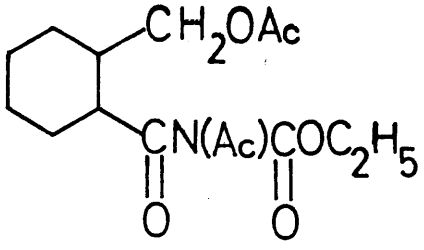

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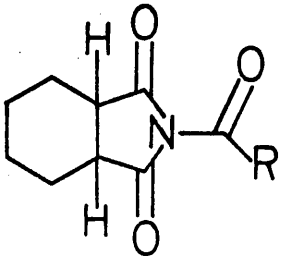

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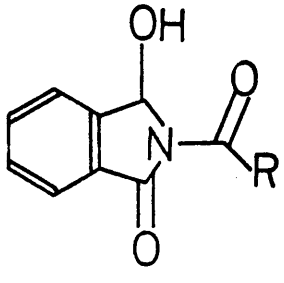

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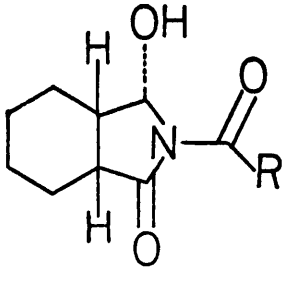

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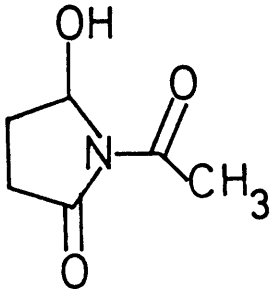

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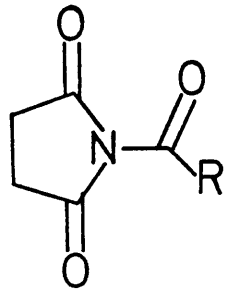

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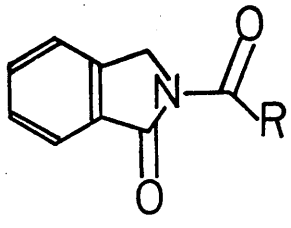

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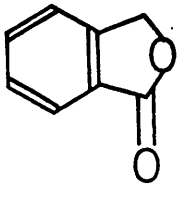

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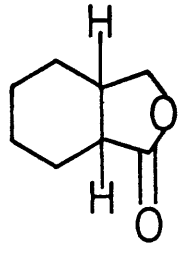

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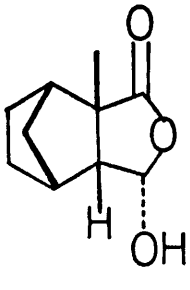

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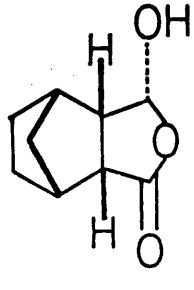

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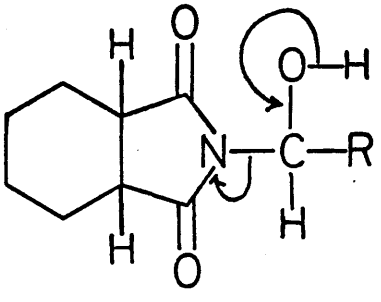

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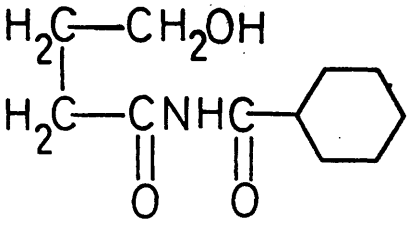

CXLV

EXPERIMENTAL SECTION.

General Procedures.

Melting points were determined on a Kofler hot stage, and are uncorrected.

Infra-red spectra were recorded on a Unicam S.P. 200 instrument, and proton magnetic ressonacne spectra on Perkin Elmer R10 and Varian Associates HA-100 spectrometers, in deuterochloroform solution, using tetramethylsilane as internal reference, the positions of signals being recorded here as τ values.

Analyses were performed by Mr. J. M. L. Cameron and his associates.

Thin layer chromatography (t.l.c.) was carried out on plates prepared with Kieselgel G (Merck), staining being accomplished in iodine vapour.

Hydrogenations in ethyl acetate were performed using AnaLaR grade solvent, at room temperature in a sloping manifold hydrogenator, pressure being maintained at, or slightly above, atmospheric, and volumes being recorded at r.t.p. Two batches of Adams' platinum oxide, one supplied by Engelhard Industries Ltd, Baker Platinum Division, 52 High Holborn, London, W.C.1., and the other by Johnson Matthey & Co. Ltd, 73/83 Hatton Garden, London, E.C.1., were employed. In the account of experimental details which follows, "platinum oxide" will refer to the former batch of catalyst, the latter being referred to as Johnson Matthey platinum oxide. 10% palladium on carbon was supplied by Engelhard Industries Ltd.

Light petroleum refers to the fraction b.p. 60-80° unless otherwise stated.

Hydrogenation of phthalimide.

Phthalimide (1.0g.) which had been crystallised to m.p. 238° from ethanol was hydrogenated in ethyl acetate (100ml.) in presence of Adams' platinum oxide (0.31g.). When absorption was complete, 560ml. of hydrogen (corresponding to 3 moles per mole of phthalimide) had been taken up. T.l.c. of the resulting product in 40% ethyl acetate/light petroleum indicated the presence of a single component. After filtration of the catalyst and evaporation of solvent, crystallisation from ethyl acetate gave hexahydrophthalimide (0.8g.) m.p. 135-136°.

Hydrogenation of succinimide.

Succinimide (0.5g.), crystallised from ethanol to m.p. 125°, was hydrogenated in ethyl acetate (30ml.) over platinum oxide catalyst (0.2g.). After 24 hr, only 35ml. of hydrogen, corresponding to the volume required for reduction of the catalyst, had been taken up. Succinimide was recovered quantitatively from the reaction mixture.

Hydrogenation of N-methyl phthalimide.

The starting material was prepared as follows. (c.f. ref. 153.) Powdered phthalic anhydride (12.0g.) was added to 25% aqueous methylamine (40ml.) with shaking so that complete dissolution occurred, and this solution was then heated for 15 min. on the steam bath. Most of the water was removed from the resulting solution by distillation at the water pump, and

the remainder removed by azeotropic distillation with benzene. The residual dry solid was powdered and heated under vaccuum at the water pump in a flask set up for distillation until a clear melt was obtained with evolution of water and methylamine, heating being continued until the resulting liquid was just about to distil. The flask was then allowed to cool, whereupon the product solidified to a crystalline mass which, on crystallisation from methanol, had m.p. 135° (8.2g.). Hydrogenation of this material (1.0g.) in ethyl acetate (100ml.) over platinum oxide catalyst (0.3g.) was complete in 8-10 hr, no further uptake being observed on leaving for an additional 24 hr. 510ml. of hydrogen (corresponding to 3 moles per mole of N-methyl phthalimide) were taken up. T.l.c. in 40% ethyl acetate/light petroleum indicated the presence of one major product and traces of two polar products. Filtration of catalyst and evaporation of solvent gave an oil whose i.r. spectrum (liquid film) showed no significant absorption in the hydroxyl region, absorption in the carbonyl region very similar to that of the starting material and strong, sharp bands at 2950 and 2875cm.$^{-1}$ (aliphatic C-H str.). The product solidified only after seeding, or on purification by distillation under reduced pressure. The crystalline material obtained on seeding had m.p. 48-50° without further purification. c.f. lit. m.p. for hexahydro-N-methyl phthalimide, 50-51°(153); 47-48°(154).

Hydrogenation of N-acetyl phthalimide.

The starting material was prepared according to the method

of Aschan,[155] by acetylation of phthalimide in refluxing acetic anhydride, and crystallised from ethanol to m.p. 133-134°. On hydrogenation of this material (1.0g.) in ethyl acetate (100ml.) over platinum oxide (0.30g.), absorption of hydrogen (approx. 600ml.) was virtually complete within 8 hr, after which there was little additional uptake of hydrogen, the volume recorded after 24 hr being 620ml., which corresponds to about 4¼ moles per mole of substrate. T.l.c. of the product in 40% ethyl acetate/light petroleum indicated the presence of four components; two principal products, of which one was in excess, and two very minor, polar products. Filtration of the catalyst and evaporation of solvent gave a cloudy, viscous oil which solidified on standing. The i.r. spectrum of the solid (nujol) showed strong absorption at 3370 (broad), 1730 and 1680cm.$^{-1}$. The components of the mixture were separated by chromatography over silica gel (40g.).

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 10% ethyl acetate/benzene.	0.62g.	Crystallised from light petroleum. Initially deposited as white crystals, but gave large clear prisms, m.p. 81°, on standing for a few days under solvent. Both forms identical by m.p., i.r. and n.m.r.
(ii) 12% ethyl acet-	0.17g.	Crystallised from ethyl

ate benzene		acetate to m.p. 136°.
(iii) 100% ethyl acetate.	0.03g.	This was a mixture containing the two minor components and some of the previous component (t.l.c.). It was not examined further.

It was found on repeating this hydrogenation that the main components could be readily separated by extraction of the major component from the hydrogenation mixture with boiling light petroleum, from which it crystallised on cooling. Crystallisation of the light petroleum-insoluble residue from ethyl acetate gave the second main component free of the minor products.

(i) This was found to be hexahydro-N-acetylhydroxyphthalimidine.

Found, C, 60.78; H, 7.37%.

$C_{10}H_{15}NO_3$ requires C, 60.89; H, 7.67%.

i.r. (nujol, cm^{-1}). 3450(s.); 1748(s.); 1693(s.).

n.m.r. (60Mc/s). 7.5-9.1 (m.,9H); 7.45 (s.,3H); 6.92 (m.,1H);
6.01 (d., J=3c/s.,1H; lost on D_2O equil.);
4.51 (d., J=3c/s.,1H; s. on D_2O equil.).

The n.m.r. spectrum at 100Mc/s. showed very clearly absorption due to two protons in the region 7.5-8.0 . The absorption at 8.05-9.1 (the other seven cyclohexane protons) was resolved into two broad, overlapping bands (axial and equatorial protons).

(ii) Mixed m.p. and i.r. comparison with an authentic sample showed this to be hexahydrophthalimide.

Acetylation of hexahydro-N-acetylhydroxyphthalimidine.

The above compound (0.11g.) was heated at reflux for 1 hr with acetic anhydride (0.10g.) in pyridine (1ml.). Cooling of the reaction mixture followed by addition of water (10ml.) resulted in precipitation of a crystalline product (0.09g.) which, on recrystallisation from light petroleum gave clear tablets of hexahydro-N-acetylacetoxyphthalimidine, m.p. 106°.

Found, C, 60.42; H, 7.14%.

$C_{12}H_{17}NO_4$ requires C, 60.24; H, 7.16%.

i.r. (nujol, $cm.^{-1}$). Max. at 1706 with shoulders due to other peaks at higher frequencies. Band centred at 1722.

n.m.r. (60Mc/s). 7.5-9.1 (m.,9H); 7.93 (s.,3H); 7.43 (s.,3H); 7.00 (m.,1H); 3.60 (s.,1H).

Preparation of N-carboethoxy phthalimide.

This material was prepared according to the method of Putokhin[156] by reaction of potassium phthalimide with ethyl chloroformate in refluxing benzene, and crystallised from acetone to m.p. 86°.

Hydrogenation of N-carboethoxy phthalimide.

N-carboethoxy phthalimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over platinum oxide (0.3g.). After 24 hr, 560ml. of hydrogen (corresponding to about 4 moles per mole of substrate) had been absorbed. T.l.c. of the resulting solution in 40% ethyl acetate/light petroleum indicated the presence of two products, the more polar of these being in very minor amount. (On some occasions on repeating this hydrogenation,

two additional very faint spots arising from material less polar than the main product could be detected on t.l.c.) On removal of the catalyst and evaporation of solvent, there was obtained a cloudy, viscous oil which could not be persuaded to crystallise or solidify, and so was chromatographed over silica gel (40g.). The major product, hexahydro-N-carboethoxyhydroxyphthalimidine, (0.71g.) was thus obtained as a clear colourless oil on elution with 10% ethyl acetate/benzene.

Found, C, 57.19; H, 7.59%.

$C_{11}H_{17}NO_4$ requires C, 58.13; H, 7.54%.

Carbon analyses for this compound were consistently about 1% low in several determinations. T.l.c. of the material obtained on attempted purification by distillation on the sublimation block at 85°/0.05m.m.Hg showed two additional faint less polar components, indicating that some decomposition was taking place under these conditions. Physical data are therefore recorded for the product obtained by chromatography.

i.r. (liquid film, $cm.^{-1}$) 3490 (m.); 1785, 1725 (str. br. overlapping peaks).

n.m.r. (60Mc/s). 7.5-9.1 (m.,9H); 8.65 (t., J=7c/s.,3H); 7.01 (m.,1H); 5.71 (quartet, J=7c/s.,2H); 5.09 (d., J=3c/s.,1H; lost on D_2O equil.); 4.72 (d., J=3c/s.,1H; s. on D_2O equil.).

The minor product (20mg.) was obtained as an oil which solidified on standing, and the i.r. and n.m.r. spectra were run directly on the material obtained by chromatography. Although

it appeared as practically a single spot on t.l.c., the n.m.r. spectrum suggested that there was more than one component present.

i.r. (liquid film, $cm.^{-1}$) Hydroxyl region - broad unsymmetrical peak with max. at 3260 (s.).
2900 (s.); 2840 (s.) - aliphatic C-H str.
Carbonyl region - 1775 (v.s.); 1700 (s.) - broad overlapping peaks.

n.m.r. (60Mc/s) 7.6-9.2 (m.); 8.69 (t., J=7.2c/s.); 8.73 (centre peak of second triplet?); 6.2-6.5 (m.); 5.72 (quartet, J=7.2c/s.); 2.0 (s.,v.br.).

Acetylation of hexahydro-N-carboethoxyhydroxyphthalimidine.

This compound (200mg.) was refluxed with acetic anhydride (250mg.) in pyridine (1ml.) for 2 hr, whereupon cooling and addition of water gave a white crystalline precipitate (180mg.) of a product which on crystallisation from light petroleum gave long clear needles of hexahydro-N-carboethoxyacetoxy-phthalimidine, m.p. 115°.

Found, C, 58.25; H, 6.89%.

$C_{13}H_{19}NO_5$ requires C, 57.98; H, 7.11%.

i.r. (nujol, $cm.^{-1}$) 1788 (s.); 1736 (s.).

n.m.r. (60Mc/s) 7.5-9.1 (m.,9H); 8.66 (t., J=7.2c/s.,3H); 7.93 (s.,3H); 7.06 (m.,1H); 5.60 (quartet, J=7.2c/s.,2H); 3.60 (s.,1H).

Hydrogenation of N-carboethoxy phthalimide.

Acetylation of the total product.

The mixture obtained on hydrogenation of N-carboethoxy phthalimide (3.0g.) under the same conditions as before was acetylated by refluxing with acetic anhydride (3.5g.) in pyridine (10ml.). Cooling and addition of water gave hexahydro-N-carboethoxyacetoxyphthalimidine (2.80g.) which appeared uniform on t.l.c. in 25% ethyl acetate/light petroleum. However, t.l.c. of the mother liquors remaining after crystallisation of this material from light petroleum indicated the presence of some product slightly more polar than the major one. Acidification with dilute sulphuric acid and extraction of the aqueous solution remaining from the acetylation reaction with ether gave an oil which also contained some of this minor product. Combination of this with the mother liquors from crystallisation of the main product gave about 200mg. of oil which appeared from t.l.c. to contain about 25-30% of the more polar product. The oil was chromatographed over silica gel (10g.), being eluted successively with solvent increasing in polarity from 2% to 5% ethyl acetate in benzene, and this gave a fraction which from t.l.c. consisted almost entirely of the more polar product (35mg.). The n.m.r. spectrum (60Mc/s) of this material, however, indicated that it was a mixture of two products.

7.6-9.0 (m.) —— cyclohexane protons.

8.68 (t., J=7c/s.) —— $-CH_3$ of carboethoxy group.

7.97 (s.) —— $-CH_3$ of O-acetate.

7.57 (s.) —— imide N-acetate?

5.72 (quartet, J=7c/s; superimposed on other absorption)

—— $-CH_2-$ of carboethoxy group.

1.93 (s., br.) —— imide NH.

Preparation of N-carbomethoxy phthalimide.

This material was prepared according to the method of Nefkens, Tesser and Nivard[157] by reaction of potassium phthalimide with methyl chloroformate in dimethylformamide, the product being isolated by precipitation with water. On crystallisation from dimethylformamide/methanol, it had m.p. 184°.

Hydrogenation of N-carbomethoxy phthalimide.

N-carbomethoxy phthalimide (1.0g.) in ethyl acetate (100ml.) was hydrogenated over platinum oxide (0.3g.). Since the starting material was rather insoluble in ethyl acetate, the reaction mixture was heated initially to about 50° in a water bath. After 24 hr, 550 ml. of hydrogen (equivalent to about four moles per mole of substrate) had been absorbed. T.l.c. of the resulting mixture in ethyl acetate indicated the presence of one major and two very minor products, one less polar and the other more polar than the main product. On removal of the catalyst, and evaporation of the solvent to smaller bulk, the principal product, hexahydro-N-carbomethoxyhydroxyphthalimidine, crystallised on standing (0.8g., m.p. 105°).

Found, C, 56.62; H, 7.38%.

$C_{10}H_{15}NO_4$ requires C, 56.32; H, 7.09%.

i.r. (nujol, $cm.^{-1}$) 3495 (m.); 1780 (v.s.); 1697 (w.).

n.m.r. (100Mc/s) 8.04-9.16 (m.,7H); 7.5-8.0 (m.,2H); 7.06 (m.,1H); 6.20 (s.,3H); 6.04 (d., J=3.5c/s.,1H; lost on D_2O equil.); 4.78 (d., J=3.5c/s.,1H; s. on D_2O equil.).

Preparation of N-dimethylcarbamoyl phthalimide.

Powdered dimethylurea (3.2g.) was suspended in pyridine (15ml.), and phthaloyl chloride (7.7g.) added dropwise with cooling in ice. The resulting mixture was left 24 hr at room temperature, then stirred into a large excess of water (250ml.), whereupon a reddish-brown oil, which soon crystallised giving discoloured flakes, precipitated out. This was crystallised from ethyl acetate, several decolourisations with animal charcoal being necessary to remove a persistant pale yellow colouration, before N-dimethylcarbamoyl phthalimide was finally obtained as lustrous white leaflets, m.p. 158° (5.60g.).

Found, C, 60.33; H, 4.64%.

$C_{11}H_{10}N_2O_3$ requires C, 60.54; H, 4.62%.

i.r. (nujol, $cm.^{-1}$) 1794 (w.); 1767 (w.); 1736 (d.); 1675 (s.); 1614 (w.); 723 (m.); 705 (m.).

n.m.r. (60Mc/s) 6.95 (s.,3H); 6.82 (s.,3H); 2.08 (m., AA'BB' system, 4H).

Hydrogenation of N-dimethylcarbamoyl phthalimide.

N-dimethylcarbamoyl phthalimide (1.0g.) in ethyl acetate (100ml.) was hydrogenated over platinum oxide (0.3g.). After

24 hr, 505ml. of hydrogen (equivalent to rather less than four moles per mole of substrate) had been absorbed. T.l.c. in 60% ethyl acetate/light petroleum indicated the presence of two major components, and one or possibly two very minor polar components. This mixture was chromatographed over silica gel, whence the two main products were obtained. The minor products were not examined further, only traces of material containing them being obtained.

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 10% ethyl acetate/benzene.	0.21g.	On crystallisation from benzene/light petroleum gave lustrous white leaflets of hexahydro-N-dimethylcarbamoyl phthalimide, m.p. 114-114.5°. Found, C, 59.16; H, 7.08%. $C_{11}H_{16}N_2O_3$ requires C, 58.91; H, 7.19%.
(ii) 12-15% ethyl acetate/benzene.	0.75g.	Viscous oil which was finally persuaded to solidify. On crystallisation from light petroleum, seeding with some solid material being required, small white prisms of hexahydro-N-dimethylcarbamoylhydroxyphthalimidine, (m.p. 95-97°) were obtained.

Found, C, 58.20; H, 7.91%.

$C_{11}H_{18}N_2O_3$ requires C, 58.39; H, 8.02%.

The physical data obtained on these products were as follows:-

(i) i.r. (nujol, $cm.^{-1}$) 1725 (s.); 1701 (s.); shoulders to both higher and lower frequencies.

n.m.r.'(60Mc/s) 7.9-8.8 (m., two humps centred at 8.15 and 8.48; 4H + 4H); 7.07 (s.,3H); 6.90 (s.,3H). The latter two peaks were superimposed on absorption arising from a further two protons.

(ii) i.r. (nujol, $cm.^{-1}$) 3350 (s.); 1679 (v.s.) with shoulders to higher frequency.

n.m.r. (60Mc/s) 7.5-9.2 (m.,9H); 7.00 (s.,6H; broadened at base due to superposition on absorption due to a further proton.); 5.21 (s., br.,1H; lost on D_2O equil.); 4.84 (s.,1H).

Preparation of N-acetyl succinimide.

The required material was obtained by treatment of succinimide with acetic anhydride, and fractional distillation, according to the method of Tafel and Stern.[158] Thus obtained, it contained a little succinimide (less than 5% as judged by integration of the n.m.r. spectrum), but was used as such in the subsequent investigation.

Hydrogenation of N-acetyl succinimide.

N-acetyl succinimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over platinum oxide (0.33g.). After 24 hr, 397ml.

of hydrogen, corresponding to about two moles hydrogen per mole of substrate, had been absorbed. T.l.c. of the product in ethyl acetate indicated the presence of a principal component with the same Rf as succinimide and small quantities of one less polar and three more polar products, two of the latter being only in trace amounts. Crystallisation of this mixture from ethyl acetate gave succinimide (0.36g.). T.l.c. of the residue showed that succinimide was still the main component, and in addition, a tail was now evident in the spot corresponding to the principal of the more polar products. The mixture was at this stage chromatographed over silica gel.

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 50% ethyl acetate/benzene.	60mg.	Contained least polar component + succinimide. Examined by n.m.r.
(ii) 50-80% ethyl acetate/benzene.	140mg.	Succinimide; m.p. 125° on crystallisation from ethyl acetate.
(iii) 100% ethyl acetate.	30mg.	Contained the most polar components + a little succinimide. Examined by n.m.r.

n.m.r. spectra (60Mc/s).

(i) 7-8 (m.; signals due to individual protons, or groups of protons, indistinguishable.);

7.48 (s.; peak, by integration, more intense than would account for the presence of only N-acetyl-5-hydroxy-

2-pyrrolidone, suggesting the presence of some other product containing the N-Ac grouping.);

7.23 (s.; succinimide $-CH_2-$); 5.63 (t., J=7c/s); 4.10 (d.d., J_1=5.6c/s; J_2=2.8c/s); 2.85 (s., br.; succinimide NH).

(iii) 7.1-8.2 (m.; signals due to individual protons, or groups of protons, indistinguishable.); 7.98 (s.); 7.64 (s.); 7.24 (s.; succinimide $-CH_2-$); 6.28 (t., J=6c/s); 5.61 (t., J=7c/s); 4.0 (s., v. br.); 0.25 (s., br.).

Preparation of N-carboethoxy succinimide.

This material was prepared by reaction of ethyl chloroformate with potassium succinimide in refluxing benzene, according to the method of Heller and Jacobsohn,[159] and crystallised from ether/light petroleum (b.p. 40-60°) to m.p. 50-51°.

Hydrogenation of N-carboethoxy succinimide.

N-carboethoxy succinimide (2.0g.) was hydrogenated in ethyl acetate (100ml.) in presence of platinum oxide (0.3g.). Hydrogenation was almost complete after 24 hr, and after 48 hr, 625 ml. of hydrogen (corresponding to two moles of hydrogen per mole of substrate) had been taken up. T.l.c. of the product in 60% ethyl acetate/light petroleum indicated the presence of practically a single component with a very minor by-product of slightly lower polarity. Crystallisation from ethyl acetate/light petroleum gave the major product, $HO(CH_2)_3CONHCOEt$, as long, white soft needles, m.p. 71-72° (1.7g.).

Found, C, 48.20; H, 7.30%.

$C_7H_{13}NO_4$ requires C, 47.99; H, 7.48%.

i.r. (nujol, $cm.^{-1}$) 3275 (with shoulder to higher frequency); 3205 (m.); 1753 (s.s.); 1690 (v.w.).

n.m.r. (60Mc/s) 8.70 (t., J=7.2c/s.,3H); 8.08 (quintet, J=6.6c/s.,2H); 7.17 (t., J=6.6c/s.,2H), superimposed on absorption at 7.05 (1H; lost on D_2O equil.); 6.29 (t., J=6.6c/s.,2H; peaks broad at base, but sharpened on D_2O equil.); 5.77 (quartet, J=7.2c/s.,2H); 1.48 (s., br., 1H; lost on D_{20} equil.).

Preparation of N-benzoyl phthalimide, N-benzoyl succinimide and N-hexahydrobenzoyl phthalimide.

The N-benzoyl derivatives were prepared by reaction of benzoyl chloride with phthalimide and succinimide in pyridine, according to the method of Titherley.[160,161] N-hexahydrobenzoyl phthalimide was prepared similarly. Thus, hexahydrobenzoyl chloride (4.0g.) was added dropwise with cooling in ice to a suspension of phthalimide (4.0g.) in pyridine (12ml.) and the mixture left overnight at room temperature. Ethanol (15ml.) was added to the solid product and the mixture stirred and cooled in ice. The resulting crystalline material (4.5g., m.p. 112-113°) was filtered off, washed once with cold ethanol, and after a single recrystallisation from the same solvent gave N-hexahydrobenzoyl phthalimide as fine white needles, m.p. 112.5-113.5°.

Found, C, 69.93; H, 6.02%.

$C_{15}H_{15}NO_3$ requires C, 70.02; H, 5.88%.

i.r. (nujol, $cm.^{-1}$) 1790 (m.); 1765 (w.); 1736 (s.); 1705 (m.); 1608 (v.w.).

The pattern of peaks in the carbonyl region was very similar to that of N-benzoyl phthalimide.

Hydrogenation of N-benzoyl phthalimide.

N-benzoyl phthalimide (1.0g.) was hydrogenated in ethyl acetate (50ml.) over platinum oxide (0.3g.). 830ml. of hydrogen, corresponding to about $7\frac{1}{2}$ moles per mole of substrate, were absorbed during 36 hr. T.l.c. of the product in 40% ethyl acetate/light petroleum indicated the presence of two principal components, the more polar of which had the same Rf as hexahydrophthalimide, and traces of a further three components, one less polar, and two more polar than the principal ones. On removal of catalyst and solvent, a very characteristic odour, arising from cyclohexylcarbinol, could be detected. The mixture was subjected to column chromatography over silica gel (40g.).

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 0-6% ethyl acetate-benzene.	0.59g.	The odour of cyclohexylcarbinol was readily detected in these fractions. After extraction with cold light petroleum (b.p. 40-60°), the residue was crystallised

		from light petroleum to give a white product m.p. 118-120°.
(ii) 10-15% ethyl acetate/benzene.	0.27g.	Crystallised from ethyl acetate to m.p. 136°. Direct comparison with an authentic sample showed this to be hexahydrophthalimide.

The minor products were not investigated, elution with ethyl acetate giving 30mg. of a mixture of these along with some hexahydrophthalimide. The crystalline product obtained in (i) was hexahydro-N-hexahydrobenzoylhydroxyphthalimidine.

Found, C, 67.87; H, 8.82%.

$C_{15}H_{23}NO_3$ requires C, 67.89; H, 8.74%.

i.r. (nujol, $cm.^{-1}$) 3480 (m.); 1746 (s.); 1678 (s.).

n.m.r. (60Mc/s) 7.50-9.10 (m.,9H); 6.97 (m.,1H); 6.50 (m.,1H); 6.05 (d., J=3c/s.,1H; lost on D_2O equil.); 4.60 (d., J=3c/s.,1H; s. on D_2O equil.).

A pure sample of cyclohexylcarbinol was obtained from the light petroleum extract from (i) above. Small amounts of the hexahydrohydroxyphthalimidine were removed from the extract by heating the oil remaining after evaporation of the light petroleum with dilute sodium hydroxide for 1-2 hr on the steam bath, followed by extraction of the cyclohexylcarbinol into ether, drying of the ether extract over magnesium sulphate, filtration, evaporation of the solvent, and distillation of

the resulting yellowish oil on the sublimation block at 180-190° and atmospheric pressure. Cyclohexylcarbinol was thus obtained as a clear, colourless oil with a characteristic persistant odour. The i.r. spectrum (liquid film) showed a strong, broad peak at 3390cm.$^{-1}$ due to the hydroxyl group, and a strong peak at 1040cm.$^{-1}$ (C-O str.). Other main peaks were at 2930 and 2870cm.$^{-1}$ (aliphatic C-H str.) and 1460cm.$^{-1}$ ($-CH_2-$ def.). The identity of this product was confirmed by conversion to the α-naphthylurethane, m.p. 109.5-110° from ethanol.

Hydrogenation of N-hexahydrobenzoyl phthalimide.

N-hexahydrobenzoyl phthalimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over platinum oxide (0.3g.). After 24 hr, 500ml. of hydrogen, corresponding to about 4½ moles per mole of substrate, had been absorbed. T.l.c. of the resulting mixture in 40% ethyl acetate/light petroleum indicated the presence of the same two principal products as were obtained in the previous hydrogenation, plus a trace of a less polar component. More polar by-products could not however be detected in this case. On evaporation of the solvent, the characteristic odour of cyclohexylcarbinol was evident, and the resulting oil was subjected to column chromatography as before.

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 0-8% ethyl acetate/benzene.	0.73g.	Crystallised from light petroleum to m.p. 118-120° after extraction of cyclohexylcarbinol as above.

(ii)	10-15% ethyl acetate/benzene.	0.24g.	Crystallised from ethyl acetate to m.p. 137°.

Direct comparison showed that, as expected, these were the same products as had been obtained in the previous hydrogenation.

Hydrogenation of N-benzoyl succinimide.

N-benzoyl succinimide (1.60g.) was hydrogenated in ethyl acetate (100ml.) over platinum oxide (0.40g.). After 24 hr, 1,024ml. of hydrogen (somewhat less than five moles per mole of substrate had been absorbed. T.l.c. of the product in 40% ethyl acetate/light petroleum showed, in addition to the main product, which had the same Rf as succinimide, two faint diffuse spots arising from less polar components. On filtration of catalyst and evaporation of solvent, the characteristic odour of cyclohexylcarbinol was evident. This was removed by extraction with cold light petroleum (b.p. 40-60°), being obtained as a pale yellow oil (0.77g.) on evaporation of the solvent. This crude product showed some absorption in the carbonyl region in the i.r. spectrum, but a pure sample of the alcohol was obtained, as in the case of N-benzoyl phthalimide, by by heating with aqueous sodium hydroxide, ether extraction, and distillation. The solid residue remaining after light petroleum extraction (0.74g.) on crystallisation from ethyl acetate first deposited succinimide (m.p. 125°, i.r. identical with that of an authentic sample), then, in later fractions, a few clear prisms of a further product. By fractional crystallisation from ethyl acetate, there was finally obtained

0.54g. pure succinimide, and 52mg. of the minor product, cyclohexanecarboxylic acid amide (clear, thin rectangular prisms), which had m.p. 186-188° with volatilisation, and in its i.r. spectrum (nujol), peaks at 3410 (m.), 3250 (m.) and 1640cm.$^{-1}$ (s., br.). Admixture with an authentic sample of the amide, prepared by reaction of hexahydrobenzoyl chloride with concentrated aqueous ammonia, did not depress the m.p.

Partial hydrogenation of N-acetyl phthalimide.

N-acetyl phthalimide (1.0g.) in ethyl acetate (100ml.) was hydrogenated over platinum oxide (0.2g.), the reaction being stopped when 420ml. of hydrogen (corresponding to about three moles per mole of substrate) had been absorbed. On t.l.c. of the reaction mixture in 40% ethyl acetate/light petroleum, a spot with the same Rf as hyeahydro-N-acetylhydroxyphthalimidine was observed, but no less polar product could be detected. On crystallisation of this mixture from ethyl acetate/light petroleum, there was first deposited practically pure hexahydro-N-acetylhydroxyphthalimidine (0.28g.), identified by i.r., n.m.r. and mixed melting point comparison with an authentic sample, followed by clear needles of a second component, N-acetylhydroxyphthalimidine, which, on crystallisation from ethyl acetate, had m.p. 162° (0.16g.).

Found, C, 62.50; H, 4.58%.

$C_{10}H_9NO_3$ requires C, 62.82; H, 4.75%.

i.r. (nujol, cm.$^{-1}$) 3475 (m.); 1721 (v.s.); 1691 (v.s.); 1616 (w.); 759 (s.); 703 (m.).

n.m.r. (60Mc/s) 7.35 (s.,3H); 5.29 (d., J=3.6c/s.,1H; lost on D_2O equil.); 3.44 (d., J=3.6c/s.,1H; s. on D_2O equil.); 2.0-2.6 (m., main peak at 2.30; 4H.).

The preparation of this compound by another route has been reported recently.[162]

Evaporation of the mother liquors remaining from these crystallisations gave a solid residue, which, after extraction with boiling light petroleum, and crystallisation from ethyl acetate, gave a product m.p. 135-136° (0.07g.), shown to be hexahydrophthalimide by direct comparison with an authentic sample.

Preparation of hexahydro-N-acetyl phthalimide.

Hexahydrophthalimide (3.0g.) was refluxed for 16 hr in acetic anhydride (15ml.) followed by distillation of most of the solvent. As no product crystallised on cooling the residue, this was taken up in chloroform and shaken with water until no further reaction was observed on addition of small quantities of sodium bicarbonate to the aqueous layer. The chloroform layer was separated and dried over magnesium sulphate. T.l.c. of this solution in 40% ethyl acetate/light petroleum indicated the presence of practically a single product. Evaporation of the chloroform left a clear, yellow oil, which, after several recrystallisations from ethyl acetate/light petroleum gave long white needles of hexahydro-N-acetyl phthalimide, m.p. 69° (0.9g.).

Found, C, 61.49; H, 6.60%.

$C_{10}H_{13}NO_3$ requires C, 61.52; H, 6.71%.

i.r. (nujol, $cm.^{-1}$) 1795 (s.,sh.); 1754 (v.s.); 1707 (s.,sh.). Pattern of peaks was very similar to that for the carbonyl region of N-acetyl phthalimide for which the central peak was however split.

Hydrogenation of hexahydro-N-acetyl phthalimide.

Hexahydro-N-acetyl phthalimide (0.5g.) in ethyl acetate (25ml.) was hydrogenated over platinum oxide (0.17g.). 102ml. of hydrogen, corresponding to one mole per mole of substrate, were absorbed. T.l.c. of the product in 40% ethyl acetate/light petroleum indicated the presence of two principal components and traces of two polar products. Evaporation of the solvent and extraction of the residue with boiling light petroleum gave a very clean separation of the two principal components as indicated by t.l.c. The light petroleum soluble fraction (0.33g.) on crystallisation gave hexahydro-N-acetyl-hydroxyphthalimidine, identical by i.r., n.m.r. and m.p. comparison with the product obtained on hydrogenation of N-acetyl-phthalimide. The light petroleum insoluble fraction (0.13g.) gave hexahydrophthalimide, m.p. 136°, on crystallisation from ethyl acetate.

Partial hydrogenation of N-carboethoxy phthalimide.

N-carboethoxy phthalimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over platinum oxide (0.13g.), hydrogenation being allowed to proceed until about 200ml. of hydrogen, cor-

responding to rather less than two moles per mole of substrate, had been taken up. T.l.c. of the resulting mixture in 40% ethyl acetate/light petroleum indicated apparently two products, the less polar of which had the same Rf as starting material, the more polar having an Rf similar to hexahydro-N-carboethoxyhydroxyphthalimidine. On closer examination, however, each spot was in turn seen to comprise two spots of very similar Rf. The mixture was separated into two main fractions by column chromatography over silica gel.

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 5% ethyl acetate/benzene.	450mg.	No absorption was observed in the hydroxyl region of the i.r. spectrum (liquid film). On dissolution in ethyl acetate, addition of light petroleum, and standing, a few crystals were deposited. On further crystallisation from ethyl acetate, this product had m.p. 82-84°, undepressed on admixture with N-carboethoxy phthalimide, and an i.r. spectrum superimposable on that of the latter. The residual oil from crystallis-

8% ethyl acetate/ benzene.	180mg.	ation was examined by n.m.r. Mixture containing all four components.
(ii) 10% ethyl acetate/benzene.	310mg.	The i.r. spectrum of this material (liquid film) showed absorption in the hydroxyl region at 3510cm.$^{-1}$, and a weak peak at 1623cm.$^{-1}$ (aromatic C=C). Treatment with ethyl acetate/light petroleum as for (i) above resulted in the deposition of a crystalline product, N-carboethoxyhydroxyphthalimidine, which, on recrystallisation from ethyl acetate, had m.p. 137°.

Found, C, 59.65; H, 5.02%.

$C_{11}H_{11}NO_4$ requires C, 59.72; H, 5.01%.

i.r. (nujol, cm.$^{-1}$) 3460 (s.); 1772 (v.s.); 1692 (w.); 1618 (w.); 702 (m.).

n.m.r. (60Mc/s) 8.61 (t., J=7.2c"s.,3H); 5.59 (quartet, J= 7.2c/s.,2H); 5.44 (d., J=4.2c/s.,1H; lost on D_2O equil.); 3.56 (d., J=4.2c/s.,1H; s. on D_2O equil.); 2.05-2.65 (m., main peak at 2.37, 4H).

The residue was examined by n.m.r.

n.m.r. spectra of the mixtures (60Mc/s).

(i) The n.m.r. spectrum indicated that this was a mixture of N-carboethoxy phthalimide, (i)a, and its hexahydro derivative, (i)b.

8.62 (t., J=7.2c/s) —— $-CH_3$ of carboethoxy group. (i)a.

8.56 (t., J=7.2c/s) —— $-CH_3$ of carboethoxy group. (i)b.

These peaks were superimposed on other absorption arising from the axial protons of the cyclohexane ring of (i)b.

7.9-8.3 (m.) —— equatorial protons of cyclohexane ring. (i)b.

7.01 (m.) —— ring junction protons. (i)b.

5.55 (quartet, J=7.2c/s) —— $-CH_2-$ of carboethoxy group. (i)b.

5.48 (quartet, J=7.2c/s) —— $-CH_2-$ of carboethoxy group. (i)a.

2.06 (m., AA'BB' system) —— aromatic protons. (i)a.

(11) The n.m.r. spectrum indicated that this mixture contained hexahydro-N-carboethoxyhydroxyphthalimidine, and N-carboethoxy-hydroxyphthalimidine.

Preparation of hexahydro-N-carboethoxy phthalimide.

A solution of potassium hydroxide (1.0g.) in absolute ethanol (10ml.) was added to hexahydrophthalimide (2.5g.) in the same solvent (20ml.). Since precipitation of the salt did not occur as was the case with potassium phthalimide,[163] benzene

was added to the solution obtained, and the solvent distilled to remove water, the remaining solvent being evaporated at the water pump. To ensure that all the ethanol had been removed, further quantities of dry benzene were added, followed by distillation at the water pump. The resulting gummy residue was refluxed for 6 hr with ethyl chloroformate (2.0g.) in dry benzene (30ml.), the solution filtered, and benzene evaporated to give a yellowish oil. Crystallisation was induced only with some difficulty from chloroform/light petroleum, and the product thus obtained (0.8g.) melted over a wide range commencing at about 47°. Further crystallisation did not lead to pronounced sharpening of the m.p., and t.l.c. of the crystalline product in 40% ethyl acetate/light petroleum showed that, in addition to the principal component, there were at least two more polar by-products present. This material was therefore chromatographed on silica gel, elution with 2-3% ethyl acetate/benzene giving the principal component free of these by-products. Crystallisation from light petroleum containing a little chloroform gave large, clear prisms of hexahydro-N-carboethoxy phthalimide (0.46g.), m.p. 71°.

Found, C, 58.30; H, 6.75%.

$C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.71%.

i.r. (nujol, $cm.^{-1}$) 1805 (s.); 1785 (v.s.); 1716 (s.).
Very similar pattern to that observed for N-carboethoxy phthalimide.

n.m.r. (60Mc/s) 8.60 (t., J=7.2c/s.,3H) —— $-CH_3$ of carbo-

ethoxy group.

Superimposed on other absorption due to cyclohexane protons (4H).

8.13 (m.,4H) —— equatorial methylene protons of cyclohexane ring.

7.02 (m.,2H) —— ring junction protons.

5.55 (quartet, J=7.2c/s.,2H) —— $-CH_2-$ of carboethoxy group.

Hydrogenation of hexahydro-N-carboethoxy phthalimide.

Hexahydro-N-carboethoxy phthalimide (0.25g.) in ethyl acetate (25ml.) was hydrogenated over platinum oxide (0.10g.). When absorption stopped, 47ml. of hydrogen (corresponding to one mole per mole of substrate) had been taken up. T.l.c. of the product in 40% ethyl acetate/light petroleum indicated the presence of practically a single product with the same Rf as the hexahydro-N-carboethoxyhydroxyphthalimidine obtained previously by hydrogenation of N-carboethoxy phthalimide, and only a faint trace of polar by-product. The identity of the principal product with the material obtained previously was shown by i.r. and n.m.r., and by conversion to the crystalline acetate (m.p. 114-115° from light petroleum).

Preparation of N-carboethoxyhydroxyphthalimidine.

N-carboethoxy phthalimide (1.5g.) in dry ethanol (50ml.) was hydrogenated over 10% palladium on carbon (1.0g.). Hydrogenation was stopped after 10 hr when 180ml. of hydrogen (corresponding to one mole per mole of substrate) had been taken

up. T.l.c. of the resulting product in 40% ethyl acetate/ light petroleum indicated the presence of a single component. On filtration of the catalyst, evaporation of solvent, and crystallisation of the residue from ethyl acetate N-carboethoxy-hydroxyphthalimidine was obtained (1.20g., m.p. 137°). The hydrogenation over 10% palladium on carbon in ethyl acetate proceeded similarly, although somewhat more slowly, one mole of hydrogen being absorbed in 16 hr. Prolonging the time of hydrogenation in either solvent led to the slow absorption of more hydrogen; e.g. N-carboethoxyhydroxyphthalimidine (0.55g.) in dry ethanol (30ml.) on hydrogenation for two days in presence of 10% palladium on carbon (0.55g.) absorbed 50ml. of hydrogen (less than one mole per mole of substrate). T.l.c. in 40% ethyl acetate/light petroleum indicated the presence of two components, the more polar of which had the same Rf as the starting material. Evaporation of the solvent gave an oil which solidified on standing, and extraction of this solid with boiling light petroleum removed mainly the less polar product. This was not purified, but the n.m.r. spectrum of the extract indicated that the less polar component was N-carboethoxy phthalimidine.

n.m.r. (60Mc/s) 8.60 (t., J=7.2c/s) —— $-CH_3$ of carboethoxy group.

5.59 (quartet, J=7.2c/s) —— $-CH_2$ of carboethoxy group.

5.56 (quartet, J=7.2c/s) —— $-CH_2$ of carbo-

ethoxy group of starting material.

5.18 (s.) —— $-CH_2-$ of phthalimidine.

3.50 (s.) —— -CHOH (starting material).

2.0-2.6 (m.) —— aromatic protons.

Hydrogenation of N-carboethoxyhydroxyphthalimidine.

N-carboethoxyhydroxyphthalimidine (0.3g.) in ethyl acetate (25ml.) was hydrogenated over platinum oxide (0.1g.). On completion of reaction, 108ml. of hydrogen (corresponding to three moles per mple of substrate) had been absorbed. T.l.c. of the product in 40% ethyl acetate/light petroleum indicated the presence of one principal component and two very minor products, one less polar and one more polar than the main product. The Rf, i.r. and n.m.r. of the main product showed that it was identical with the hexahydro-N-carboethoxyhydroxyphthalimidine obtained previously. This was further confirmed by conversion to the acetate in refluxing acetic anhydride-pyridine, the derivative being found to have identical m.p. (114.5-115°) and mixed m.p. with the acetate of the material obtained by hydrogenation of hexahydro-N-carboethoxy phthalimide.

Preparation of N-acetylhydroxyphthalimidine.

N-acetyl phthalimide (1.0g.) in dry ethanol (100ml.) was hydrogenated over 10% palladium on carbon (0.5g.). After 6 hr, 100ml. and 24 hr, 155ml. of hydrogen (corresponding to rather more than one mole per mole of substrate) had been taken up. Filtration of catalyst, evaporation of solvent and crystallisation of the residue from ethyl acetate gave N-acetylhydroxy-

phthalimidine (0.70g.), m.p. 162°.

Preparation of N-carbomethoxyhydroxyphthalimidine.

N-carbomethoxy phthalimide (1.0g.) in dry ethanol (100ml.) was hydrogenated in presence of 10% palladium on carbon (0.5g.). The reaction mixture was heated initially on a water bath at 50° to keep the starting material in solution. After 8 hr, 107ml. of hydrogen (rather less than one mole per mole of substrate) had been absorbed. Filtration of the catalyst, evaporation of the solvent and crystallisation of the residue from ethyl acetate gave N-carbomethoxyhydroxyphthalimidine (0.6g.), m.p. 175-177°.

Found, C, 57.88; H, 4.51%.

$C_{10}H_9NO_4$ requires C, 57.97; H, 4.38%.

i.r. (nujol, $cm.^{-1}$) 3460 (s.); 1765 (v.s.); 1694 (w.); 1615 (w.); 708 (m.).

Since this product was insoluble in chloroform, the n.m.r. spectrum was not run.

Hydrogenation of hexahydro-N-dimethylcarbamoyl phthalimide.

Hexahydro-N-dimethylcarbamoyl phthalimide (0.1g.), obtained from the hydrogenation of N-dimethylcarbamoyl phthalimide, in ethyl acetate (25ml.) was hydrogenated in presence of platinum oxide (0.1g.). Hydrogenation was stopped after 16 hr when 29ml. of hydrogen had been absorbed. (Measurements of such small volumes were not very accurate.) T.l.c. in 60% ethyl acetate/light petroleum showed the presence of two components,

the less polar having the same Rf as starting material, and the more polar the same Rf as the hexahydro-N-dimethylcarbamoyl-hydroxyphthalimidine obtained previously. These were separated by column chromatography as before, and their constitution confirmed by direct comparison with the materials previously characterised.

'Hydrogenation of N-dimethylcarbamoyl phthalimide over Johnson Matthey catalyst.

(1) N-dimethylcarbamoyl phthalimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over Johnson Matthey platinum oxide (0.3g.). Hydrogenation initially appeared to occur fairly rapidly, then the rate slowed markedly, 280ml. of hydrogen (corresponding to about two moles per mole of substrate) being absorbed in 24 hr. T.l.c. of the reaction mixture in 60% ethyl acetate/light petroleum indicated the presence of one major product whose Rf was similar to that of hexahydro-N-dimethyl-carbamoylhydroxyphthalimidine, one (or possibly two) somewhat less polar product, a faint trace of a more polar product, and the absence of starting material. Crystallisation of the mixture from ethyl acetate gave the major product, N-dimethyl-carbamoylhydroxyphthalimidine, (0.42g.) as clear, stout needles m.p. 169-171°.

Found, C, 60.15; H, 5.37%.

$C_{11}H_{12}N_2O_3$ requires C, 59.99; H, 5.49%.

i.r. (nujol, $cm.^{-1}$) 3390 (m.); 1704 (s.); 1688 (s.(;
1619 (v.w.); 710 (m.).

n.m.r. (60Mc/s) 6.93 (s.,6H); 4.14 (d., J=6c/s.,1H; lost on D_2O equil.); 3.35 (d., J=6c/s.,1H; s. on D_2O equil.); 2.08-2.60 (m.,4H).

(2) This hydrogenation was repeated using the same quantities of materials and the Johnson Matthey catalyst, but the reaction was stopped when 185ml. of hydrogen (corresponding to about one mole per mole of substrate) had been absorbed, this requiring a period of 55 min. T.l.c. of the product in 60% ethyl acetate/light petroleum indicated the presence of one major and two minor, less polar components, these last having the same Rfs as starting material and its hexahydro derivative. Crystallisation from ethyl acetate gave the major product (0.65g., m.p. 169-171°). Examination of the residue by n.m.r. indicated the presence of the major product, starting material and the hexahydro derivative in the approximate ratio of 1:1:1. No significant quantity of the fully hydrogenated product, hexahydro-N-dimethylcarbamoylhydroxyphthalimidine was present, as judged from the absence of the low field signal at about 4.84τ. The ratios given above were obtained from the integration of the n.m.r. spectrum as follows:-

aromatic protons (2.0-2.6)/cyclohexane methylene protons (7.95-8.7) ≈ (starting material + N-dimethylcarbamoylhydroxyphthalimidine)/2 hexahydro-N-dimethylcarbamoyl phthalimide ≈ 1.

Area of peak at 7.06 ($N-CH_3$ of hexahydro derivative) ≈ area of peak at 6.84 and of peak at 6.96 ($N(CH_3)_2$ group of starting material).

The second N-CH_3 group of the hexahydro derivative lay under a singlet at 6.91τ due to the N$(CH_3)_2$ group of hexahydro-N-dimethylcarbamoylhydroxyphthalimidine.

Hydrogenation of N-acetyl phthalimide over Johnson Matthey catalyst.

(1) N-acetyl phthalimide (1.0g.) in ethyl acetate (100ml.) was hydrogenated over Johnson Matthey platinum oxide (0.3g.). After 24 hr, 510ml. of hydrogen (corresponding to less than four moles per mole of substrate) had been taken up. T.l.c. in 40% ethyl acetate/light petroleum indicated the presence of two main components, and a trace of polar material. The product obtained on removal of solvent and catalyst was extracted with boiling light petroleum, crystallisation of the extract giving a product (0.71g.) which melted over a range up to 80°. Further crystallisation from light petroleum raised the m.p. to 81°, and direct comparison with the material previously obtained showed this to be hexahydro-N-acetylhydroxyphthalimidine. The light petroleum-insoluble residue (0.16g.) on crystallisation from ethyl acetate gave material m.p. 162°, identical with N-acetylhydroxyphthalimidine.

(2) The hydrogenation was repeated as above, reaction being stopped when 200ml. of hydrogen (corresponding to about one mole per mole of substrate) had been absorbed, the required volume being taken up within 30 min. Crystallisation from ethyl acetate gave N-acetylhydroxyphthalimidine (0.55g., m.p. 162°).

Partial hydrogenation of N-carboethoxy phthalimide using Johnson Matthey catalyst.

N-carboethoxy phthalimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over Johnson Matthey platinum oxide (0.3g.), the reaction being stopped when 180ml. of hydrogen (corresponding to about one mole per mole of substrate) had been taken up. Absorption of the first 165ml. required 30-35 min, the total being taken up in 45 min. T.l.c. of the product in 40% ethyl acetate/light petroleum indicated the presence of one principal component, some material with the same Rf as the starting material, and a minor product (or products) of intermediate polarity. On removal of solvent and catalyst, and crystallisation from ethyl acetate, N-carboethoxyhydroxyphthalimidine (0.60g.; m.p. 137°) was obtained. The n.m.r. spectrum (60Mc/s) of the residue from this crystallisation indicated that this major product and starting material were the principal components still remaining, being accompanied by smaller quantities of the analogous compounds in which saturation of the benzene ring had occurred.

Preparation of N-pivaloyl succinimide.

Pivaloyl chloride (4.0g.) was added dropwise to succinimide (3.2g.) in pyridine (10ml.) with cooling in ice, and the resulting mixture left overnight at room temperature. Upon addition of water, an oil precipitated which solidified on standing. Crystallisation of this product from methanol gave large white flakes of N-pivaloyl succinimide (2.54g.) m.p. 100°.

Found, C, 58.91; H, 7.27%.

$C_9H_{13}NO_3$ requires C, 59.00; H, 7.15%.

i.r. (nujol, $cm.^{-1}$) 1792 (w.); 1733 (m.); 1706 (s.).

Hydrogenation of N-pivaloyl succinimide.

N-pivaloyl succinimide (1.0g.) in ethyl acetate (25ml.) was hydrogenated over platinum oxide (0.33g.). After 24 hr, 343ml. of hydrogen (corresponding to two moles per mole of substrate) had been taken up. T.l.c. of the resulting product in ethyl acetate showed the presence of practically a single component whose Rf was the same as that of succinimide. Traces of two more polar products could be detected on prolonged standing of the plate in iodine vapour. Careful distillation of the solvent (to minimise loss of the expected neopentyl alcohol) to small bulk, and cooling, led to crystallisation of succinimide (0.35g., m.p. 125°). Most of the remaining solvent was distilled from the mother liquors, heating being carried out on a water bath, to leave an oil which was treated with cold light petroleum (b.p. 40-60°), by which means, a further 0.13g. of succinimide was recovered. The oil remaining on evaporation of the light petroleum was distilled on the sublimation block at atmospheric pressure. The distilled product had the very characteristic odour of neopentyl alcohol, and its i.r. spectrum (liquid film) showed a strong, broad band in the hydroxyl region at 3450$cm.^{-1}$. It could not, however, be persuaded to solidify, and further, the i.r. spectrum showed weak absorption in the carbonyl region. In the course of the dis-

tillation, one or two very fine flat crystals formed in the sublimation tube just below the main distillate. On the Kofler block, this material volatilised without melting, between 125 and 145° on rapid heating before melting could be observed. This behaviour was very similar to that observed for pivalamide (see below).

'Preparation of N-pivaloyl phthalimide.

Pivaloyl chloride (4.0g.) was added dropwise, with cooling in ice, to a suspension of phthalimide (4.9g.) in pyridine (10ml.), and the mixture left overnight at room temperature. Addition of water precipitated the product as large, somewhat discoloured flakes, which could be crystallised, althougb only with some difficulty, from methanol. Deposition of phthalimide occurred if the product remained in methanol solution for any length of time. Subsequently, however, light petroleum was found to be a much more satisfactory solvent for purification of the product, N-pivaloyl phthalimide, which was thus obtained as large, clear flakes, m.p. 84.5-85° (5.4g.).

Found, C, 67.81: H, 5.59%.

$C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67%.

i.r. (nujol, $cm.^{-1}$) 1784 (s.); 1733 (v.s.); 1711 (v.s.); 1609 (v.w.); 728 (s.).

Hydrogenation of N-pivaloyl phthalimide.

(1) N-pivaloyl phthalimide (1.0g.) in ethyl acetate (50ml.) was hydrogenated over platinum oxide (0.33g.). After 24 hr, 530ml. of hydrogen (rather more than $4\frac{1}{2}$ moles per mole of

substrate) had been absorbed. T.l.c. of the resulting mixture in 40% ethyl acetate/light petroleum indicated the presence of a major component with the same Rf as hexahydrophthalimide, at least three less polar, and two minor, more polar components. Removal of solvent and catalyst, and extraction of the residue with boiling light petroleum left an insoluble fraction (0.48 g.) which was found by t.l.c., m.p. (132-134°) and i.r. examination to consist of almost pure hexahydrophthalimide.

(2) The above hydrogenation was repeated using Johnson Matthey platinum oxide (0.3g.). After 24 hr, 425ml. of hydrogen (corresponding to rather less than $3\frac{1}{2}$ moles per mole of substrate) had been taken up. T.l.c. of the resulting mixture in 40% ethyl acetate/light petroleum showed the presence, in addition to a main product with the same Rf as hexahydrophthalimide, of a complex mixture of at least four less polar components and a large, diffuse spot due to a more polar component. The mixture was chromatographed over silica gel (50g.).

Eluting solvent.	Wt. of fraction.	Further treatment.
(i) 5-8% ethyl acetate/benzene.	445mg.	Examined by n.m.r. Due to the complexity of this mixture and the similarity in polarity of the components, an attempted separation by chromatography was not very successful.
(ii) 10-15% ethyl	230mg.	Crystallisation from ethyl

acetate/benzene.		acetate gave hexahydrophthalimide (m.p. 136°).
(iii) 100% ethyl acetate.	100mg.	Crystallisation from ethyl acetate gave large clear flakes which volatilised without melting on the Kofler block, disappearance being first observable above 100°. Identified as pivalamide by direct comparison (i.r. and behaviour on melting block) with material prepared by reaction of pivaloyl chloride with concentrated aqueous ammonia.

i.r. (nujol, cm^{-1}) 3435 (m.); 3235 (m.); 1658 (s., br.); 1629 (shoulder).

The n.m.r. spectrum (60Mc/s) of fraction (i) showed the following features:-

7.90-9.20 (m.) —— cyclohexane methylene protons.

8.78 (s.); 8.67 (s., very low intensity); 8.59 (s., principal one of three) —— $(CH_3)_3C$-groups.

7.39 (s., sharp peak, very broad at base) —— unassigned.

5.69-6.23 (m.) —— possibly the AB portion of an ABX system.

4.60 (s., broadened at base) —— methylene group of phthalide.

3.41 (s.) —— CHOH of N-pivaloylhydroxyphthalimidine.

2.0-2.6 (m.) —— aromatic protons.

(3) N-pivaloyl phthalimide (1.0g.) in ethyl acetate (100ml.) was hydrogenated over 10% palladium on carbon. This hydrogenation proceeded more slowly than that of the other N-acyl phthalimides, the volumes of hydrogen absorbed after 24 and 48 hr amounting to 100 and 153ml. respectively. T.l.c. in 40% ethyl acetate/light petroleum showed the presence of at least two components of Rf similar to that of the starting material. Crystallisation of this mixture from light petroleum proceeded only with great difficulty, but when a seed of N-pivaloylhydroxyphthalimidine, obtained in poor yield from a further hydrogenation of N-pivaloyl phthalimide over 10% palladium on carbon, by direct crystallisation, was added, rapid deposition of large clear prisms occurred. Recrystallisation from light petroleum gave N-pivaloylhydroxyphthalimidine (0.35g.) m.p. 82-83°.

Found C, 66.94; H, 6.44%.

$C_{13}H_{15}NO_3$ requires C, 66.93; H, 6.48%.

i.r. (nujol, $cm.^{-1}$) 3495 (s.); 1736 (v.s.); 1668 (v.s.); 1619 (v.w.); 773 (s.); 744 (m.); 708 (w.).

n.m.r. (60Mc/s) 8.58 (s.,9H); 5.22 (d., J=4.2c/s.,1H; lost on D_2O equil.); 3.42 (d., J=4.2c/s.,1H; s. on D_2O equil.); 2.0-2.6 (m.,4H).

Hydrogenation of N-isobutyryl phthalimide.

(1) N-isobutyryl phthalimide was prepared by acylation of phthalimide with isobutyryl chloride in pyridine, and had m.p. 98°(164) on crystallisation from ethanol. This material (1.0g.) in ethyl acetate (75ml.) was hydrogenated over Johnson Matthey platinum oxide (0.3g.). After 24 hr, 430ml. of hydrogen (corresponding to about 3½ moles per mole of substrate) had been taken up. T.l.c. in 40% ethyl acetate/light petroleum indicated what at first appeared to be two main components, and a faint trace of a polar product. Closer examination of the spot arising from the less polar of the two main components showed that it in fact represented two products of very similar polarity. Column chromatography over silica gel (50g.) permitted separation of the mixture into the following fractions:-

(i) a mixture of the two close-running components (0.79g. on elution with 5% ethyl acetate/benzene), and,

(ii) the other main component (0.12g. on elution with 10-15% ethyl acetate/benzene.

Further elution with ethyl acetate gave only traces of material containing the polar product. Crystallisation of fraction (i) from light petroleum first gave N-isobutyrylhydroxyphthalimidine (0.21g. after purification by crystallisation to constant m.p.), m.p. 89-90°.

Found, C, 65.72; H, 5.91%.

$C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98%.

i.r. (nujol, $cm.^{-1}$) 3460 (m.); 1717 (s.); 1691 (s.);

1619 (w.); 759 (s.); 706 (m.).

n.m.r. (60Mc/s) 8.73 (d., J=6.6c/s.,3H); 8.72 (d., J=6.6c/s., 3H); 6.08 (septet, J=6.6c/s.,1H); 5.21 (d., J=3c/s.,1H; lost on D_2O equil.); 3.43 (d., J=3c/s.,1H; s. on D_2O equil.); 2.00-2.60 (m.,4H).

Further crystallisation of the mother liquors gave clumps of white needles of the second component, hexahydro-N-isobutyryl-hydroxyphthalimidine (0.26g. on purification), m.p. 103.5-104.5°.

Found, C, 64.12; H, 8.52%.

$C_{12}H_{19}NO_3$ requires C, 63.97; H, 8.50%.

i.r. (nujol, cm^{-1}) 3425 (s.); 1736 (s.); 1675 (s.).

n.m.r. (60Mc/s) 7.5-9.2 (m.,9H); 8.85 (d., J=6.6c/s.,3H); 8.83 (d., J=6.6c/s.,3H); 6.97 (m.,1H); 6.28 (septet, J=6.6c/s.,1H); 6.00 (d., J= 3c/s.,1H; lost on D_2O equil.); 4.60 (d., J= 3c/s.,1H; s. on D_2O equil.).

The component in fraction (ii) had m.p. 136° on crystallisation from ethyl acetate, and was identified as hexahydrophthalimide by direct comparison with an authentic sample.

(2) N-isobutyryl phthalimide (1.0g.) in ethyl acetate (75ml.) was hydrogenated over 10% palladium on carbon (1.0g.), being allowed to absorb 150ml. of hydrogen (corresponding to rather more than one mole per mole of substrate), at which point (after 18 hr) the reaction was stopped. T.l.c. of the product

in 40% ethyl acetate/light petroleum showed the presence of one principal component. Crystallisation from light petroleum initially gave material with m.p. 85-89° (0.76g.). Recrystallisation of this from light petroleum finally gave white prisms of N-isobutyrylhydroxyphthalimidine, m.p. 89-89.5°, whose i.r. and n.m.r. spectrum were identical with those of the material obtained in (1) above.

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CATALYSED REACTIONS

PART 2

THE ACID-CATALYSED REARRANGEMENT OF THE TETRACYCLIC DITERPENES AND TRACHYLOBANE

CONTENTS

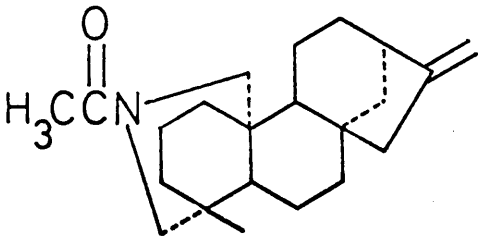
Diagrams and tables not facing the appropriate page in the text follow the discussion section (following p.188).

THE ACID-CATALYSED REARRANGEMENT OF THE TETRACYCLIC DITERPENES AND TRACHYLOBANE.

INTRODUCTION. The Structural Relationship of the Polycyclic Diterpenes.

In 1955, Wenkert suggested[1] that the tetracyclic diterpenes known at that time might all derive from tricyclic precursors such as pimaradiene (1A, fig. 1) and isopimaradiene (1B, fig. 2), cyclisation being envisaged as proceeding via carbonium ion formation at C_8 followed by nucleophilic attack by the C_{13} vinyl substituent. Deprotonation of the resulting tetracyclic carbonium ion intermediates (2A and 2B) would give rise to hibaene (3A) and isohibaene (3B). On the other hand, rearrangement of these initially formed secondary carbonium ions (2A and 2B), through intermediates conveniently summarised by hydrogen bridged structures (4A and 4B), could be envisaged to give kaurene (5A), isokaurene (6A), atisirene (7A) and isoatisirene (8A) (from 2A), and phyllocladene (5B), isophyllocladene (6B), neoatisirene (7B) and isoneoatisirene (8B) (from 2B). These hydrocarbons can exist in enantiomeric forms, the stereochemistry represented in figs 1 and 2 being that of the normal (10β) series. (In accordance with a scheme of nomenclature based on suggestions by a number of chemists in the natural products field, to be submitted for publication, the names of diterpenes in the enantiomeric (10α) series will be prefixed by ent- in the following discussion.) All of the possible tetracyclic diterpenes of the pimaradiene-derived

series (fig. 1) have been isolated from natural sources, but of those theoretically derivable from isopimaradiene (fig. 2), only phyllocladene (5B) and isophyllocladene (6B) have so far been found. Isohibaene (3B),[2] neoatisirene (7B)[3] and isoneoatisirene[3] have however been synthesised in anticipation of their discovery in nature. The pentacyclic diterpene trachylobane (9A), obtained by Ourisson and co-workers,[4] and its analogue in the isopimaradiene-derived series, isotrachylobane (9B), which is as yet unknown, are readily accommodated in Wenkert's scheme, indeed the hydrogen-bridged species (4A and 4B) being effectively protonated trachylobane and isotrachylobane. The scheme, in addition to predicting new skeletons for diterpenes likely to be discovered, has stimulated numerous attempts to interconvert the tetracyclic diterpenes by rearrangements of the bicyclooctane system.



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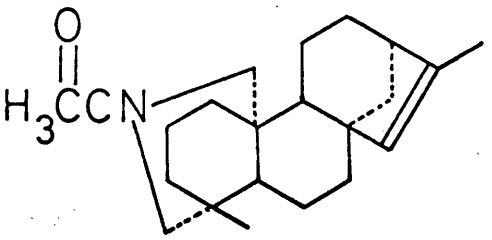

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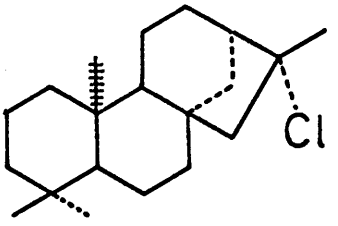

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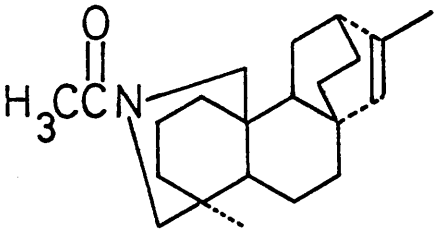

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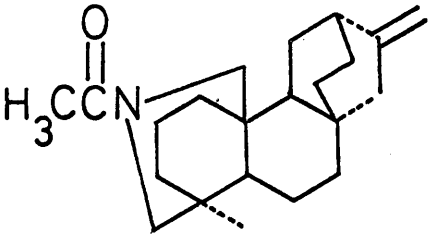

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Isomerisation and Rearrangement of the Polycyclic Diterpenes.

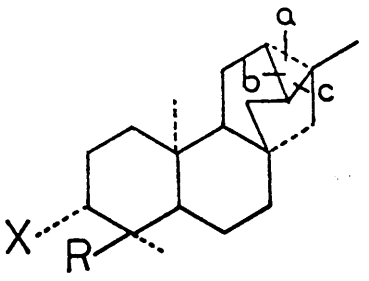
(1) Double bond isomerisations and cleavage of trachylobanes.

Kaurene (5A) and phyllocladene (5B) are readily isomerised to the endocyclic isomers (6A and 6B) on treatment with acid under various conditions, e.g. refluxing acetic acid,[5] sulphuric acid in ethanol,[5] methanol[6] or acetone,[7] and hydrochloric acid in acetone.[8] Kaurene generally gives a mixture containing 75-80% of isokaurene, whereas phyllocladene gives almost entirely isophyllocladene. Jefferies[8] has suggested that this difference may be due to the fact that the formation of isophyllocladene from phyllocladene is favoured by the relief of a 1,3-diaxial interaction, between C_{15} and C_{20} in the latter, no such relief being possible in the kaurene-isokaurene transformation. Masamune[9] has reported the conversion of a synthetic intermediate with the kaurene skeleton (10) into a mixture containing 75% of the endocyclic isomer (11) by treatment with hydrogen chloride in cold acetic acid, conditions which have been reported to give the hydrochloride (12) with kaurene itself.[10] Briggs and co-workers[40] have reported the conversion of kaurene and phyllocladene into the endocyclic isomers in high yield by refluxing in benzene with a few crystals of iodine, but later workers have found that on repeating this reaction with kaurene, a considerable quantity of starting material was present in the product.[8,11]

The acid-catalyst isomerisation of atisirene (7A) to isoatisirene (8A) has been reported,[11] the product apparently

consisting of a mixture of the two isomers, but details were not given. This conversion has also been found to take place in the presence of base.[12] Guthrie, Valenta and Wiesner have prepared an isoatisirene derivative (13) by heating a synthetic intermediate with the atisirene skeleton (14) with p-toluenesulphonic acid in benzene.[13] Zalkow and Oehlschalager[3] have reported the complete conversion of neoatisirene (7B) to isoneoatisirene (8B) in refluxing acetic acid, the formation of a single product being verified by thin layer and vapour phase chromatography. By analogy with the explanation suggested for the different extents of isomerisation of kaurene and isokaurene, the apparent difference in the behaviour of atisirene and neoatisirene may be due to the fact that isomerisation of the latter relieves a 1,3-diaxial interaction between C_{15} and C_{20}. These authors also report that the treatment of neoatisirene (7B) with 88% formic acid, in an attempt to bring about rearrangement to isophyllocladene (6B), gave a mixture of formate esters, alcohols and a negligible amount of olefinic products. No further details of this investigation have as yet been published.

Ourisson and co-workers have studied the acid-catalysed cleavage of ent-trachylobane (15; R=CH_3, X=H) and two derivatives (15; R=CO_2Me, X=H and R=CO_2Me, X=OAc).[14] Products derived from each of the three possible modes of cleavage of the cyclopropane ring (15, a,b,c) were isolated. On reaction in acetic acid/acetic anhydride containing a little perchloric



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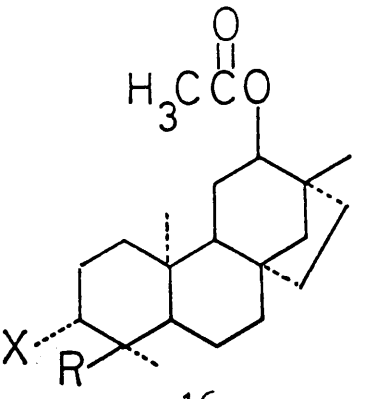

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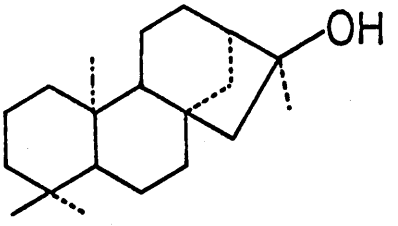

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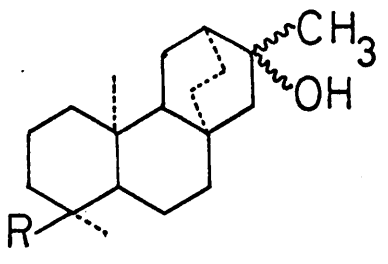

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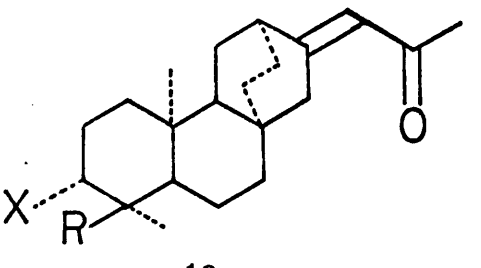

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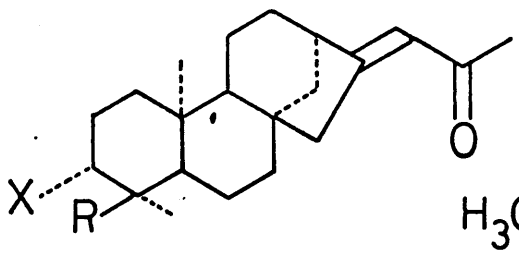
acid, three types of product were obtained;

(i) an olefinic fraction (small, accounting for 4,7 and 4% respectively of the total product from the three compounds, 15.),

(ii) an acetate fraction (35, 30 and 30% respectively), and

(iii) an α-β-unsaturated ketonic fraction, arising from a Friedel-Crafts reaction between olefins initially formed and CH_3CO^+ ion (55, 57 and 57% respectively).

The olefinic fraction was examined only in the case of trachylobane, two hydrocarbons, ent-isoatisirene (enantio-8A) and probably ent-hibaene (enantio-3A) being isolated. The principal product in the acetate fraction was, in all three cases, the 12 -acetoxyhibane (16; R=CH_3, X=H; R=CO_2Me, X=H and R=CO_2Me, X=OAc), minor products isolated, after conversion of the acetates to the alcohols, being ent-kauran-16β-ol (17) and the ent-atisiran-16-ols (18; R=CH_3 and CO_2Me) for which the configuration at C_{16} was not determined. From the α,β-unsaturated ketonic fractions, products derived by acylation of ent-kaurene and ent-atisirene were isolated. In two cases, the atisirenes (19; R=CH_3, X=H and R=CO_2Me, X=OAc) were present in great excess over the kaurenes (20; R=CH_3, X=H and R=CO_2Me, X=OAc) whereas in the third case the kaurene (20; R=CO_2Me, X=H) was the major, and the atisirene (19; R=CO_2Me, X=H) the minor product. Treatment of ent-trachyloban-18-oic acid methyl ester (15; R=CO_2Me, X=H) with trifluoroacetic acid in cyclohexane/diethyl ether gave, as the main product, an ent-atisiran-16-ol



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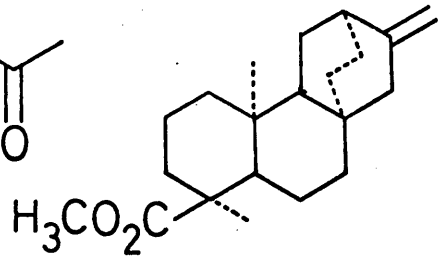

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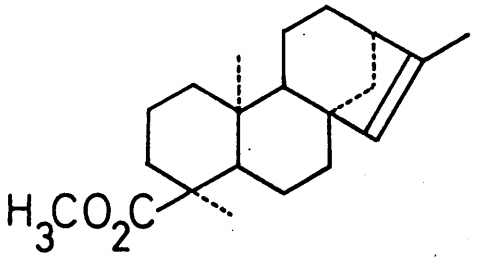

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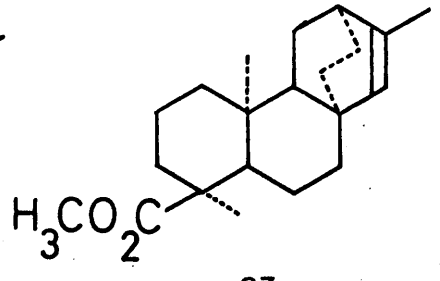

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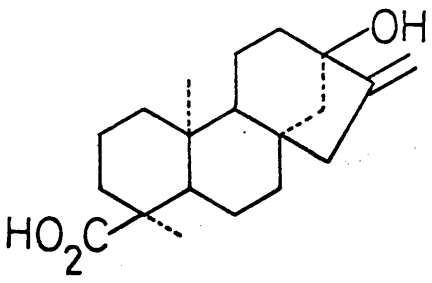

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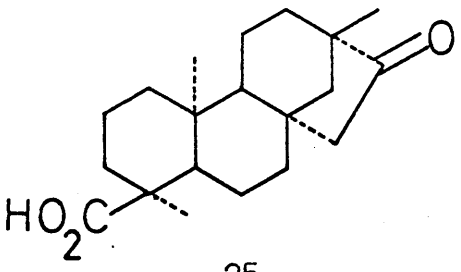

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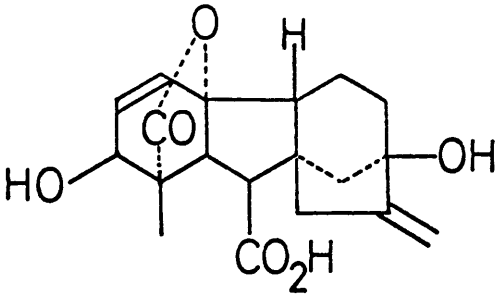

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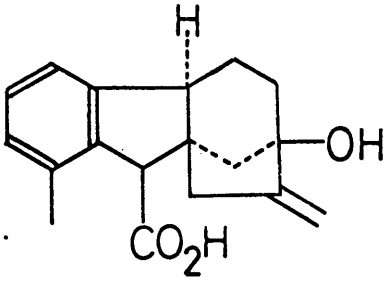

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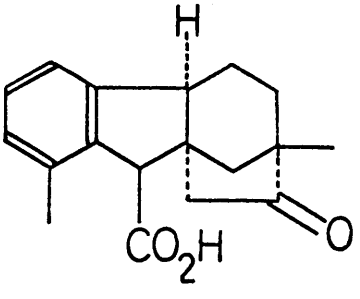

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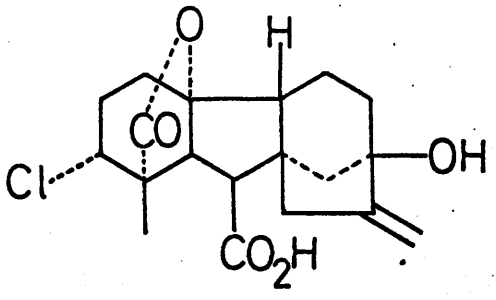

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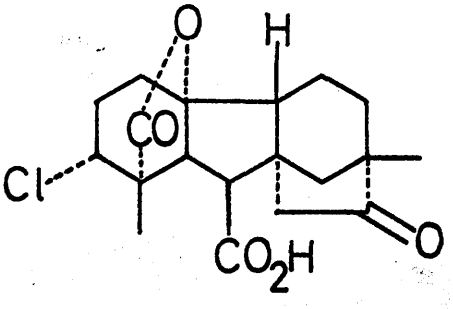

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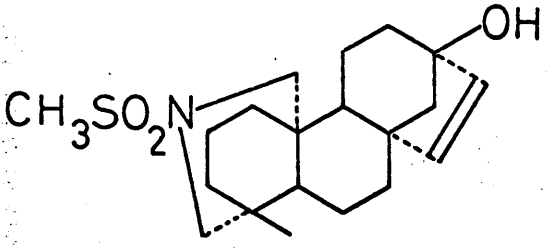
[whose configuration at C_{16} was not determined, but was the opposite of that of the atisiran-16-ol (18; R=CO_2Me) obtained by treatment of the same starting material with acetic acid/acetic anhydride/perchloric acid], and an olefinic fraction, from which the methyl esters of ent-atisirene-18-oic acid (21) and ent-isokaurene-18-oic acid (22) were isolated. In one run, a small quantity of a product believed to be ent-isoatisirene-18-oic acid methyl ester (23) was isolated.

(2) Skeletal rearrangements.

A. Acid-catalysed rearrangements.

An example of the conversion of the kaurane to the hibane skeleton is provided by the steviol-isosteviol rearrangement[15] (24→25), a reaction also employed by Ireland and co-workers in their synthesis of hibaene.[11] In this reaction, the electronically unfavourable requirement of conversion of a tertiary to a secondary carbonium ion, by a Wagner-Meerwein rearrangement involving migration of the C_{12}-C_{13} bond (of 24) to C_{16} is outweighed by the readily available supply of electrons from the O-H bond, resulting in formation of a ketone. Numerous examples of a similar type of rearrangement are known in the gibberellin series, e.g., refluxing either gibberellic acid (26) or allogibberic acid (27) in hydrochloric acid gives the rearranged product, gibberic acid (28).[16-18] A recent example is the conversion of the hydrochloride of gibberellin A_5 methyl ester (29) to the ketone (30).[19] In their synthetic route to the diterpene alkaloids,[20] Nagata and co-workers



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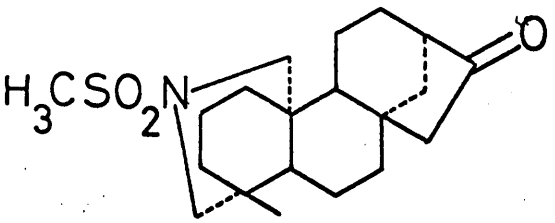

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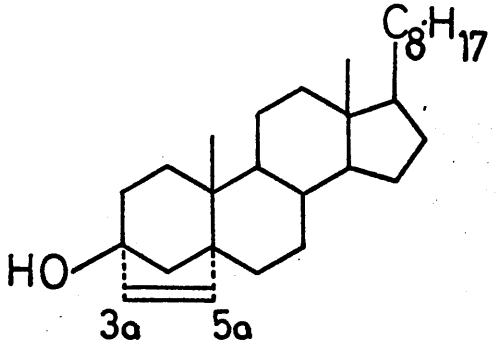

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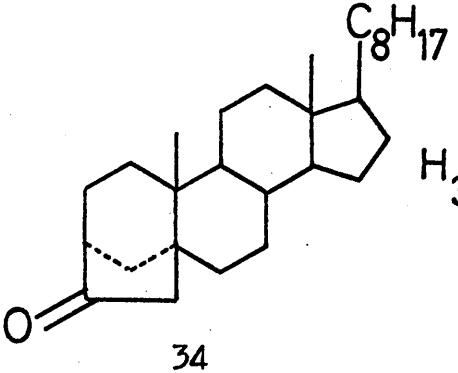

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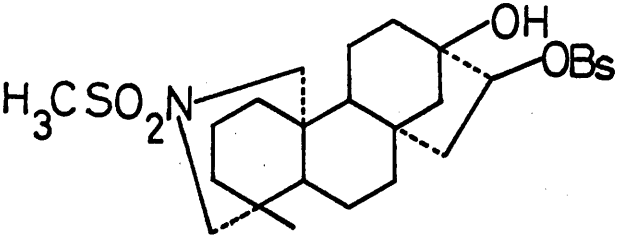

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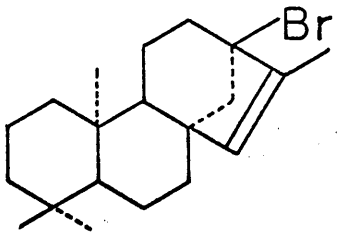

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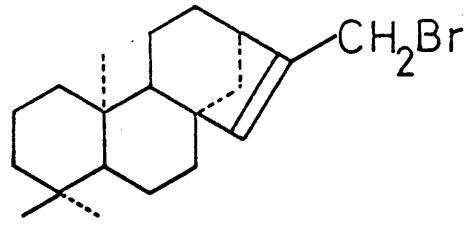

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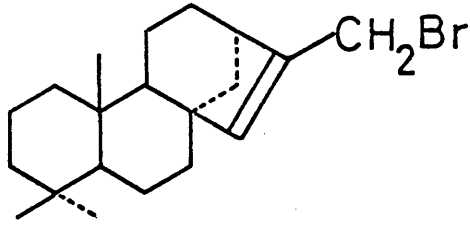

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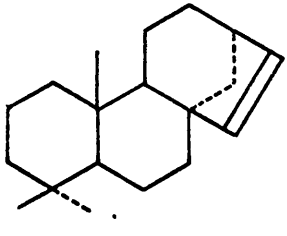

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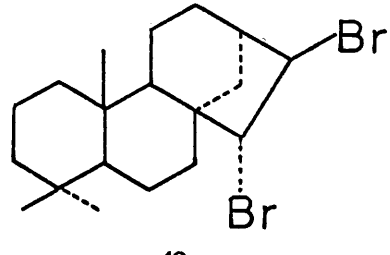

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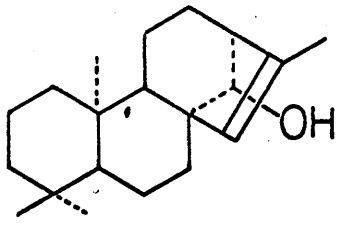
prepared an intermediate possessing the norhibaene skeleton (31) which might have been expected to undergo an analogous type of acid-catalysed rearrangement to give a norkauranone (32). However, since the rearrangement of a model system (33→34) did not take place, this reaction was not attempted. The authors offered the explanation that protonation of the model compound (33) occurred preferentially at C_{3a}, since the carbonium ion so produced, which could not undergo rearrangement, was less hindered than that which would have resulted from protonation at C_{5a}, and predicted that protonation of the norhibaene (31) would, for similar reasons, occur at C_{16} rather than at C_{15}. Since it was expected that rearrangement should take place if carbonium ion formation could be directed to C_{16}, the 16-p-bromobenzenesulphonate (35) was prepared. Treatment of this with base indeed gave the rearranged product (32).

In the isopimaradiene-derived series (fig. 2) the analogous interconversions have not as yet been reported, no bridgehead substituted derivatives of phyllocladene (5B) being known. The observation that the allylic bromination of ent-isokaurene (enantio-6A) with N-bromo succinimide gave some of the bridgehead substituted derivative, ent-13-bromokaur-15-ene (36) in addition to the main product, ent-17-bromokaur-15-ene (37) led to an attempt to prepare the bridgehead bromide from isophyllocladene (6B), but the only product obtained in this case was 17-bromophylloclad-15-ene (38).[21] Similar treatment of 17-



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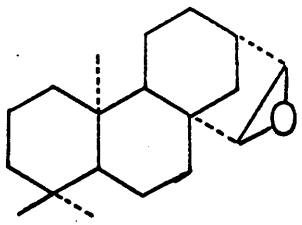

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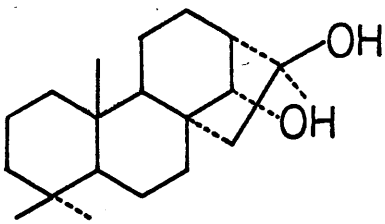

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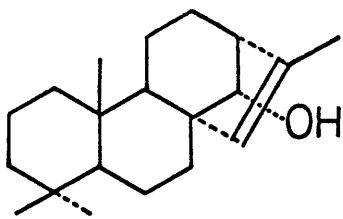

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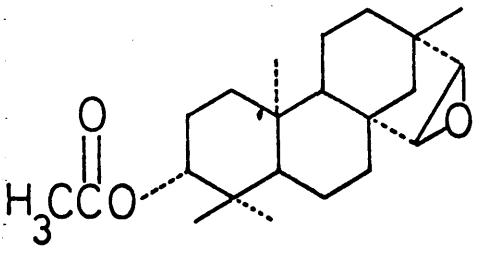

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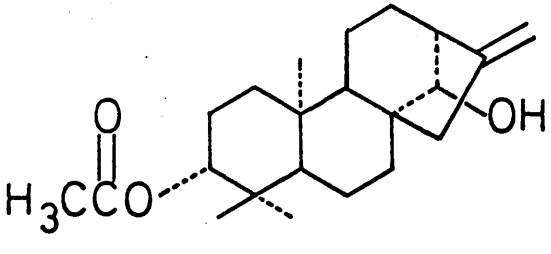

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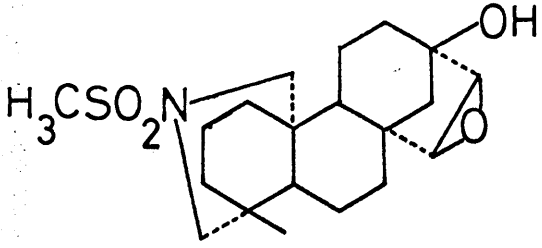

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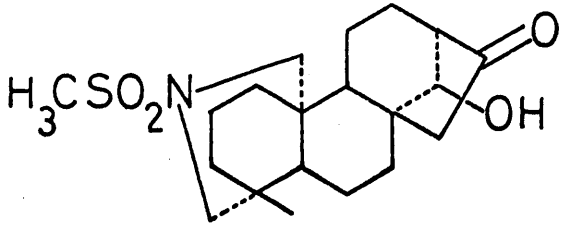

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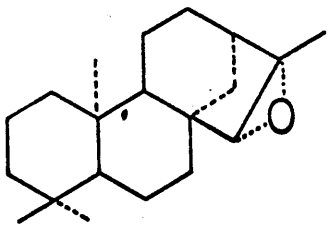
norphyllocladene (39), in which the only available allylic position is at the bridgehead, gave only the 15,16-dibromide (40).

B. Cleavage of epoxides.

Several authors have reported the rearrangement of the hibane to the kaurane skeleton on treatment of hibaene epoxide with Lewis acids. The earliest report of this reaction is that of Kapadi and Dev,[22] who obtained ent-kaur-15-ene-14β-ol (41) on treatment of ent-15β,16β-epoxyhibane (42) with boron trifluoride etherate. Treatment of the enantiomeric epoxide, 15α, 16α-epoxyhibane with boron trifluoride etherate in benzene was reported to give some of the 14α, 15β-diol (43) in addition to kaur-15-en-14α-ol (44).[23] The diol was the main product when the rearrangement was carried out in benzene saturated with water. ent-3α-acetoxy-15β, 16β-epoxyhibane (45), on treatment with boron trifluoride etherate, apparently gave the kaurene derivative, ent-3α-acetoxykaur-16-en-14β-ol (46) rather than the isokaurene ddrivative.[24] This type of reaction was also employed by Nagata et al.[20] in the conversion of the norhibane to the norkaurane skeleton, as an alternative to the already mentioned route via the p-bromobenzenesulphonate (p.167). The treatment of a bridgehead hydroxyl-substituted norhibane epoxide (47) with diethylaluminium chloride gave the corresponding norkauranolone (48).

In contrast to these results, no skeletal rearrangements were observed on cleavage of the epoxides derived from iso-



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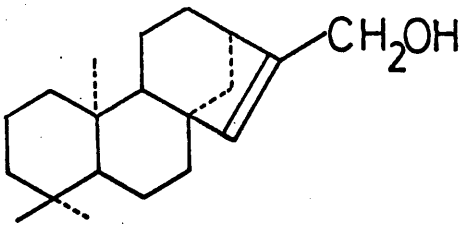

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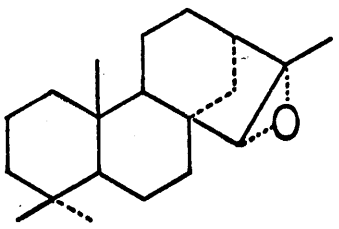

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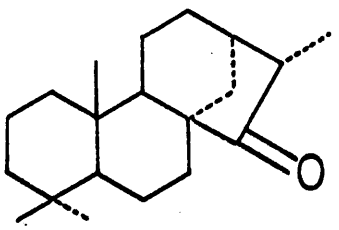

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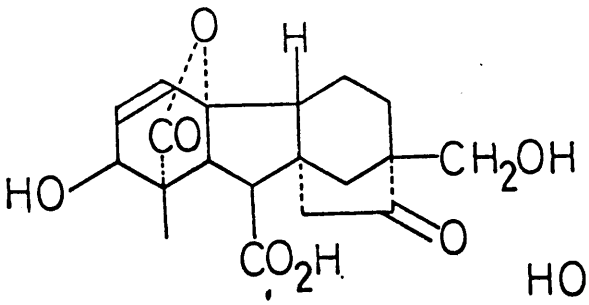
kaurene and isophyllocladene.[25] Thus, ent-15α,16α-epoxykaurane (49), on treatment with magnesium bromide etherate, gave mainly the allylic alcohol, ent-kaur-16-en-15α-ol (50), whereas 15α,16α-epoxyphyllocladane (51) gave the ketone, phyllocladan-15-one (52) via a hydride shift from C_{15} to C_{16}. It was suggested that the preference for ketone formation in the latter case was due to the fact that migration of the C_{15} hydrogen resulted in the relief of a non-bonded interaction with the angular methyl group at C_{10}. Although the C_{12}-C_{13} bond in these epoxides is suitably aligned to participate in a concerted attack at C_{16} as the epoxide ring is cleaved, the unfavourable electronic requirement of the transfer of positive charge from the tertiary position at C_{16} to the secondary carbon atom, C_{13}, must preclude the possibility of rearrangement. That such a rearrangement can however occur when an additional driving force is brought into play is illustrated by the formation of the rearranged ketone (53) from the 8,15-epoxide of gibberellic acid (54) in warm aqueous solution.[26] Here, as in the acid-catalysed rearrangements of this type of system already discussed, formation of the ketone provides the driving force for the reaction.

C. Solvolytic rearrangements.

An alternative approach to the interconversion of the diterpenes involves the generation of the necessary intermediate carbonium ions by solvolysis of esters. This may be illustrated by the work of Sobti and Dev,[27] who obtained a mixture of



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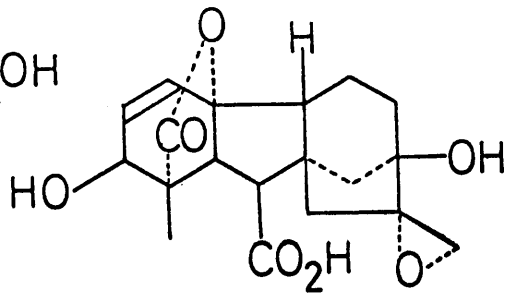

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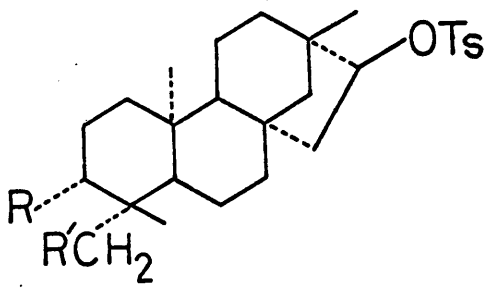

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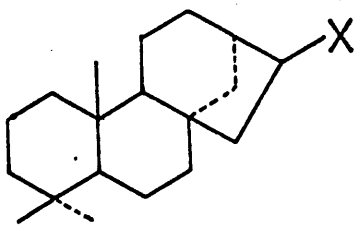

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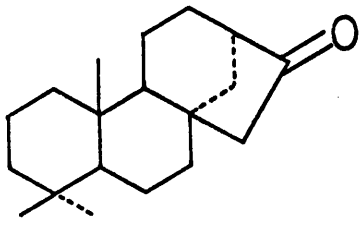

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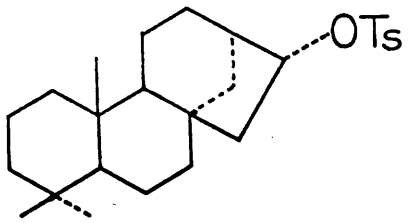
products containing ent-hibaene, ent-kaurene and ent-isokaurene on treatment of ent-hibane-16β-p-toluenesulphate (55; R=R'=H) with a buffered solution of lithium carbonate in 66% aqueous dioxan. These products were also obtained in similar proportions when a hexane solution of the ester (55; R=R'=H) was passed over alumina. The authors examined the products of these reactions specifically to see if any rearrangement to products having the atisirene, isoatisirene or trachylobane skeletons had occurred, but no compounds of these types could be detected. This kind of rearrangement has also been observed by Ghisalberti and Jefferies[28] on solvolysis of a substituted derivative of hibane-16β-p-toluenesulphonate (55; R,R'=$CH_3CH<^{O-}_{O-}$). The C_{12}-C_{13} bond in these compounds (55) is ideally orientated to undergo concerted migration as the ester function leaves. The theoretically possible analogous rearrangement of the isohibaene (3B) to the phyllocladene skeleton has not as yet been reported.

Examination of the skeletons of 17-norkaurene and 17-norphyllocladene suggests that their interconversion, by generation of a carbonium ion at C_{16}, should be possible. This interconversion has been attempted by two groups of workers, but both attempts failed. Thus, on solvolysis of 17-norphyllocladan-16β-ol-p-toluenesulphonate or m-nitrobenzenesulphonate (56; X=OTs or Om-NO_2Bs) in potassium acetate/acetic acid, only 17-norphyllocladan-16-one (57) was recovered.[29] It may be noted that in these derivatives (56), the leaving group is



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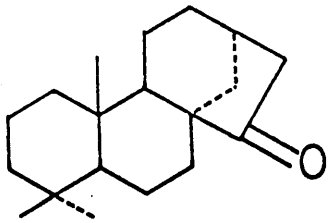

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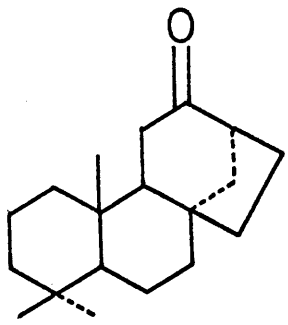

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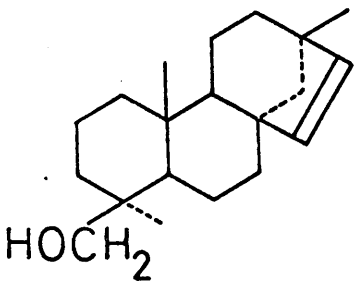

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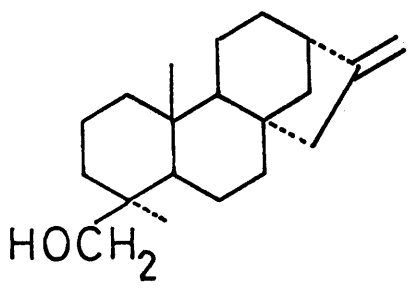

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endo with respect to the bicyclo[3.2.1]octane system, and hence not in the trans-antiparallel alignment with the C_{12}-C_{13} bond most favourable for concerted participation by the latter in the reaction. Turner and co-workers have however examined the solvolysis of 17-norphyllocladan-16α-ol-p-toluenesulphonate (58) in sodium acetate/acetic acid containing some acetic anhydride.[30] They obtained an olefinic fraction which appeared to be largely norphyllocladene (39), traces of acetate (detected only by i.r.) and some starting material. Thus, although in this case the C_{12}-C_{13} bond is suitably aligned to participate in the solvolysis, no rearrangement was observed. In a further attempt to convert the norphyllcladane to the norkaurane skeleton, these authors carried out the deamination, in aqueous acetic acid and under nitrogen, of the amine obtained by sodium-alcohol reduction of the oxime of 17-norphyllocladan-16-one (57). The resulting mixture was then treated with lithium aluminium hydride, to convert any acetates to alcohols, followed by oxidation to the ketones with chromium trioxide and chromatographic separation. This gave 17-norphyllocladan-16-one (57) as the main product, some 17-norphyllocladene (39), 17-norphyllocladan-15-one (59) and a fourth product which was not characterised, but which showed absorption due to a six-ring carbonyl function in the i.r. spectrum. The last two products were thought to have arisen from hydride shifts, which might imply that the authors believed the uncharacterised product to be 17-norphyllocladan-12-one (60), which would result

from a hydride shift from C_{12} to C_{16}. The analogous conversion of norkaurane to norphyllocladane has apparently not been attempted.

D. Rearrangements catalysed by iodine.

The interconversion of the hibaene (3A) and kaurene (5A) skeletons by reflux in xylene containing a few crystals of iodine was first reported by Yoshikoshi. (See ref. 31, footnote 6b.) This reaction was employed by Mori and co-workers in a synthesis of monogynol (hiba-15-ene-19-ol;61) from kaur-16-en-19-ol (62), a mixture, from which the hibaene, kaurene and isokaurene were isolated in the ratio 1:1:1, being obtained after refluxing for nine hours.[31] More recently, Yoshikoshi and co-workers have published their results on the parent hydrocarbons,[23] isomerisation of either hibaene or kaurene being reported to yield the same equilibrium mixture containing hibaene, kaurene and isokaurene in the ratio 5:2:3. They were however unable to suggest a mechanism for this reaction.

THE ACID-CATALYSED REARRANGEMENT OF THE DITERPENE HYDROCARBONS.

RESULTS AND DISCUSSION.

As has been outlined in the introductory section, Wenkert's scheme (figs 1 and 2) not only summarises the relationship among the polycyclic diterpenes, but has also stimulated numerous attempts to interconvert them through carbonium ion rearrangements. The scheme suggested to us another approach to the same end, presenting a challenge to devise *in vitro* conditions under which any one of the diterpenes, on protonation, would be converted through the hydrogen-bridged ion (4A or 4B), or equivalents, to an equilibrium mixture containing other members of the same series. The only reported acid-catalysed interconversions of the diterpene hydrocarbons are the double bond isomerisations and the cleavage of trachylobane already summarised in the introduction, no skeletal rearrangements having been observed. Briggs and co-workers have reported that hibaene (3A) was recovered unchanged after heating with p-toluenesulphonic acid in benzene,[32] and Yoshikoshi and co-workers have reported that the isomerisation of kaurene (5A) with p-toluenesulphonic acid in boiling xylene gave a complicated mixture of products, but no details have as yet been published (ref. 23, footnote 24). Accordingly, we undertook a study of the action of dry hydrogen chloride in a variety of aprotic solvents first of all on *ent*-hibaene (enantio-3A, fig. 3). Aprotic solvents were utilised to ensure the formation of

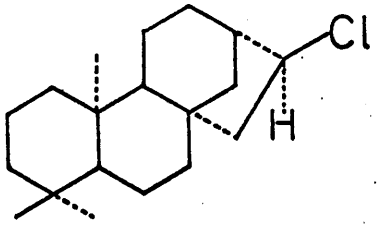
hydrocarbons rather than of products arising from the addition of solvent-derived nucleophiles to the intermediate carbonium ions. The initial experiments were carried out on ent-hibaene since it was anticipated, for reasons discussed below, that this would be the tetracyclic member of the ent-pimaradiene-derived series most likely to undergo rearrangement.

Rearrangement of ent-hibaene (enantio-3A).

In a series of trial experiments, samples of ent-hibaene were dissolved in light petroleum (b.p. 60-80°), benzene, chloroform, diethyl ether, ethyl acetate and acetonitrile (concentration 2mg./ml.), and the resulting solutions saturated with dry hydrogen chloride and kept at room temperature. Aliquots were removed at intervals, the solvent was evaporated, and the residue filtered in light petroleum through a short column of alumina and examined by thin layer chromatography (t.l.c.) and gas-liquid chromatography (g.l.c.). This examination showed that virtually no reaction had taken place in light petroleum, diethyl ether or ethyl acetate within a period of 48 hr, but that in benzene, chloroform and acetonitrile, isomerisation had occurred. T.l.c., on silver nitrate-impregnated silica gel, of the aliquots from reactions performed in the last three solvents showed that in addition to the starting material, there were four other products, two of these being present in only trace amounts. The two major products had the same Rfs as ent-kaurene (enantio-5A) and ent-isokaurene (enantio-6A), and the minor products had the same Rfs as ent-atis-

irene (enantio-7A) and ent-isoatisirene (enantio-8A). On g.l.c., only three peaks showed although a large number of column packings were tried in an attempt to find conditions which would result in resolution of all the components. Indeed when authentic samples of ent-kaurene, ent-isokaurene, ent-atisirene and ent-isoatisirene were run, no separation of the pairs ent-kaurene/ent-atisirene or ent-isokaurene/ent-isoatisirene could be obtained. However, estimation of the areas of the peaks on g.l.c. showed that the rate of isomerisation in benzene was very slow (about 10% conversion of ent-hibaene in two days) but was more rapid in chloroform (about 50% disappearance of ent-hibaene in 7 days) and acetonitrile (about 60% disappearance in 4 days). The feasibility of isomerisation of ent-hibaene under the chosen conditions having now been demonstrated, the reaction was repeated on a larger scale to permit the isolation and characterisation of the products. The solvent chosen for this reaction was chloroform rather than acetonitrile since, although isomerisation appeared to occur more rapidly in the latter, the recovery of hydrocarbon from it was more difficult. After standing for two weeks in hydrogen chloride/chloroform, about 65% of the ent-hibaene initially present (as judged by measurement of peak areas on g.l.c.) had undergone rearrangement, the reaction after this time coming virtually to a standstill. On removal of solvent, and filtration of the residue in light petroleum through alumina as before, an almost quantitative yield of hydrocarbon was

obtained. Attempted separation of the components of this mixture by column chromatography over silver nitrate-impregnated silica gel was only partly successful, only one compound (about 3% of the total), the least polar of the five hydrocarbons in the mixture, and the principal of the two minor components, with an Rf on t.l.c. corresponding to isoatisirene, being recovered in about 90% purity. The remainder of the material was therefore subjected to preparative g.l.c., by which means a clean separation into fractions corresponding to each of the three peaks was obtained. Crystallisation of the fastest running product (single spot on t.l.c. and single peak on g.l.c.) gave pure ent-hibaene, identified by direct comparison with an authentic sample. The products corresponding to the second and third peaks were similarly confirmed to be ent-isokaurene and ent-kaurene respectively, but the small quantities obtained of the products believed to be ent-atisirene and ent-isoatisirene precluded the possibility of purifying them for direct comparison with authentic material, so that some doubt as to their identity remained in spite of the evidence of their retention behaviour on t.l.c. and g.l.c. However, the availability of the technique of combined gas chromatography and mass spectrometry (g.c.m.s.) shortly after the initial part of this work was completed permitted the comparison of the cracking patterns of the suspected ent-isoatisirene and authentic material. These were found to be identical, thus resolving this problem.



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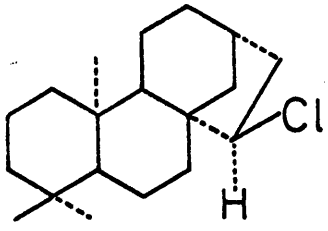

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Just at the commencement of this work, Kapadi and Dev reported that the treatment of ent-hibaene with hydrogen chloride in benzene/chloroform at 0° afforded only the corresponding hydrochloride.[22] This result may have been due to a concentration effect, since in one experiment in the present work, when an ent-hibaene concentration of 5mg./ml. in chloroform was used, hydrochloride formation occurred to a considerable extent. All subsequent experiments were therefore carried out at concentrations of 1-2mg. of substrate per ml. of solvent, under which conditions this side-reaction was minimised. Apparently no structure has been assigned to ent-hibaene hydrochloride in the literature. The addition of chloride ion to the carbonium ion formed on protonation of ent-hibaene would be expected to take place on the less hindered exo side of the five-membered ring. Since protonation might conceivably occur at either C_{15} or C_{16} (see p,167), the hydrochloride could be either the ent-15β-(63) or 16β-(64) chlorohibane. In the 16β-chloro derivative (64), the chloro substituent is trans-anti-parallel with respect to the C_{12}-C_{13} bond, so that rearrangement via participation of this bond might be expected to occur on solvolysis. Accordingly, the ent-hibaene hydrochloride obtained above was refluxed in acetic acid containing anhydrous sodium acetate. T.l.c. of the recovered product showed that it consisted almost entirely of a single hydrocarbon with the same Rf as ent-hibaene, and only a trace of a polar product. The n.m.r. spectrum confirmed this, being virtually identical

TABLE 1

Product composition after acid treatment

Hydrocarbon	Time of isomerisation*		Product composition (%; approx.)		
	a	b		a	b
Hibaene	4 days	21 days	Hibaene	44%	35%
			Kaurene	11	13
			Isokaurene	33	38
			Isoatisirene	11	13
			Atisirene	1	1
Kaurene	.2 hr	14 days	Kaurene	25	23
			Isokaurene	75	71
			Isoatisirene	0	5
			Atisirene	0	1
Isoatisirene	2 hr	14 days	Kaurene	0	-
			Isokaurene	0	0.5
			Isoatisirene	92	91
			Atisirene	8	8
Trachylobane	15 min.	14 days	Kaurene	1	1
			Isokaurene	3	3
			Isoatisirene	90	90
			Atisirene	6	6

* Only two representative experiments are quoted.

with a spectrum of authentic ent-hibaene, showing only a small additional singlet at 7.96τ, presumably due to a trace of acetate. This was readily removed on filtration of the solvolysis product in light petroleum through a short alumina column. The ent-hibaene crystallised on removal of the solvent and standing at room temperature. The fact that not even a trace of rearrangement product could be detected suggests that the hydrochloride obtained from ent-hibaene is in fact ent-15β-chlorohibane (63).

The availability of g.c.m.s. permitted the study of the isomerisation, under conditions analogous to those used for ent-hibaene, of other hydrocarbons of the ent-pimaradiene-derived series, namely ent-kaurene, ent-isoatisirene and ent-trachylobane (enantio-9A), which were available only in quantities which precluded the separation and identification of products by the usual techniques, since it was believed that conclusions based solely on the retention behaviour of products on t.l.c. and g.l.c. could not be completely unambiguous. The results of product analysis by a combination of all three techniques are summarised in table 1 and fig. 3. All of these isomerisations were carried out under standard conditions involving saturation of solutions of the appropriate hydrocarbon in chloroform (1mg./ml.) with dry hydrogen chloride and allowing the resulting mixture to stand at room temperature. Removal of aliquots, evaporation of the solvent, and filtration of the residue in light petroleum through a short alumina

column resulted in virtually quantitative recovery of hydrocarbon in all cases. Since, as has already been noted, the pairs of hydrocarbons ent-atisirene/ent-kaurene and ent-isoatisirene/ent-isokaurene could not be resolved by g.l.c., the measurement of peak areas on chromatograms gave only the proportions of ent-hibaene: (ent-atisirene + ent-kaurene): (ent-isoatisirene + ent-isokaurene). However, by taking advantage of characteristic differences in the mass spectra of ent-isoatisirene and ent-isokaurene, it was possible to estimate the relative proportions of these compounds from g.c.m.s. by a procedure devised by Dr. A. McCormick, the details of which have been submitted for publication.[33] Furthermore, by assuming that equilibrium had been established between, on the one hand ent-kaurene and ent-isokaurene, and on the other ent-atisirene and ent-isoatisirene, and using the proportions determined for these equilibria (see table 1), the ratio of ent-atisirene to ent-kaurene was estimated.

Isomerisation of ent-kaurene (enantio-5A).

ent-Kaurene was found to equilibrate rapidly to give a mixture of ent-kaurene and ent-isokaurene. After prolonged treatment, however, small quantities of ent-atisirene and ent-isoatisirene could be detected in the product.

Isomerisation of ent-isoatisirene (enantio-8A).

ent-Isoatisirene came rapidly to equilibrium with ent-atisirene, but prolonged treatment of this mixture led to little (if any) change. On t.l.c., only the two expected spots could

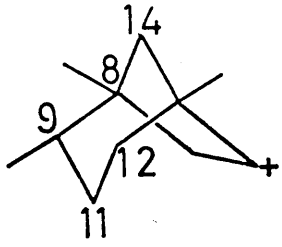
be detected although g.c.m.s. suggested that a trace of ent-isokaurene (ca 0.5%) might be present. This suggestion can however only be tentative since the presence of small amounts of ent-isokaurene in ent-isoatisirene is less readily detectable than the reverse.[33]

Cleavage of ent-trachylobane (enantio-9A).

ent-Trachylobane was cleaved very rapidly under the conditions employed, a preliminary g.l.c. examination of the reaction mixture after 15 min. showing that none had survived. The products were ent-atisirene, ent-isoatisirene, ent-kaurene and ent-isokaurene, the first two being the major components. Significantly, little or no ent-hibaene could be detected, although this hydrocarbon, had it been formed, should have survived such a short period of reaction virtually unchanged. (c.f. the isolation of products with the hibaene skeleton from the cleavage of trachylobane and derivatives with acetic acid/acetic anhydride/perchloric acid.[14]) No significant change in the product composition could be detected on prolonging the reaction time.

Rearrangements in the isopimaradiene-derived series.

Of the diterpenes of the isopimaradiene-derived series, only phyllocladene (5B) and isophyllocladene (6B) were available to us. Isomerisation of either of these under the conditions used previously resulted in rapid conversion to a mixture of the two which consisted very largely of isophyllocladene, containing only a little phyllocladene (approx. 3%). No other products



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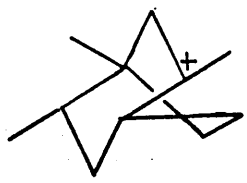

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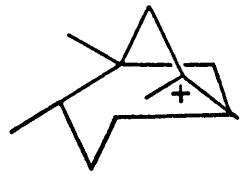

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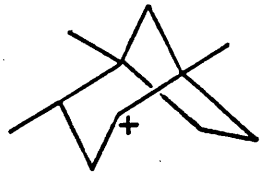

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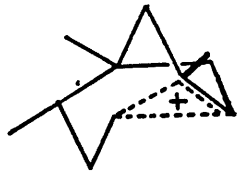

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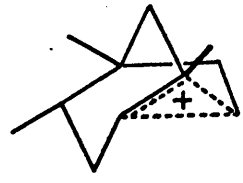

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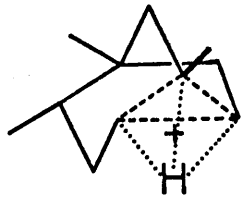

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could be detected, even on prolonging the reaction time to several weeks.

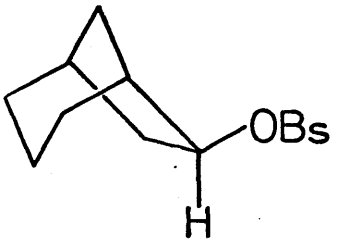
Discussion.

The results obtained bear out the initial suggestion that the acid-catalysed, *in vitro*, rearrangement of the tetracyclic diterpenes, at least of the pimaradiene-derived series, is possible, although under the conditions employed, the rate of interconversion of distinct skeletal types is so slow as to preclude the attainment of equilibrium among them. Furthermore although it is impossible to define the nature of the intermediates from these results, it can be concluded that since the (iso)atisirene : (iso)kaurene ratio is substantially different depending on whether the mixture is derived from hibaene or trachylobane, there cannot be any unique intermediate (e.g. the hydrogen-bridged ion 4A) in these isomerisations.

Formally, acid-catalysed cleavage of trachylobane may proceed[14] to one of six possible carbonium ions via protonation and scission of any one of the three cyclopropyl carbon-carbon bonds. Of the six possible carbonium ions, four are secondary (at C_{12} and C_{16}), and include one (65), produced by protonation at C_{12} and cleavage of the C_{12}-C_{16} bond, from which hibaene should be derivable. That only (iso)atisirene and (iso)kaurene were detected in the products from trachylobane reflects on the enhanced stability of the remaining two carbonium ions (66 and 67) (both of which are tertiary) from which they can be derived. One factor which may play a role in the preferred

formation of (iso)atisirene is the following. In the carbonium ion (66) from which (iso)atisirene can be formally derived, the ionic charge is in a six-membered ring, whereas in that from which (iso)kaurene may be similarly derived (67), the ionic charge is in a five-membered ring. The former case will be preferred because of the smaller angle strain involved.[34] (See also below.)

The conversion of hibaene into (iso)kaurene results from migration of the C_{12}-C_{13} bond to C_{16} (formally via 65 and 67). Formation of (iso)atisirene, on the other hand, requires a hydride shift from C_{12} to C_{16} and migration of the ethane bridge to C_{12} (formally via 65, 68 and 66). Both of these rearrangements are electronically favourable, involving conversion of a secondary to a tertiary carbonium ion. In all of these rearrangements non-classical ions (69,70) or even the hydrogen-bridged ion (71) may also play a role. The preponderance of (iso)kaurene over (iso)atisirene in the products from the rearrangement of hibaene demonstrates that bond migration occurs more readily than hydride shift, a situation analogous to that found for the norbornane system.[34] Recently, however, Wiberg and Hess have reported that solvolysis of the 6-exo or 6-endo-p-bromobenzenesulphonate of the parent bicyclo[3.2.1]octane system (72 and 73 respectively) has been found by Goering and Padmanathan to lead to mixtures containing a considerable proportion of products derived from a 1,3-hydride shift.[35] (See fig. 4). Further, Wiberg and Hess found that the rearranged



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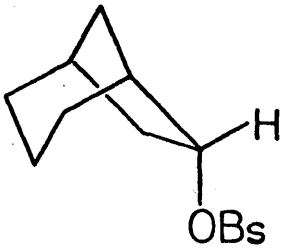

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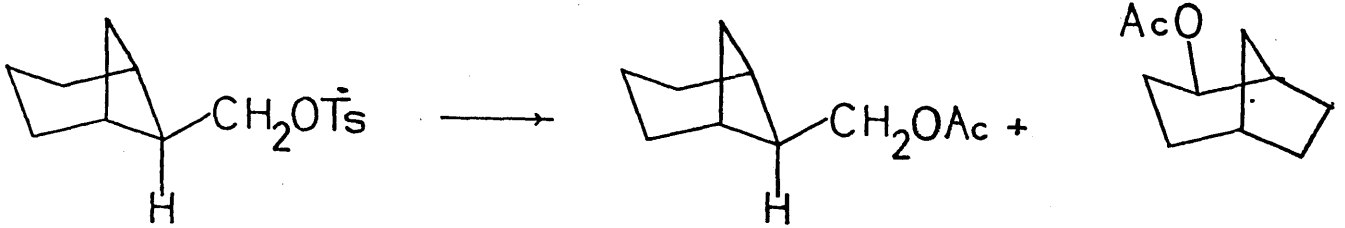
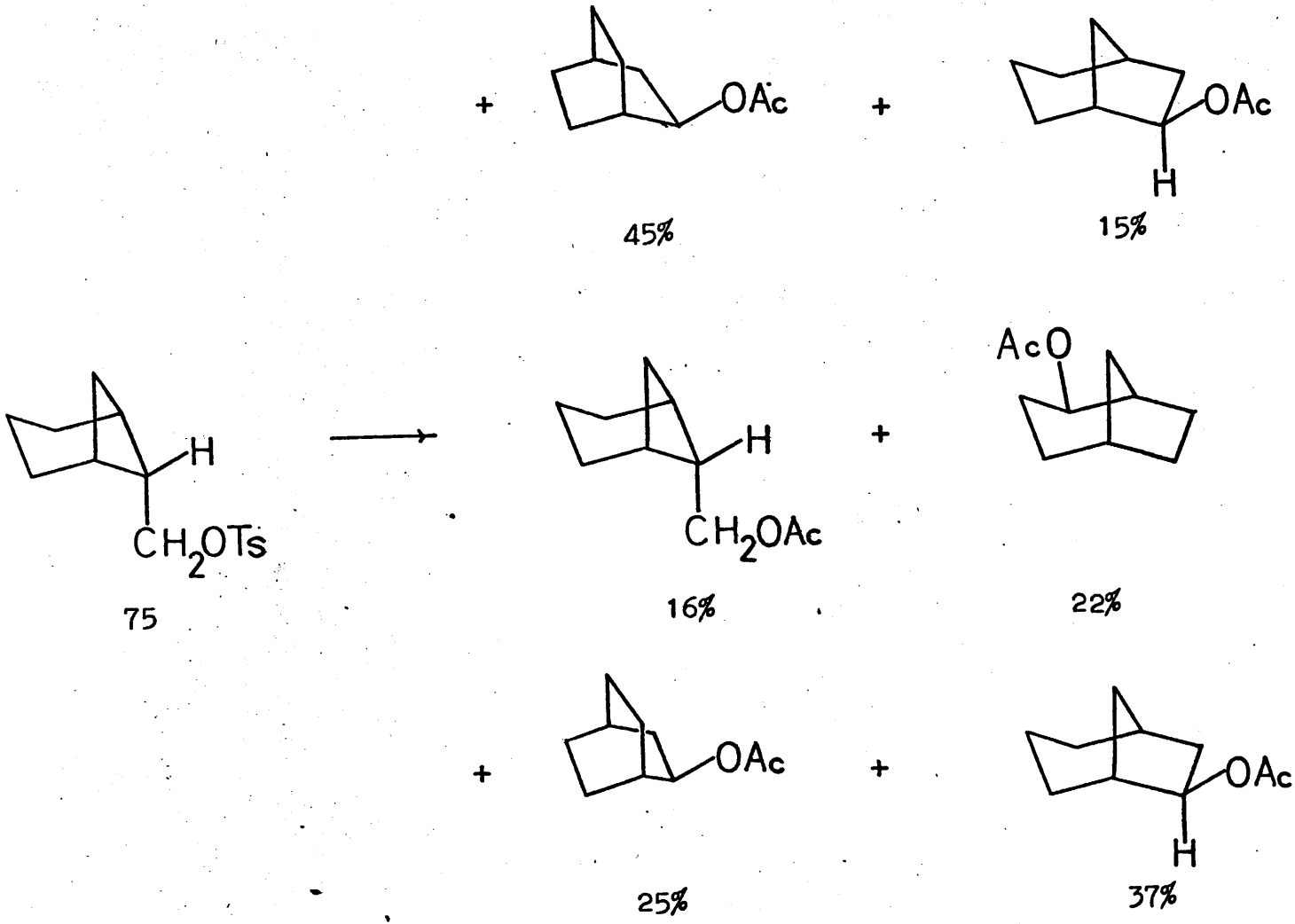
FIGURE 4

Acetolysis of bridged cyclobutylcarbinyltosylates after Wiberg and Hess.[35]



74 ~0.4% 40%


OAc
OAc
H
45%
15%
H
CH2OTs
75
H
CH2OAc
16%
AcO
22%
OAc
OAc
H
25%
37%

products from the solvolysis of exo-(74) and endo-(75) bicyclo-[3.1.1]heptane-6-methyl-p-toluenesulphonate were the same in both structure and relative quantity as those obtained by Goering and Padmanathan from the solvolysis of exo-(72) and endo-(73)bicyclo[3.2.1]octane-6-p-bromobenzenesulphonate respectively. The exo isomers (72 and 74) gave more of the products in which hydride shift had occurred than the corresponding endo isomers (73 and 75). (See figures in fig. 4.) To explain this, it was suggested that the leaving anion, when exo, forms an ion pair with the resulting carbonium ion hindering exo attack by solvent anion, thus giving the carbonium ion a greater opportunity to rearrange. When the leaving anion is endo, exo attack is less hindered, and the initially formed carbonium ion is captured more rapidly. The large proportion of 1,3-hydride shift products found by these authors shows that charge transfer from the five to the six-membered ring of the bicyclo[3.2.1]octane system is a favourable process, lending further support to the above-suggested explanation for the preferred formation of (iso)atisirene from trachylobane.

The variation of the ease of rearrangement of hibaene with the solvent in which the reaction was carried out would be expected to depend on at least two factors:-

(a) polarity; a more polar solvent favouring the charge separation necessary to give a carbonium ion, and permitting a longer lifetime for the latter, so that it has more opportunity to rearrange, and,

(b) ability to solvate the chloride ion formed at the protonation stage. In solvents which are unable to solvate the chloride ion effectively, this will form an intimate ion pair with the carbonium ion initially formed, followed by either rapid collapse to the hydrochloride, or by reabstraction of the proton to regenerate the hydrocarbon.

The effect of polarity is shown by the fact that no rearrangement was observed in the least polar solvent tried, namely light petroleum, and that in the slightly more polar solvent, benzene, only a very slow reaction took place. The effect of the second factor, ability to solvate the chloride ion, is shown by the observation that no rearrangement took place in diethyl ether or ethyl acetate, which would not be expected to solvate anions effectively. The solvent employed, chloroform, has a polarity intermediate between the first and second pairs of solvents mentioned, and in addition, should be able to solvate the chloride ion by forming a hydrogen-bonded species, namely $Cl^{-}\cdots\overset{\delta+}{H}\text{-}\overset{\delta-}{C}Cl_3$. The situation with acetonitrile, the most polar solvent tried, is rather more complicated, but the anion present in solutions of HCl in this solvent has been shown to be HCl_2^- rather than Cl^-.(36)

The rearrangement of hibaene was very slow, even in chloroform and acetonitrile. This might be explained by examination of a model of the hibaene molecule (3A, fig. 1) in which protonation may occur at one of two positions, C_{15} or C_{16}. Protonation at C_{15}, to give the C_{16} carbonium ion necessary for re-

arrangement would result in the introduction of a non-bonded interaction between the resulting C_{15} methylene group and the C_{20} methyl group, so that protonation at C_{16} light be expected to be preferred. (This argument is similar to that put forward by Nagata et al. in discussing the protonation of the 17-nor-hibaene skeleton. See p.167.) The C_{15} carbonium ion thus formed, being unable to rearrange, can only be discharged by deprotonation to starting material, or by attack by a nucleophile on the less hindered exo side of the bicylcooctane system to give a 15α-substituted hibane (or 15β-substituted ent-hibane). It has already been concluded (p.178) that the hydrochloride obtained from ent-hibaene is ent-15β-chlorohibane. The rearrangement of hibaene would then, under the conditions employed, have to proceed via the C_{16} carbonium ion in equilibrium with the more favoured C_{15} carbonium ion, or formed from it by a 1,2-hydride shift.

The conversion of kaurene into (iso)atisirene involves, in the formal sense, initial conversion of a tertiary (67) into the energetically less favourable secondary (65) carbonium ion, followed by a hydride shift and migration of the ethane bridge as in the conversion of hibaene to (iso)atisirene. The observed very slow overall rate of reaction might be expected since the first step is energetically unfavourable. Similarly, the reverse reaction, formation of (iso)kaurene from isoatisirene would involve initial conversion of a tertiary (66) into a secondary (68) carbonium ion, hydride shift to give a further

secondary carbonium ion (65) and finally rearrangement (to 67) as for hibaene. This interconversion would be even less favourable than the reverse, involving both the conversion of a tertiary into a secondary carbonium ion, and the transfer of ionic charge from a six to a five-membered ring. The results of our experiments agree with this expectation, although there may be a trace of isokaurene in the reaction product from isoatisirene.

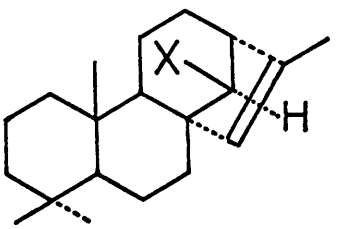
The only diterpenes of the isopimaradiene-derived series available to us were phyllocladene (5B) and isophyllocladene (6B), which, by analogy with the results obtained with kaurene, would not be expected to undergo ready rearrangement. Indeed, rearrangement via the isohibaene skeleton (3B) would involve the introduction of an additional non-bonded interaction, between the C_{12} methylene and C_{20} methyl groups, not present in phyllocladene or isophyllocladene. Although this interaction is not as severe as that between the C_{14} methylene and C_{20} methyl groups, being somewhat relieved by twisting of ring C by the bridging ring D, conversion of a tertiary into a secondary carbonium ion is also involved, so that this reaction should be even less favourable than the analogue in the pimaradiene-derived series. This expectation is borne out by the fact that no products other than phyllocladene and isophyllocladene could be detected in the reaction mixtures. As to the rearrangement of isohibaene, this would be expected to proceed more readily than that of hibaene for the following reasons.

(a) As with hibaene, protonation of isohibaene may conceivably take place at one of two sites, C_{15} or C_{16}, but in the latter case, no additional unfavourable non-bonded interactions are introduced by protonation at C_{15} to give the C_{16} carbonium ion necessary for rearrangement.

(b) Migration of the C_{12}-C_{13} bond to C_{16}, leading to phyllocladene and isophyllocladene, will relieve the non-bonded interaction between the C_{12} methylene and C_{20} methyl groups. In the analogous rearrangement of hibaene to (iso)kaurene, such an interaction is introduced.

Neoatisirene (7B), under the conditions used in the present work, should give isoneoatisirene (8B) rapidly (c.f. ref. 3), but any further rearrangement is highly unlikely since, in addition to the involvement of electronically unfavourable steps analogous to those required for the rearrangement of isoatisirene, non-bonded interactions are introduced on going from the bicyclo[2.2.2] to the bicyclo[3.2.1]octane system.

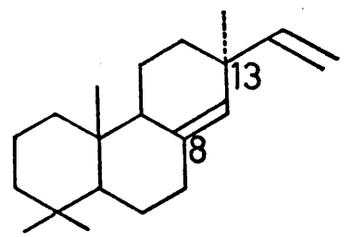
The electronic and steric factors involved in the interconversion of the tetracyclic diterpenes have been discussed recently by Oehlschalager and Ourisson.[37] In their discussion of the <u>in vivo</u> formation of the tetracyclic diterpenes, the cation (corresponding to 2B) formed directly by cyclisation of isopimaradiene (1B), and from which isohibaene may be directly derived, is considered to have ring C in the boat rather than in the chair conformation as shown in 2B. The examination of models of isohibaene and (iso)kaurene (5A)



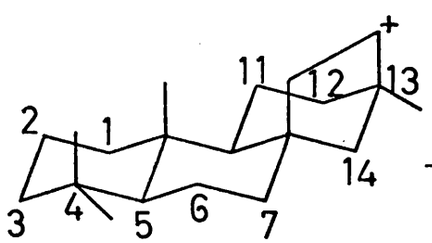
76

shows that flipping of ring C from the chair into the boat conformation relieves the two 1,3-diaxial interactions between the C_{12} and C_{14} methylene groups and the C_{20} methyl group, so that the energy difference between the two forms is probably small. The n.m.r. spectra of a series of isokaurene derivatives have been interpreted as showing that ring C in this molecule is in fact in the chair conformation.[38] (See also ref. 23.) On the other hand, in kaur-15-en-14β-ol and its acetate (76; X=OH or OAc), where there would be considerable non-bonded interaction between the hydroxyl or acetoxyl group and the C_{20} methyl group if ring C were in the chair conformation, this ring apparently adopts the boat conformation, although in the latter there would be a considerable flagpole-bowsprit interaction between these substituents and the β-hydrogen at C_{11}.

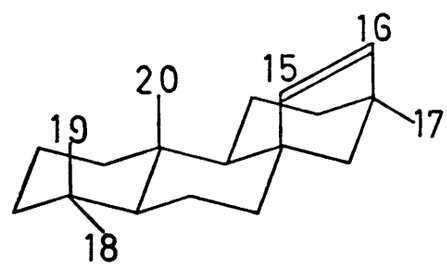
FIGURE 1



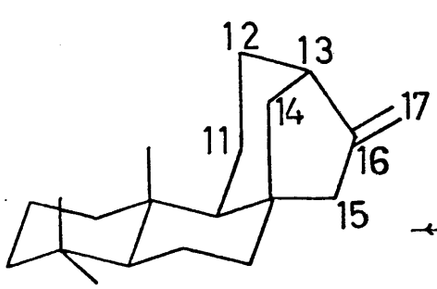
1A



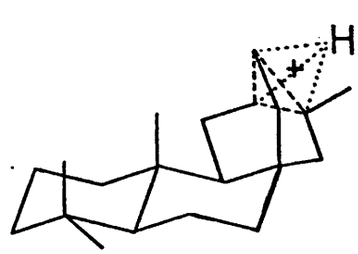
2A



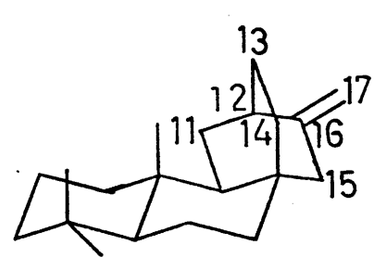
3A



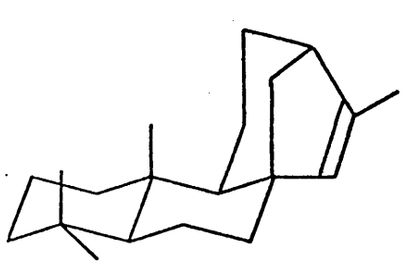
5A



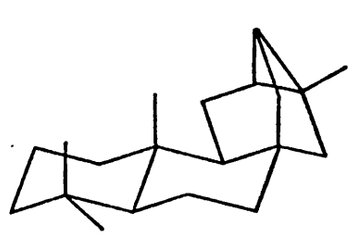
4A



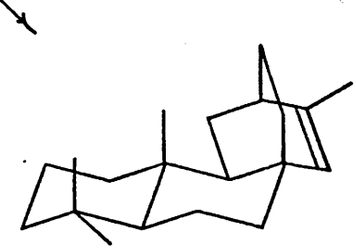
7A



6A



9A



8A

FIGURE 2

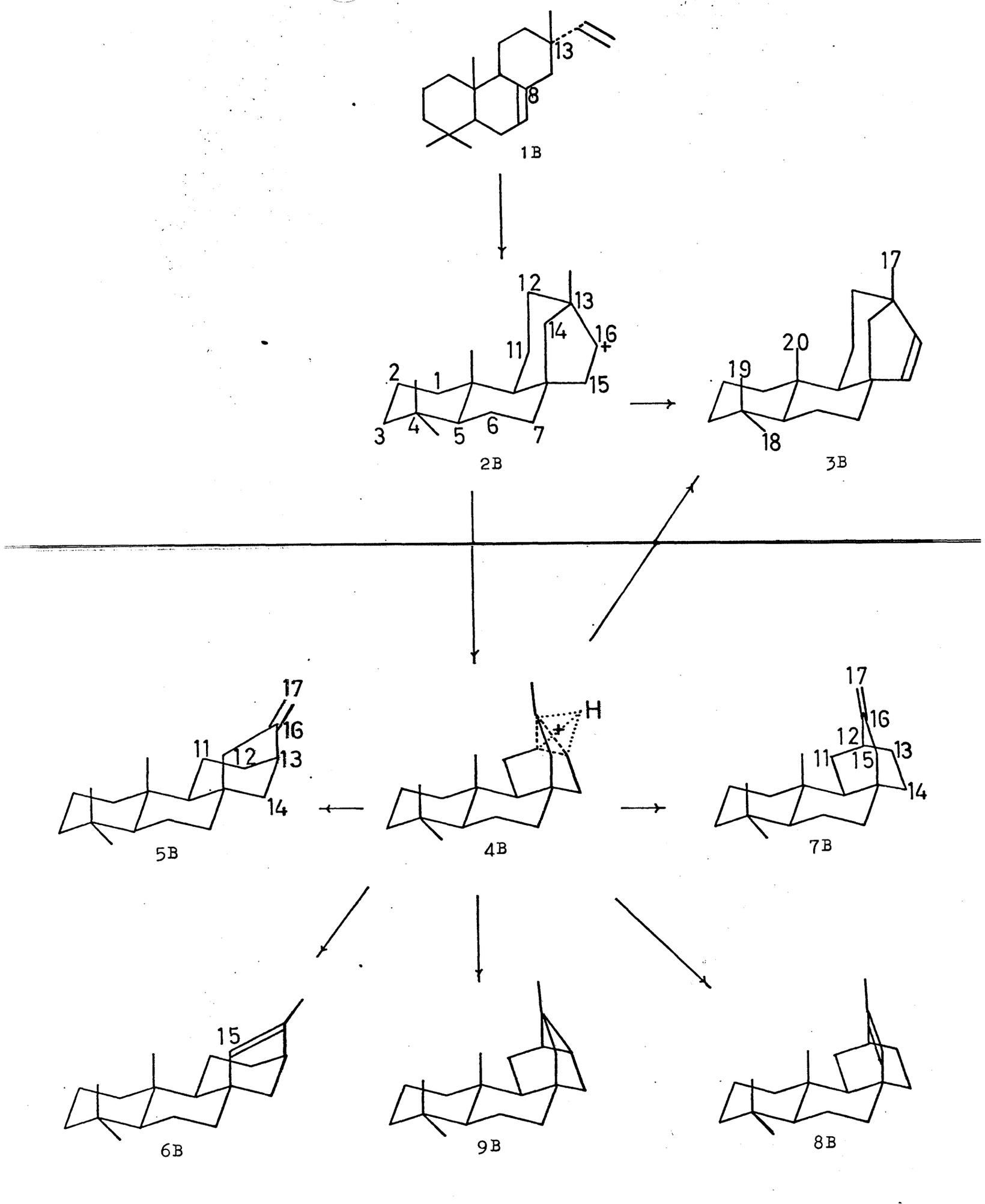

13
8
1B
12
13
14
16
11
2
1
15
3
4
5
6
7
2B
17
20
19
18
3B
17
16
11
12
13
14
5B
H
4B
17
16
12
11
15
13
14
7B
15
6B
9B
8B

FIGURE 3

Isomerisation of the diterpenes of the pimaradiene-derived series with hydrogen chloride/chloroform.

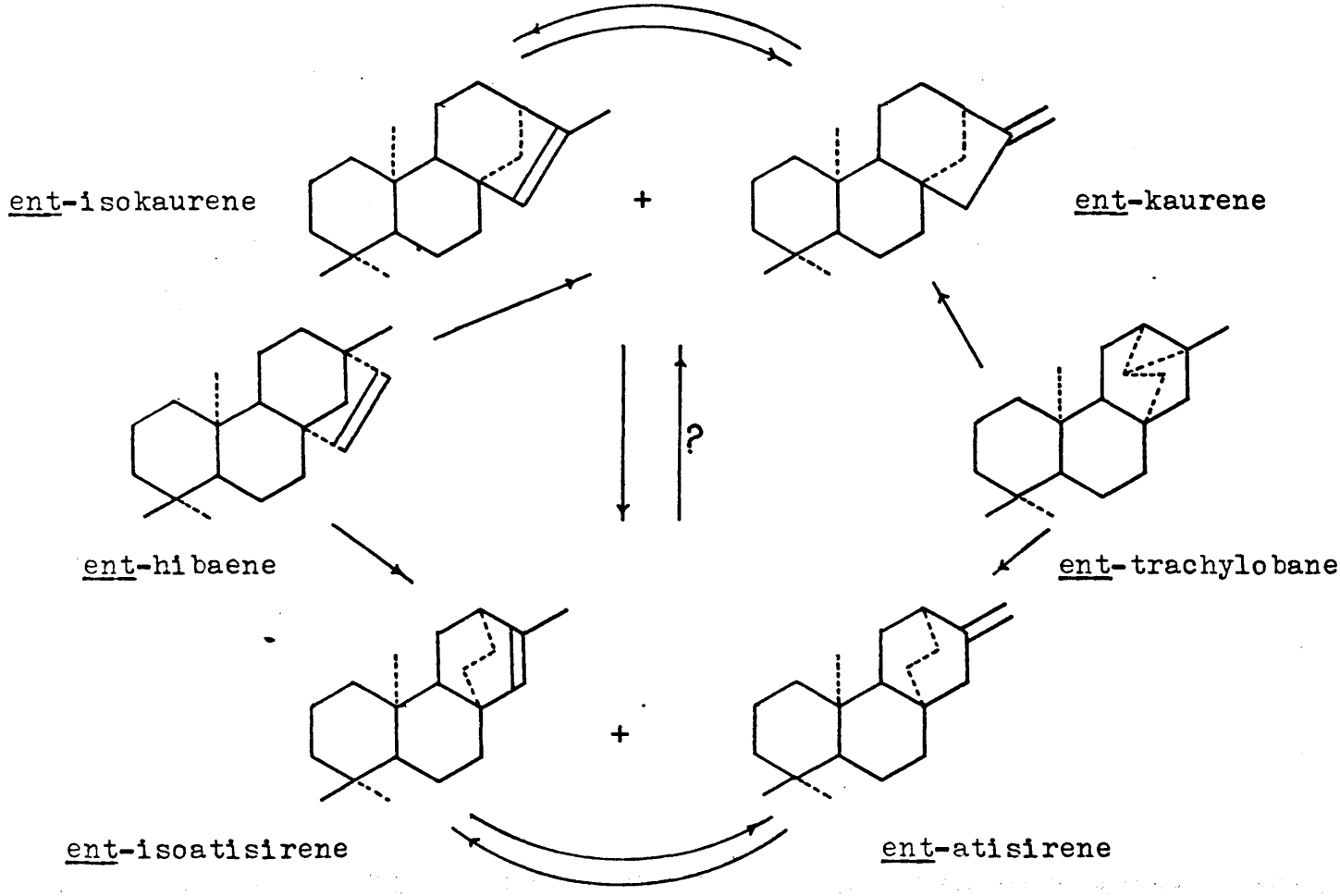


TABLE 2.

Compound.	M.p.	$[\alpha]_D$ ($CHCl_3$).	Retention index* (I).
ent-atisirene**	55-57°	-38°	2298
ent-isoatisirene**	81-83	-75	2232
ent-kaurene	51-52	-78	2298
ent-isokaurene	61-63	-37	2230
ent-hibaene**	30-33	+39	2152
ent-trachylobane	45-46	-43	2202
phyllocladene	96-97	+16	2270
isophyllocladene	112-113	+23	2192

* Here, and in the text, I refers to Carbowax 20M-Polyethylene Glycol at 150°.

** These compounds were isolated (R. D. H. Murray and R. M^{c}Crindle, Chem. & Ind., 1964, 500; A. H. Kapadi and Sukh Dev, Tetrahedron Letters, 1965, 2729.) from an extract of Erythroxylon Monogynum by a combination of column chromatography, over silica gel impregnated with silver nitrate (10%), and preparative g.l.c.

EXPERIMENTAL SECTION.

General Procedures.

Thin layer chromatography (t.l.c.) was carried out on Kieselgel G (Merck) impregnated with silver nitrate (10% with benzene/light petroleum (b.p. 60-80°) (3:7) as developing solvent. All of the tetracyclic diterpenes of the pimaradiene-derived series were separable by this means, running in the order isoatisirene (least polar), kaurene, atisirene, isokaurene and hibaene, although the last two were often difficult to distinguish.

Gas liquid chromatographic (g.l.c.) analyses were performed on a Pye "Argon" gas chromatograph using glass columns (1/8in. x 4ft). A wide range of column packings was tried, e.g. 1% S.A.I.B., 1% XE60, 1% SE-30, 1% QF1 and 1% C.H.D.M.S. at 150° with a gas flow rate of 35-40ml./min., and 10% P.E.G.A. (at 175°) and 10% Ap.L. (at 200°) with a flow rate of 65ml. argon/min., but no column which would separate the pairs of hydrocarbons kaurene-atisirene and isokaurene-isoatisirene was found. Although the columns containing 10% of liquid phase gave the widest separation of peaks, a 2% Carbowax 20M column (at 150°, 35ml. argon/min.) was preferred since this gave an equally clean resolution of the peaks while permitting much faster runs. Retention indices,[39] which were reproducible (±2 units) over several runs at different times using the same column are recorded in table 2 for the diterpenes studied.

Gas chromatography-mass spectral (g.c.m.s.) analyses were

performed on an L.K.B. 9000A Gas Chromatograph-Mass Spectrometer using a glass column ($\frac{1}{4}$in. x 10ft) with a 10% SE-30 packing at 150° with helium as the carrier gas at a flow rate of 35ml./min. Again, kaurene-atisirene and isokaurene-isoatisirene were not resolved.

Preparative g.l.c. was carried out on an Aerograph "Autoprep" Model A-700 using a 3/8in. x 20ft column packed with 5% Carbowax at 215° and with helium as the carrier gas at a flow rate of 200ml./min.

All starting materials and reference compounds were shown to be homogeneous by t.l.c. and g.l.c., and gave the expected n.m.r. and i.r. spectra. Physical data are collected in table 2.

Isomerisation of ent-hibaene.

(1) Dry hydrogen chloride was bubbled vigorously through solutions of hibaene (10mg.) in each of the solvents light petroleum (b.p. 60-80°), benzene, chloroform, diethyl ether, ethyl acetate and acetonitrile (5ml., AnaLaR grade solvents.) for 10 min., and the resulting solutions left at room temperature. At intervals of 2 hr, 1 day, 2 days, 4 days and 7 days, aliquot portions were removed and evaporated to dryness under reduced pressure. The residues, dissolved in light petroleum (b.p. 40-60°), were filtered through a short column of alumina (Woelm Grade 1, neutral) and examined by t.l.c. and g.l.c. The samples from the light petroleum, diethyl ether and ethyl acetate solutions were found to contain only starting material. T.l.c.

of aliquots from benzene, chloroform and acetonitrile solutions indicated five observable products (Additional faint solvent line spots observed in all cases may have been due to the presence of some hydrochloride. See below.) whose retentions were identical to those of isoatisirene, kaurene, atisirene, isokaurene and hibaene. G.l.c. showed only three peaks (I 2153, 2232 and 2298; see footnote to table 2.) corresponding to hibaene, isokaurene and/or isoatisirene and kaurene and/or atisirene respectively, the relative intensity of the latter two peaks increasing with increasing reaction time.

(2) In one experiment with hibaene (50mg.) in chloroform (10 ml.), isomerisation for 30 days, and work up as above, gave a solid (52mg.) which on g.l.c. showed the three expected hydrocarbon peaks, and a fourth (85% of the total) of much larger retention period (Relative retention 4.22; hibaene=1). Crystallisation of the mixture from methanol containing a few drops of methylene chloride furnished the major component (one peak on g.l.c.) as colourless prisms, m.p. 67-72°. This compound had an n.m.r. spectrum very similar to that published[22] for hibaene hydrochloride. (Lit.,[22] m.p. 73-74°.)

(3) In a larger scale experiment, hibaene (150mg.) was isomerised in chloroform (100ml.) for 14 days and worked up as before. The product (145mg.) was chromatographed on silica gel impregnated with silver nitrate (15g.; 10% $AgNO_3$), elution being performed with 0-5% ethyl acetate/light petroleum (b.p. 40-60°). This gave early fractions in which the least polar component

(isoatisirene) was concentrated free of isokaurene, one of these (3mg.) consisting largely (approx. 90% by g.l.c.) of this component, whose identity was confirmed by its retention behaviour on t.l.c. and g.l.c., and comparison of its mass spectrum (obtained by g.c.m.s.) with that of authentic material. Later fractions all contained mixtures, so that the residue (112mg.), from which most of the isoatisirene had been removed, was subjected to preparative g.l.c. Thereby a clean separation of the products corresponding to each of the three peaks was obtained, as indicated by analytical g.l.c. The first component eluted (12mg.) proved on comparison by i.r., n.m.r., $[\alpha]_D$ and mixed m.p. after crystallisation from methanol/methylene chloride to be ent-hibaene. The second (13mg.) and third (6.5mg.) components were found similarly to be ent-isokaurene and ent-kaurene respectively. The amount of atisirene in the last must have been very small as it could not be detected in the n.m.r. spectrum of the crude fraction.

(4) In a further experiment with hibaene (15mg.) in chloroform (15ml.), aliquots were removed after periods of 2, 4, 7, 21 and 35 days, and worked up as before. T.l.c. showed the presence of the same five products as before, and from peak area measurements on the chromatograms obtained on g.l.c., the ratio hibaene: (isokaurene + isoatisirene): (kaurene + atisirene) was obtained. The identity of the products was confirmed by comparison of their mass spectra (obtained by g.c.m.s.) with those of the pure hydrocarbons, obtained under the same conditions,

and the ratios isokaurene:isoatisirene and kaurene:atisirene were calculated.[33] Representative results are in table 1.

Acetolysis of ent-hibaene hydrochloride.

The hydrochloride (27mg.) was refluxed in acetic acid (AnaLaR, 5ml.) containing anhydrous sodium acetate (200mg.) for 24 hr. Water was then added to the mixture and the product extracted with light petroleum (b.p. 40-60°), the extract washed with sodium bicarbonate solution then water, dried over sodium sulphate and the solvent evaporated to give a pale yellow oil (20mg.). T.l.c. of this indicated the presence of a single hydrocarbon with the same Rf as hibaene, and a trace of polar material. The n.m.r. spectrum of the oil confirmed that it was indeed largely hibaene, showing only a small additional peak at 7.96τ(s., acetate-CH_3?). The polar component was readily removed by filtration of the mixture in light petroleum (b.p. 40-60°) through a short column of alumina.

Isomerisation of ent-kaurene.

Kaurene (20mg.) in AnaLaR chloroform (20ml.) was isomerised under the same conxitions as were employed for hibaene above (4). T.l.c. indicated only two products, starting material and isokaurene, after isomerisation times of 2 hr and 2 days. With prolonged times (2-6 weeks), a faint spot on t.l.c. corresponding in retention behaviour to isoatisirene was observed. No hibaene was detected in the products, g.l.c. showing only two peaks (I 2230 and 2298). G.c.m.s. indicated that, in addition to kaurene, isokaurene and isoatisirene, some atisirene was

formed (table 1).

Isomerisation of ent-isoatisirene.

Isoatisirene (8mg.) under the above isomerisation conditions, even after prolonged reaction times (2-6 weeks), gave a mixture which showed only two spots on t.l.c. and two peaks on g.l.c. (I 2232 and 2298), the retentions in each case corresponding to isoatisirene and atisirene. The mass spectra, from g.c.m.s., of samples after prolonged reaction times were interpreted satisfactorily by postulating the presence of a trace (ca 0.5%) of isokaurene under the isoatisirene peak (table 1).

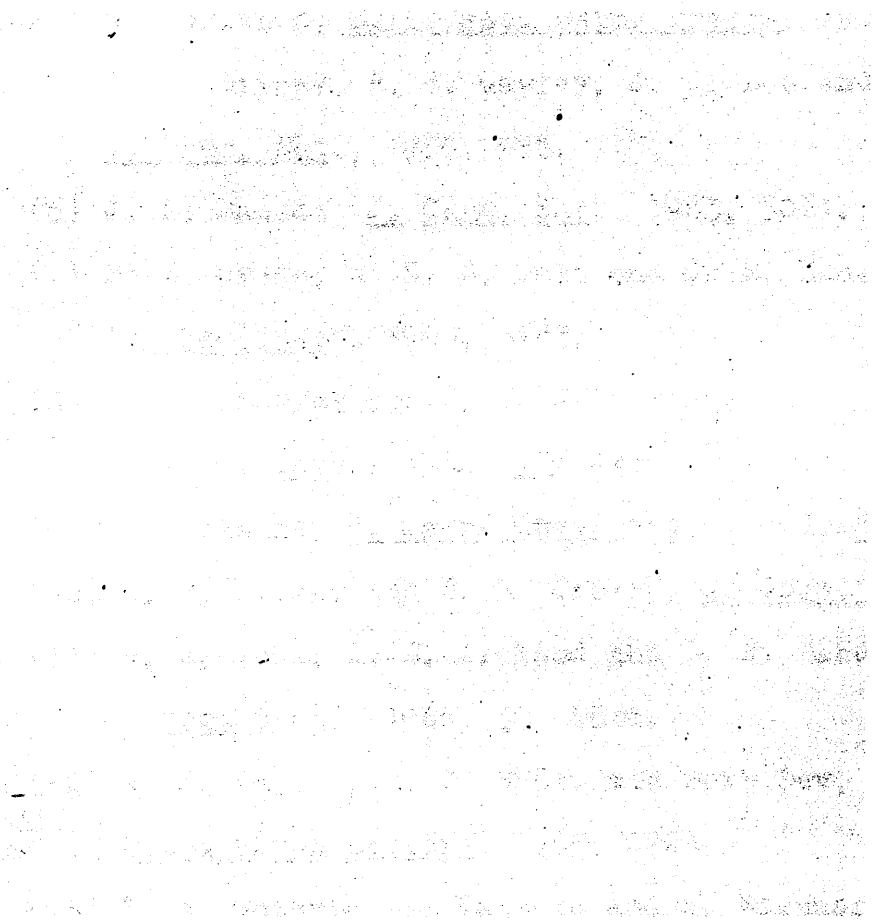
Isomerisation of ent-trachylobane.

Trachylobane (15mg.) on isomerisation for 15 min. produced a mixture of atisirene, isoatisirene, kaurene and isokaurene. The presence of these four products was shown by t.l.c. and g.c.m.s., and from the latter, the product composition was calculated. G.l.c. showed two peaks (I 2233 and 2298) and only a trace of product with an Rf similar to that of hibaene. No change in product composition was detected after acid treatment for a further 14 days (table 1).

Isomerisation of phyllocladene and isophyllocladene.

Phyllocladene (10mg.) or isophyllocladene (10mg.) under the above conditions were both rapidly isomerised to a mixture which showed two spots on t.l.c. and two peaks on g.l.c. whose retention behaviour was identical to that of the starting materials. Prolonged acid treatment (up to 6 weeks) led to no detectable change in the product composition. The mass spectra,

obtained by g.c.m.s., confirmed the absence of other products. The equilibrium mixture contained very largely isophyllocladene (97-98%).



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