1). SYNTHESIS OF DIBENZCYCLOHEPTADIENONE.

2). STEREOCHEMISTRY OF TWO METABOLIC DIOLS.

A Thesis

submitted for the degree of

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at the

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by

William F. Williamson, B.Sc.

University of Glasgow,

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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The work contained in Part I forms part of a paper, 'Colchicine and Related Compounds Part IX' which has been accepted for publication by the Chemical Society.

1949.

A brief résumé of part of the work contained in Part II has appeared in the 26th Annual Report of the British Empire Cancer Campaign (1948), p.249.

Contents.

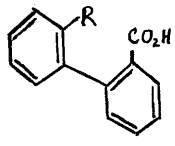
Part I.

Synthesis of Dibenzcycloheptadienone.

Summary.

Part I.

An attempt has been made to synthesise derivatives of dibenzcycloheptadiene by appropriate transformation of the two carboxylic acid groups of diphenic acid (I; R=CO_2H)



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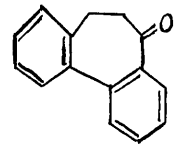

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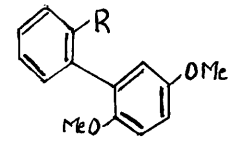
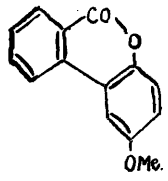


(III)

By an adaptation of the McFadyen-Stevens process[14] the aldehydo acid (I; R = CHO) has been prepared and hence via the derived acrylic (I; R = CH = $CH.CO_2H$) and propionic (I; R = $CH_2.CH_2.CO_2H$) acids cyclisation to dibenzcycloheptadienone (II) has been demonstrated. The yields, however, are not good and attempted improvement by desulphurisation of the p-tolyl thiol ester (I; R = $CO.S.C_6H_4.CH_3$ (p)) afforded only the alcohol (I; R = CH_2OH).

An alternative method, involving the synthesis of (III; R = CO_2H) and the projected expansion of the carboxylic to the propionic acid side chain, failed by reason of the unreactive nature of the ester (III; R = CO_2Me) and the facility with which (III; R = CO_2H) yielded the diphenylmethylolid (IV)



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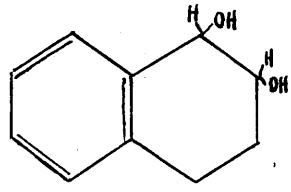

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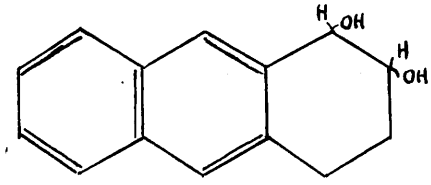


(VI)

Part II.

As a contribution to knowledge of the stereochemical configuration of the 1:2-dihydroxy-1:2-dihydronaphthalene and - anthracene, metabolites of the respective aromatic hydrocarbons isolated by Young[8] and by Boyland[1] from rat and rabbit urine, the cis- and trans- forms of the diols (V) and (VI) have been synthesised. In each case the configuration has been assigned on the basis of the general criteria established by Criegee.

In the case of (V) optical resolution of the trans-compound into its d and l- forms shows that the former is identical with the dihydride obtained by Young through catalytic hydrogenation of the naphthalene metabolite. In the case of (VI) the physical properties of the synthetic dl-trans- compound indicate its identity with the dihydride of the optically inactive anthracene metabolite described by Boyland. In conjunction therefore with the fact that the 9:10-dihydroxy-9:10-dihydrophenanthrene, the corresponding metabolite of phenanthrene from rats, is said to be optically

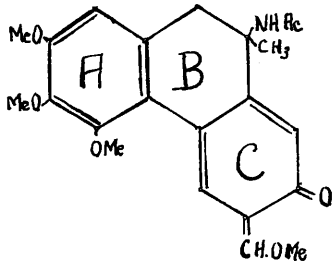
active[34] and must accordingly be the trans isomer, it appears that the metabolic process of hydroxylation leads to the trans- and not to the cis- configuration.

Part I.

Introduction.

The widespread interest in colchicine, the alkaloid of the meadow saffron (Colchicum autumnale L.) derives, primarily, from its biological properties. The most pronounced of these is its antimitotic action which makes it an invaluable reagent for producing polyploid varieties of plants. It has also been found to inhibit tumour growth, although its use in this latter respect is limited by its very high toxicity.

The chemical constitution of colchicine is still unknown although recent work in these laboratories has added considerably to our knowledge in this field.



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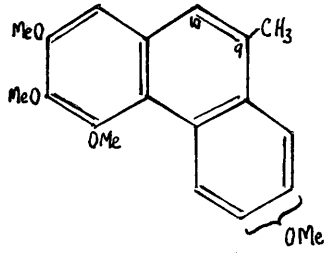

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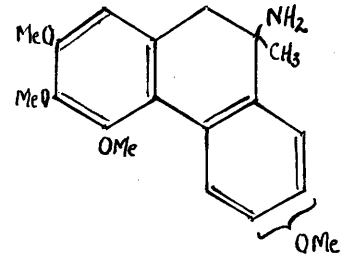


(III)

The formula (I) for colchicine proposed in 1924 by Windaus[1] has been shown in recent years to be unsatisfactory. It is conceded that colchicine contains a tricyclic system and that ring A has the structure assigned to it by Windaus. The six-membered ring structures of B

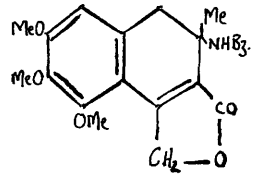
and C however have been subject to adverse criticism as being incompatible with the known chemical properties of colchicine. In the present discussion we will consider only the nature of ring B. This problem has been partly elucidated by a consideration of the degradation product of colchicine, deaminocolchinol methyl ether, to which Windaus assigned the structure (II).

Colchicine contains one methoxyl group which is readily hydrolysed, the product of hydrolysis being colchiceine. Treatment of colchiceine with iodine in the presence of alkali yields N-acetyliodo colchinol:-

$$C_{21}H_{23}O_6N + I \longrightarrow C_{20}H_{22}O_5NI + (CHO)$$

Dehalogenation followed by deamination of this product yields deaminocolchinol methyl ether and the isomeric iso-deaminocolchinol methyl ether. When demethylated by treatment with hydriodic acid and then distilled with zinc dust, deaminocolchinol methyl ether was converted to 9-methylphenanthrene and on this basis Windaus assumed it was a tetramethoxylated methylphenanthrene. Windaus decided it was a 9-methylphenanthrene (II) rather than a 10-methyl derivative on the following evidence. Colchicine is oxidised by chromic acid to a ketone, oxycolchicine, $C_{22}H_{23}O_7N$ and the methylene group implied by this oxidation can be provided only in ring B. If such a methylene group

is present in ring B then the two substituents present in this ring, viz. $-CH_3$ and $-NHCOCH_3$, must be attached to the same carbon atom. Now colchinol methyl ether (III) was oxidised by chromic acid to 4-methoxyphthalimide, suggesting that the nitrogen atom is separated from ring C by a single carbon atom. It follows therefore that the $-NHCOCH_3$ group, and hence also the $-CH_3$ group, is attached to the 9-position in ring B. Another piece of evidence brought forward by Windaus in favour of the six-membered nature of ring B was the oxidation of N-benzoyl trimethylcolchinic acid. Trimethylcolchinic acid is formed by deacetylation of colchiceine, and treatment of its N-benzoyl derivative with cold alkaline permanganate leads to the oxidation of ring C with formation of N-benzoylcolchide and N-benzoylcolchinic acid anhydride.



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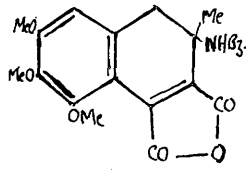

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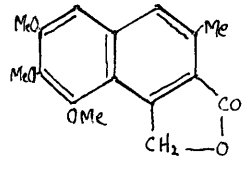

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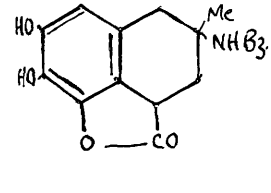


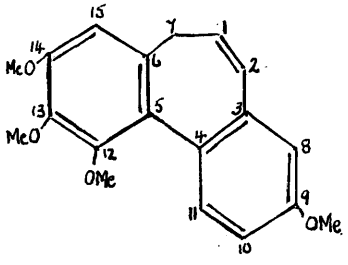
(VII)

The structures postulated by Windaus for these oxidation products, (IV) and (V) respectively, were consistent with; (a) the ready deamination of the former, which would be represented as (IV) ⟶ (VI) on this

formulation, and (b) the formation of a lactone, supposedly peri-linked as in (VII), by treatment of the anhydride with hydriodic acid.

That Windaus's formulation of deaminocolchinol methyl ether and of colchinol methyl ether as (II) and (III) respectively was not in accordance with the properties of these compounds was first pointed out by Cohen, Cook and Roe[2]. Thus (III) is a derivative of 9-amino-9:10-dihydrophenanthrene which should readily eliminate ammonia and pass into the wholly aromatic state. Colchinol methyl ether however displays no such readiness to eliminate ammonia. Moreover, when colchinol methyl ether is converted to a carbinol by treatment with nitrous acid, the carbinol obtained is much more resistant to the elimination of water than would be the case with the tertiary carbinol that would arise from formula (III). These indications that the formula (II) was incorrect were confirmed by the synthesis of both compounds corresponding to this formula, neither of which was identical with deaminocolchinol methyl ether[3].

An alternative structure (VII) for deaminocolchinol methyl ether was proposed by Barton, Cook and Loudon[4].



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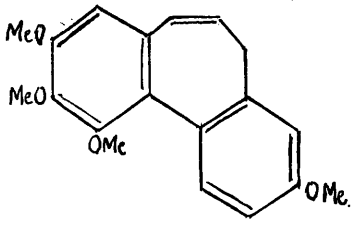

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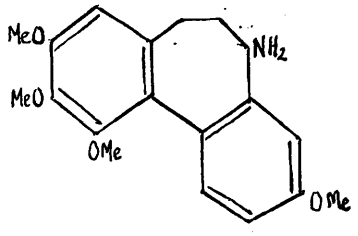
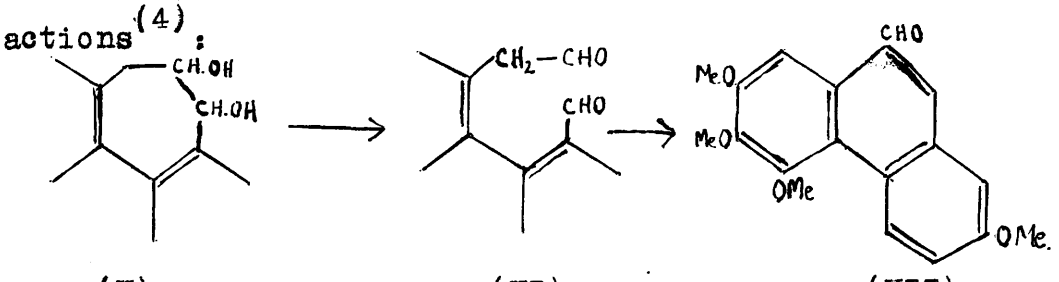


(IX)

On the basis of this dibenzcycloheptatriene structure all the facts explained by Windaus by his six-membered ring B structure can be equally well explained. Thus the formation of 9-methylphenanthrene from deamino-colchinol methyl ether by demethylation followed by zinc dust distillation means that the drastic conditions have brought about a contraction of the seven-membered ring. That the dibenzcycloheptatriene framework does rearrange itself under these conditions has been proved by the observation that 3:4:5:6-dibenz-$\Delta^{1:3:5}$-cycloheptatriene affords 9-methyl phenanthrene when heated with hydriodic acid and then distilled with zinc. The oxidation of colchinol methyl ether to 4-methoxyphthalimide and of colchicine to oxycolchicine are still understandable if ring B is seven-membered and furthermore the presence of succinic acid among the oxidation products of colchicine and its derivatives, which was observed by Windaus, now becomes understandable also. The formation of N-benzoyl colchide and

N-benzoylcolchinic acid anhydride does not invalidate this new proposal since the structure of these oxidation products has not been rigorously proved and it may be that they also contain a seven-membered ring. A more positive proof of the correctness of the postulated seven-membered ring structure is provided by the following series of reactions[4]:



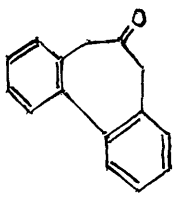
(X) (XI) (XII)

Deaminocolchinol methyl ether (VII) and the isomeric iso-deaminocolchinol methyl ether (VIII) are both readily hydrogenated with production of the same dihydride. The ethylenic linkage thus disclosed in deaminocolchinol methyl ether is subjected to stepwise oxidation, first with osmium tetroxide to a glycol (X) then by cleavage with lead tetra-acetate to a di-aldehyde (XI) which cyclises to the 10-phenanthraldehyde (XII). The structure of this aldehyde is proved by its oxidation to the carboxylic acid and comparison of the latter with a synthetic specimen of 2:3:4:7-tetramethoxyphenanthrene-10-carboxylic acid. A similar series of reactions starting from iso-deaminocolchinol methyl ether gives rise to the corresponding 9-phenanthr-

aldehyde. Since Hofmann degradation does not generally involve any change in the carbon skeleton[5], it may be assumed that colchinol methyl ether also contains a seven-membered ring as shown in (IX).

While it is not yet certain that colchicine itself contains a seven-membered ring, the presence of such a ring in certain of its degradation products makes it obviously desirable to evolve a method of synthesising similar dibenzcycloheptatrienes. Such a method would need to be applicable to the synthesis of dibenzcycloheptatrienes unsymmetrically substituted in the aromatic nuclei. Most of the syntheses hitherto achieved fail to fulfil this latter condition.

The first successful synthesis of a dibenzcycloheptadiene was due to Kenner[6] who obtained the ketone (XIII) from 2:2'-ditolyl-$\omega:\omega'$-dicarboxylonitrile.



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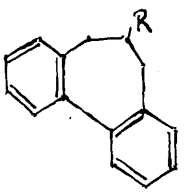

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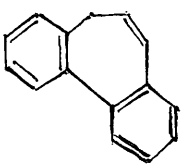

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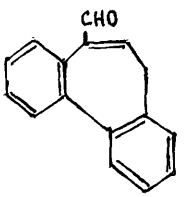
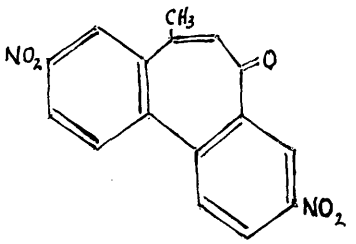


(XVI)

Continuing this work on the cyclisation of derivatives of 2:2'-ditolyl, Kenner[7] obtained from $\omega:\omega'$-dibromo-2:2'-ditolyl by condensation with malonic ester, diethyl-3:5-dibenz-$\Delta^{3:5}$-cycloheptadiene-1:1-dicarboxylate which on

hydrolysis and decarboxylation yielded the acid (XIV) ($R = CO_2H$). The amine (XIV, $R = NH_2$) was obtained from this acid by the Curtius reaction and dry distillation of its hydrochloride afforded 3:5-dibenz-$\Delta^{1:3:5}$-cycloheptatriene (XV). A similar synthesis of a dibenzcycloheptatriene recorded by Weitzenböck[8] is the cyclisation of biphenylene-2:2'-diacetaldehyde tetramethylacetal to the aldehyde (XVI). Somewhat similar is the formation of the ketone (XVII) by heating 2-bromo-5-nitro-acetophenone with copper where intramolecular condensation of the intermediary diphenyl (XVIII) occurs[9].



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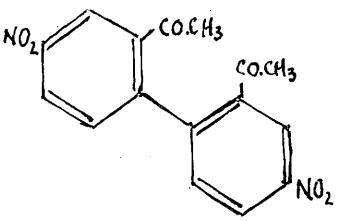

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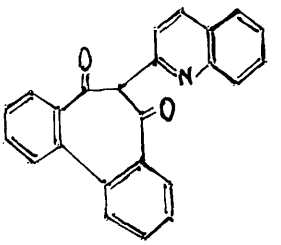
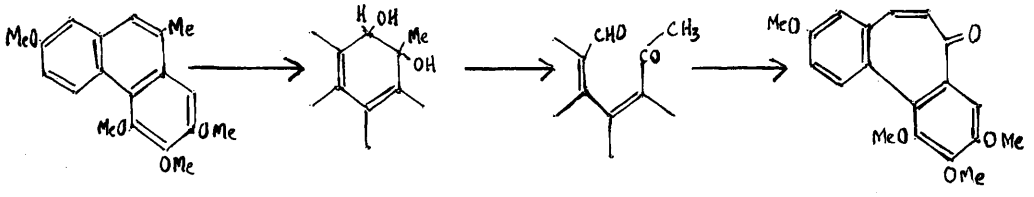


(XIX)

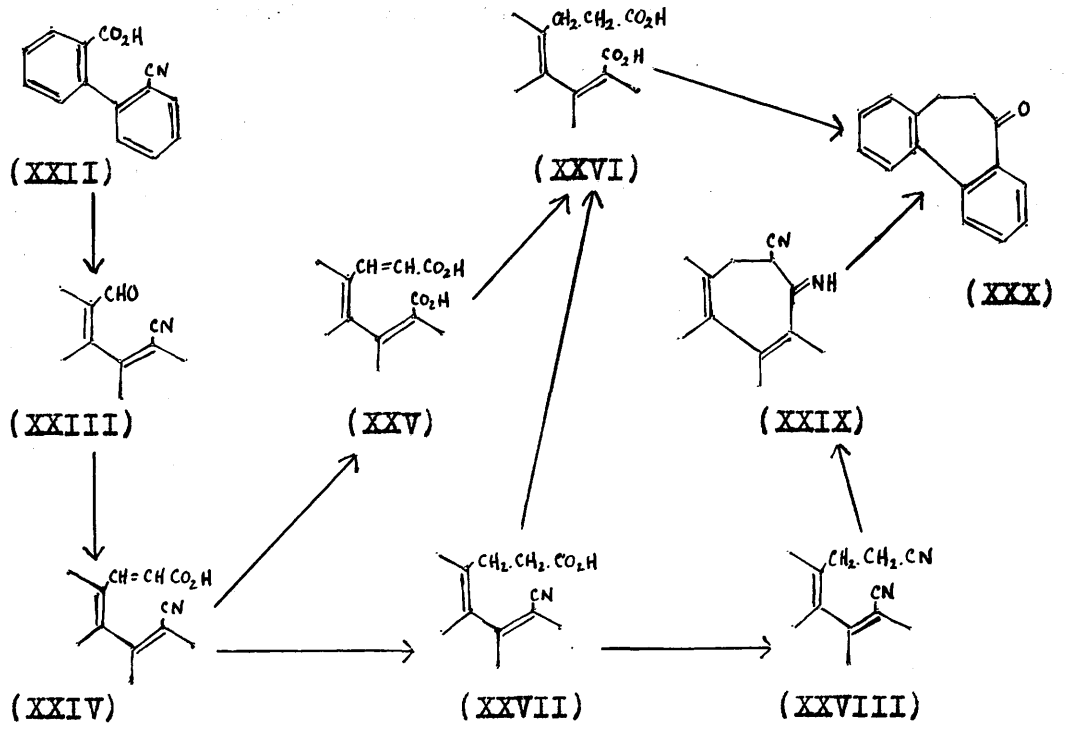
The condensation of diphenic anhydride with α-picoline and quinaldine gives rise to dibenzcycloheptadienes of the type (XIX)[10,11]. None of these methods, however, gave promise of being applicable to the synthesis of unsymmetrically substituted dibenzcycloheptatrienes, but this condition is fulfilled in a recently described synthesis[12]. Here the starting material is a 9- or 10-methyl phenanthrene which is oxidised with osmium tetroxide. Cleavage of the

diol so formed with lead tetra-acetate affords an aldehyde which cyclises to a dibenzocycloheptatriene. In this way 9:12:13:14-tetramethoxy-3:4:5:6-dibenzocyclohepta-1:3:5-triene-7-one (XXI) has been synthesised from 2:3:4:7-tetramethoxy-9-methylphenanthrene (XX) as illustrated in the following scheme:-



(XX) (XXI)

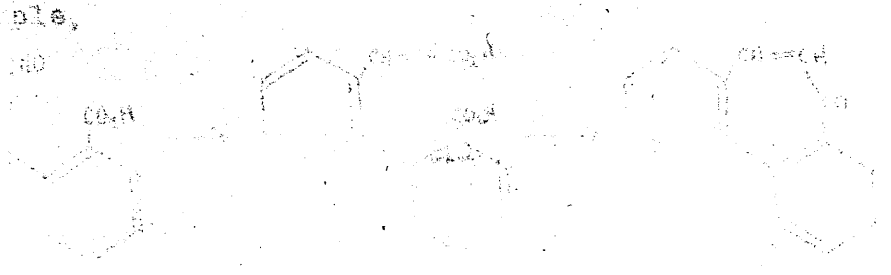
This synthetic product has been found to be identical with an oxidation product of deaminocolchinol methyl ether. A synthesis described in a recent publication by Rapoport and Williams[13] which may also prove adaptable to the synthesis of unsymmetrically substituted derivatives, and which in part duplicates the work to be described in this thesis, is shown in outline below.



The cyano acid (XXII) is obtained by Beckmann rearrangement of phenanthrenequinonemonoxime and converted to the aldehyde (XXIII) by Rosenmund reduction of its chloride. Condensation of this aldehyde with malonic acid afforded the cyanocinnamic acid (XXIV) which was converted to the saturated dibasic acid (XXVI) by either of the two routes indicated. The acid (XXVI) was cyclised to the ketone (XXX) by two methods: a) by pyrolysis of the thorium salt and b) by the Dieckmann method followed by saponification and decarboxylation of the intermediate β -keto ester. An alternative, and more efficient method for converting

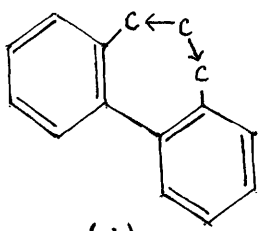
the cyanocinnamic acid (XXIV) to the cycloheptadiene is also outlined. This involves formation of the dinitrile (XXVIII) which is cyclised by the Ziegler procedure to the cyano-imine (XXIX). Hydrolysis of this cyano-imine affords the ketone (XXX) in excellent yield.

In the following section the present author's attempts to find an alternative approach to the desired synthesis are described.

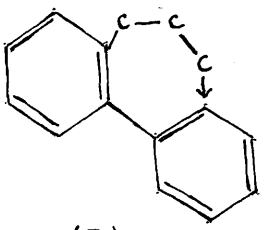


Discussion.

In the present work two methods of approach to the synthesis of dibenzcycloheptatriene derivatives were considered:-

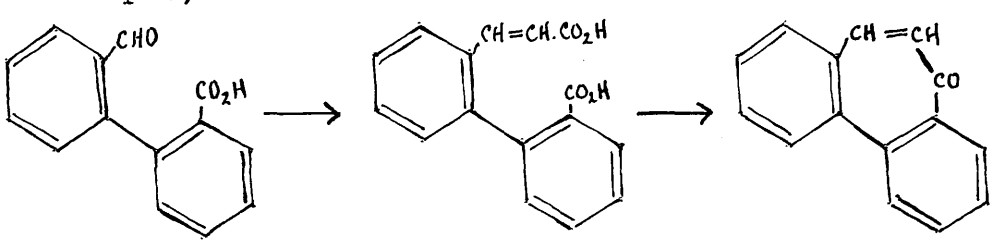


(A)



(B)

A diphenyl nucleus is present in the starting material in each case. In (A) the starting material is diphenic acid or its derivatives and an attempt is made to complete the ring by the introduction of a carbon atom as sketched. In (B) an attempt is made to bridge the two phenyl residues by a three carbon atom chain attached to one of them, i.e., the starting material in this case is a phenyl hydrocinnamic acid. A particular approach by the first route would be for example,



The initial problem is to make the half aldehyde and to that end the procedure first considered was an adaptation

of that used for the preparation of aldehydes from monobasic acids by McFadyen and Stevens[14], viz:-

$$R.CO_2H \longrightarrow R.CO.NH.NH.SO_2Ph \xrightarrow{Na_2CO_3} R.CHO + PhSO_2Na + N_2$$

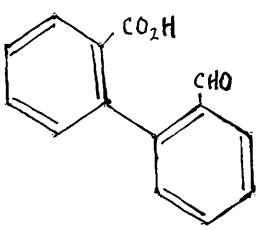
Since in the present case this would need to be applied to only one of the carboxyl groups of diphenic acid, it had first to be ascertained that the desired monophenylsulphonhydrazide could be made available. Two methods of obtaining the monophenylsulphonhydrazide of diphenic anhydride were successfully elaborated:

(a) by treatment of the anhydride with hydrazine hydrate to form the monohydrazide, followed by reaction with benzenesulphonyl chloride, and

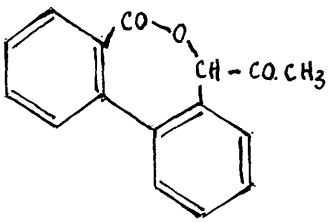
(b) directly, by treating the anhydride with benzenesulphonhydrazide. The latter, though giving a product contaminated with a small amount of an isomeric compound, had the advantage of fewer stages and better yield based on the anhydride. It was also applicable to phthalic anhydride which, throughout this series of experiments, was frequently used as a guide to the probable behaviour of diphenic anhydride.

Attempted decomposition of the phenylsulphonhydrazide of phthalic acid failed to produce any aldehyde. On the other hand, initial attempts in the diphenic acid

series showed that in this case the aldehyde could be obtained. The yield however was poor and the usual separation of the neutral aldehyde product from both unchanged sodium carboxylate and the sodium sulphinate produced is rendered inapplicable by the presence of the residual carboxyl group in the half aldehyde (XXXI).



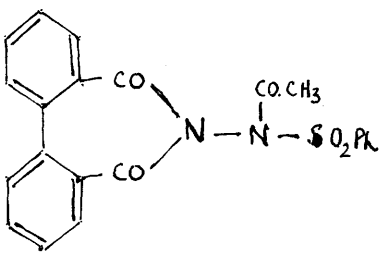
(XXXI)



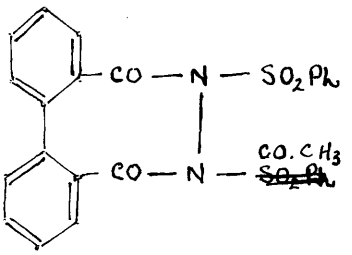
(XXXII)

Modifications of the reaction conditions, with respect to both temperature and duration of the reaction failed to effect a satisfactory increase in the yield of aldehyde, a considerable percentage of the phenylsulphonhydrazide resisting decomposition. Further attempts were then made along the line of more efficient separation of the aldehyde from the unchanged sulphonhydrazide and the sodium sulphinate produced. It was considered that a separation could possibly be effected by forming an acetoxy-lactone (XXXII) of the aldehydo acid (XXXI) which could be readily separated from the phenylsulphonhydrazide and the sodium sulphinate because of its alkaline insolubility, and from which the aldehydo-acid could be readily regenerated. It

was ascertained that the aldehydo-acid did indeed form an alkaline insoluble acetoxy-lactone, conveniently prepared by treatment of the aldehydo-acid with acetic anhydride in presence of a little concentrated sulphuric acid, and that the aldehydo-acid was regenerated by hydrolysis. This, therefore, would be a satisfactory process if the phenylsulphonhydrazide were unchanged by the above treatment with acetic anhydride. Unfortunately however under these conditions the phenylsulphonhydrazide also yielded an alkali insoluble compound of empirical formula $C_{22}H_{16}O_5N_2S$ and possessing therefore either structure (XXXIII) or (XXXIV)



(XXXIII)



(XXXIV)

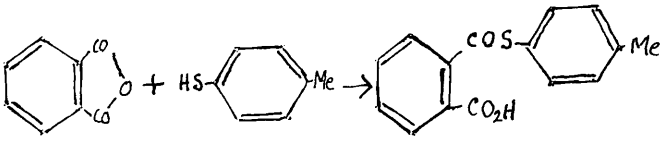
The phenylsulphonhydrazide was then treated with acetic anhydride in the presence of pyridine in the hope that the pyridine would preserve the carboxyl group intact and lead to the formation of an alkali soluble product. The compound obtained by this method however was again insoluble in alkali and was in fact identical with the previous compound. The method of separation finally adopted was based on the observation that the phenylsulphonhydrazide, but not

the aldehydo-acid, was precipitated from alkaline solution by sulphur dioxide. Accordingly the desired separation was effected by treating the alkaline solution from the reaction with sulphur dioxide till all unchanged phenylsulphonhydrazide was precipitated and then obtaining the aldehyde free from by-products by acidification with mineral acid. By this method a yield of 34% of the aldehyde, based on the phenylsulphonhydrazide, was attained.

At this stage in the synthesis better yields than these realised in the above process are imperative. Accordingly other methods for the conversion of carboxyl to aldehydo groups were considered. The method described by Wolfrom and Karabinos[15] for the synthesis of aldehydes from thiol esters by desulphurisation with Raney nickel in alcohol appeared to be the most promising. It was necessary to ascertain that a half thiol ester could be obtained from diphenic acid and it was also desired to determine if the method were applicable to thiols other than ethyl mercaptan which had been employed by Wolfrom and Karabinos. In this case the thiol used was thio-p-cresol of which a supply was available. As before, the behaviour of phthalic anhydride was first studied.

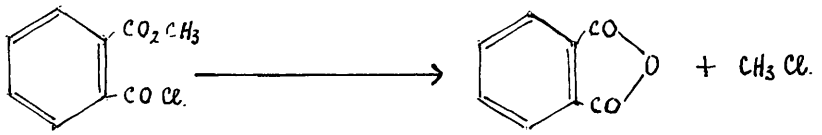
The dithiol esters of phthalic acid have been described by Chakravarti and Saha[16] who obtained them by

the condensation of phthalic anhydride with the thiol at 140°C and with phosphorus pentoxide as condensing agent. They reported that no condensation could be effected by employing sulphuric acid, dry hydrochloric acid, anhydrous zinc chloride or anhydrous zinc chloride and hydrochloric acid as condensing agents. The mono thiol ester of phthalic acid which was required is not described in the literature.

The condensation 

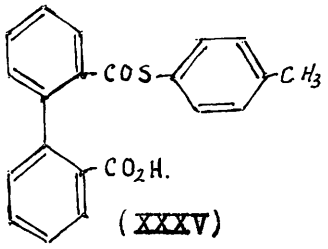
was first attempted by allowing the reagents to stand overnight in dry pyridine. No condensation took place under these conditions, nor was any success achieved by heating the reagents in pyridine. The condensation was then attempted under Schotten-Baumann conditions, but again without success. Closely analogous to the desired condensation is the reaction between 3-nitrophthalic anhydride and thiols to yield mono thiol esters; which has been described by Wertheim[17] as a suitable means for the identification of thiols. The conditions described by Wertheim were applied to phthalic anhydride but failed to bring about any reaction. It appeared that phthalic anhydride could not be used directly for the production of the mono thiol ester. It was therefore decided to prepare the more reactive o-carbomethoxy benzoyl chloride.

According to H. Meyer[18] this acid chloride is obtained as a colourless oil which does not solidify on cooling to -18°C, by the reaction of monomethyl phthalate with thionyl chloride. The chloride is decomposed by heating on a water bath or more slowly on standing at room temperature according to the equation:-

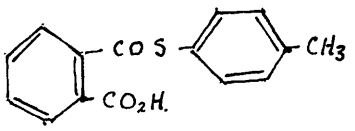


The oil obtained by treating monomethyl phthalate with thionyl chloride was freed from thionyl chloride and treated with thio-p-cresol and pyridine at 0°C. A crystalline solid was obtained from the reaction which was the desired p-tolyl-o-carbomethoxythiolbenzoate (XXXVI).

It had meantime been found that the behaviour of diphenic anhydride towards thio-p-cresol was quite different from that of phthalic anhydride. By allowing the reagents to stand overnight in pyridine a 40% yield of the half thiol ester (XXXV) was obtained.



(XXXV)

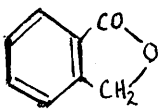


(XXXVI)

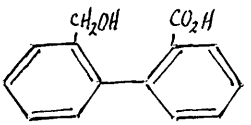
The reaction in hot pyridine was then studied in an attempt to improve on this yield. The optimum conditions were found

to be heating at 70°C for ninety minutes. Under these conditions a yield of 70% of the half thiol ester was attained.

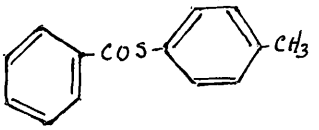
The desulphurisation of these thiol esters with Raney nickel was carried out under the conditions described by Wolfrom and Karabinos. The product obtained from p-tolyl-o-carbomethoxythiolbenzoate (XXXVI) was phthalide (XXXVII), i.e., the thiol ester grouping was reduced to the alcohol and the methyl ester hydrolysed. Lactonisation between the alcoholic and carboxyl groups produced would then give rise to phthalide.



(XXXVII)



(XXXVIII)



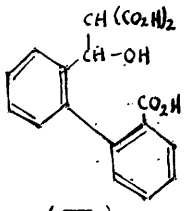
(XXXIX)

The p-thiotolyl hydrogen diphenate (XXXV) treated in the same way gave rise to the alcohol, 2-hydroxymethyl-diphenyl-2'-carboxylic acid (XXXVIII). In this case lactonisation did not occur during the reaction. In neither case could more than 20% of the material be accounted for in the products. Similar results were obtained with p-tolyl thiolbenzoate (XXXIX), i.e., low yield of the alcohol with no trace of any aldehyde, and this method was therefore abandoned.

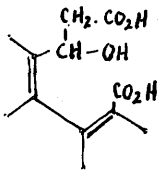
The results obtained here are in accordance with those of Prelog[19], Frank, Fanta and Tarbell[20] and McMillan[21], all of whom have reported the formation of primary alcohols by Raney nickel desulphurisation of thiol esters. The last named author has also reported the formation of hydrocarbons in this reaction by removal of the entire thiol ester group. More recently[22] it has been reported that, while freshly prepared Raney nickel leads to the formation of alcohols, aldehydes can be obtained by deactivating the catalyst.

An investigation of another possible route to the half aldehyde of diphenic acid was then undertaken. This was based on a synthesis of phthalaldehydic acid[23] but in the case of diphenic acid, reduction of diphenimide yielded diphenamic acid instead of the desired intermediate, diphenide, and the method was therefore inapplicable.

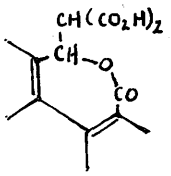
With the half aldehyde of diphenic acid obtained via the phenylsulphonhydrazide the next stage in the synthesis was attempted. This involved, as already explained, the introduction off a carbon atom to form a link between the aldehydo and carboxyl groups. The method adopted to achieve this was a condensation of the aldehyde with malonic acid. On paper there are a variety of possible products from this reaction, e.g.



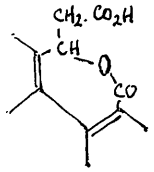
(XL)



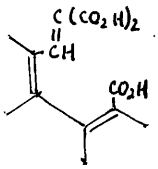
(XLI)



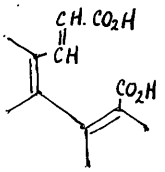
(XLII)



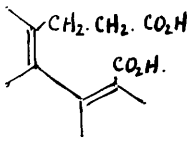
(XLIII)



(XLIV)



(XLV)



(XLVI)

The reaction was carried out in pyridine with the addition of a few drops of piperidine and a crystalline compound obtained in 60% yield. Analysis of this compound showed it to be either (XLIII) or (XLV); titration experiments suggesting it had in fact the latter structure, and the compound on catalytic hydrogenation took up two atoms of hydrogen to yield the dibasic acid (XLVI).

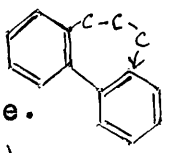
Phthalic anhydride on heating with acetic anhydride and fused potassium acetate yields phthalyl acetic acid[27].

If diphenic anhydride underwent an analogous reaction the product would, on hydrogenation, yield the acid (XLVI) which could thus be obtained without the necessity of preparing the half aldehyde. The reaction between diphenic anhydride

and acetic anhydride was therefore investigated but did not lead to any crystalline product.

The ring closure of the acid (XLVI) to a dibenzcycloheptatriene was attempted by three different routes. Sublimation of the barium salt[24] and treatment of the sodium salt with acetic anhydride[25] was carried out on hundred milligram portions of the acid. In each case the product was an uncrystallisable gum which could however be converted to a crystalline 2:4-dinitro phenylhydrazone which was found, melting point and mixed melting point, to be identical with the 2:4-dinitrophenylhydrazone of 3:4:5:6-dibenzcyclohepta-1:3:5-triene-7-one. The remainder of the acid, 280 milligrams, was converted to its dimethyl ester by treatment with diazomethane and the ester subjected to the Dieckmann condensation[26]. By treatment with sodium in benzene (cf. [7], p.626) 3:4:5:6-dibenzcyclohepta-3:5-diene-2-one-1-carboxylic ester was obtained as an oil. This oil when refluxed with dilute sulphuric acid did not yield the desired ketone and, since the product was found to give still the ferric chloride colouration characteristic of the Dieckmann ester, the treatment with dilute sulphuric acid was renewed. The product from this attempted hydrolysis was purified by distillation and yielded a small amount of liquid distillate which could not be crystallised.

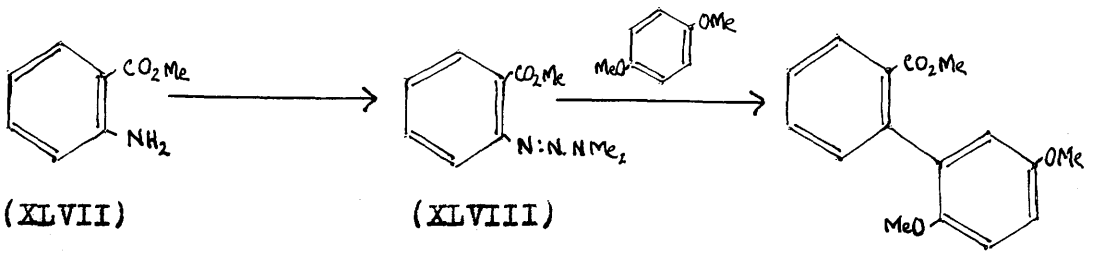
No crystalline ketone was obtained therefore from this synthesis although the gummy products obtained yielded the 2:4-dinitrophenylhydrazone of the desired ketone.

With regard to method (B), i.e., ring closure of a phenylhydrocinnamic acid  (see page 15) several considerations emerge.

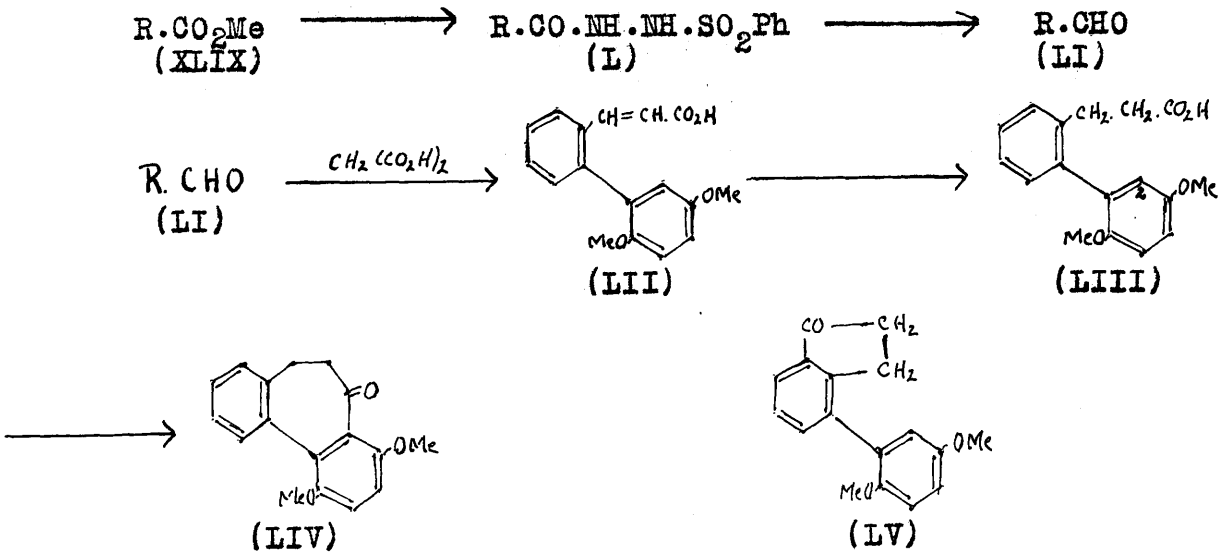
1). According to v. Braun[28] ring closure to a five-membered ring is likely, ceteris paribus, to take preference over closure to a seven membered ring.

2). By appropriate substitution in the diphenyl nucleus seven-membered ring formation might be facilitated; moreover the unsymmetrically substituted diphenyls so required would have the advantage of leading to unsymmetrically substituted dibenzcycloheptatrienes.

These considerations have led to a general investigation of this method of approach in these laboratories, the following work being one particular aspect with the materials and route proposed as shown:-



(XLVII) (XLVIII) (XLIX)



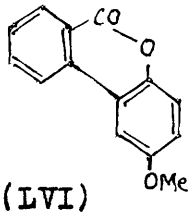
The dimethyltriazene (XLVIII) was obtained from methyl anthranilate by diazotisation and coupling with dimethylamine. It was condensed with hydroquinone dimethyl ether to form the unsymmetrical diphenyl (XLIX) by the method of Elks and Hey[29].

The choice of hydroquinone dimethyl ether as the component with which to condense the triazen was governed by the following considerations:-

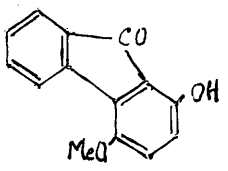
1). It eliminated the possibility of isomers being formed during the condensation since all positions in the hydroquinone dimethyl ether at which coupling could occur are equivalent.

2). The presence of an ortho methoxy group might activate position 2 in (LIII) and favour seven-membered ring formation rather than the formation of the hydrindone derivative (LV).

In practice by this route the ester (XLIX) was obtained satisfactorily but it was not possible to obtain its hydrazide by reaction with hydrazine hydrate. An ethanolic solution of the ester when refluxed for a week with 99% hydrazine hydrate was not converted to the hydrazide. The acid was then treated with thionyl chloride under mild conditions in an effort to obtain the acid chloride. The compound obtained however was not the acid chloride; its analysis corresponds to the empirical formula $C_{14}H_{10}O_3$ and its structure will therefore be either (LVI) or (LVII).



(LVI)



(LVII)

The fluorenone structure is unlikely since the compound is almost colourless when pure and does not give the characteristic reactions of phenolic or carbonyl groups. The compound is therefore assumed to have the lactonic structure (LVII) and this is borne out by its behaviour with alkali.

Since neither the acid hydrazide nor the acid chloride could be obtained from the ester (XLIX), this method had to be abandoned.

Experimental.

Diphenic acid monophenylsulphonhydrazide.

(1) Action of Hydrazine Hydrate on Diphenic Anhydride.

Diphenic anhydride (2 g.) was treated slowly with hydrazine hydrate (2 cc., 90%) cooling being applied to control the vigorous reaction. After warming at 100°C for 90 minutes water was added and the solution cautiously acidified. The resulting sticky mass slowly solidified. It was powdered and crystallised from ethanol. The filtered needle-shaped crystals appeared to be homogeneous, sintered ca 176°C and melted at 185°C with gas evolution. Yield, 1.3 g. (62%).

This appears to be the acid hydrazide (CO_2H; $CO.NH.NH_2$) since it dissolves in aqueous sodium bicarbonate with effervescence and this result confirms the description (viz., m.p. 183°C) given to the compound by Labriola[30] in contrast to that of Kalb and Gross[31], viz., m.p. 164°C with foaming.

Action of benzenesulphonyl chloride on above compound.

A suspension of the hydrazide (1.3 g.) in pyridine (4 cc.) was treated in the cold with benzenesulphonyl chloride (10.9 g.) washed in with pyridine (2 cc.). The yellow solution after standing overnight was diluted with

water and acidified with dilute sulphuric acid. The resulting precipitate solidified and was filtered and washed free of acid. It crystallised from dilute ethanol as a rather nondescript buff coloured solid, m.p. (with some decomposition and previous sintering) 220°C. Yield, 1.9 g. (94%).

(2). Action of Benzenesulphonhydrazide on Diphenic Anhydride.

Diphenic anhydride (6.6 g.) was added slowly, with cooling, to benzenesulphonhydrazide (5.1 g.) in pyridine (30 cc.). After standing overnight it was poured into dilute hydrochloric acid. The oil that was precipitated slowly solidified and was filtered and washed with water, m.p. 184°C. The m.p. was raised to 220°C by repeated crystallisation from dilute ethanol. Yield, 8.3 g. (70%).

The compound was soluble in aqueous sodium hydroxide and sodium carbonate and was precipitated from these solutions by sulphur dioxide, but not by carbon dioxide. This is the $\alpha:\beta$ di-acyl hydrazide, R.CO.NH.NH.SO_2Ph. (Found: C, 60.3; H, 4.1; N, 7.3%. $C_{20}H_{16}O_5N_2S$ requires C, 60.6; H, 4.0; N, 7.1%).

In the purification of this compound from the crude material there was obtained from the ethanolic mother liquors a very small amount of an isomeric substance, m.p.

220°C, mixed m.p. with above compound 215°C.
(Found: C, 60.8; H, 4.0; N, 6.9%. $C_{20}H_{16}O_5N_2S$ requires C, 60.6; H, 4.0; N, 7.1%).
This is presumably the $\alpha:\alpha$ di-acyl hydrazide, $R.CO(SO_2Ph)N.NH_2$.

The second method is thus the simpler and more efficient in this case. Only the main product was subjected to McFadyen-Stevens' decomposition, insufficient of the other isomer being obtained for detailed investigation.

N-benzenesulphonamino phthalimide.

Phthalic anhydride (5 g.) was slowly added to a solution of benzenesulphonhydrazide (5.8 g.) in pyridine (18 cc.). After standing overnight the solution was poured into dilute hydrochloric acid. The resulting solid was crystallised from glacial acetic acid and had m.p. 262°C. It was soluble in aqueous sodium hydroxide and sodium carbonate and was reprecipitated by sulphur dioxide, but not by carbon dioxide. Yield, 6.6 g. (66%).
(Found: C, 55.4; H, 3.2; N, 9.1%. $C_{14}H_{10}O_4N_2S$ requires C, 55.6; H, 3.3; N, 9.3%).

Attempted McFadyen-Stevens' Decomposition of N-benzenesulphonamino phthalimide.

N-benzenesulphonamino phthalimide (4 g.) in ethylene glycol (50 cc.) was treated with sodium carbonate (7.7 g.)

at 160°C. The alkali was added in the course of 30 seconds and the reaction allowed to proceed for a further 240 seconds. The reaction was terminated by the careful addition of boiling water (100 cc.) and the cooled solution was filtered through charcoal. There was no precipitate formed on treating the filtrate with sulphur dioxide. Acidification with dilute sulphuric acid precipitated phthalic acid. There was no trace of any aldehydic product.

2'-formyldiphenyl-2-carboxylic acid (XXXI).

Diphenic acid monophenylsulphonhydrazide (2 g.) in ethylene glycol (20 cc.) was treated with sodium carbonate (2.5 g.) at 165°C. The alkali was added in the course of 30 seconds and the reaction allowed to proceed for a further 240 seconds, when it was terminated by the careful addition of boiling water (up to 100 cc.). After cooling and filtering through charcoal to remove suspended matter, sulphur dioxide was passed into the solution till there was no further precipitation. This precipitated material was recrystallised from dilute methanol and then had m.p. 220°C. It did not depress the melting point of the monophenylsulphonhydrazide of diphenic acid and was re-treated in later runs. When the solution no longer gave a precipitate with sulphur dioxide it was acidified with dilute sulphuric acid. A solid was slowly precipitated, of which the melting point

after crystallisation from dilute methanol was 132°C.
Yield, 0.51 g. (45%).
(Found: C, 74.5; H, 4.4%. $C_{14}H_{10}O_3$ requires C, 74.4; H, 4.4%).

Other attempts at this decomposition were made with modified conditions in respect of a) volume of solvent, b) temperature of reaction (155 - 185°C), and c) duration of reaction (165 - 320 seconds).

The yields were variable < 45%.

By-products obtained:-

In one case only was diphenic acid obtained.

There was also obtained during one attempt an unidentified acid which was precipitated by sulphur dioxide. It was recrystallised from dilute methanol, m.p. 163- 165°C.
(Found: C, 67.3; H, 5.2%).

ω -acetoxy diphenide (XXXII).

The crude aldehyde was dissolved in the minimum quantity of acetic anhydride and three drops of concentrated sulphuric acid added. After standing overnight in a tightly corked flask the solution was poured into cold water sufficient to remove the acetic anhydride and was then extracted with ether. After washing with alkali the ether solution was dried over anhydrous sodium sulphate and concentrated. The solid thus obtained was crystallised from

methanol (m.p. 125°C) and was insoluble in alkali. (Found: C, 71.6; H, 4.3%. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%).

Hydrolysis of ω-acetoxy diphenide.

By dissolving the compound in acetic acid, adding a little dilute sulphuric acid and refluxing for 90 minutes it was converted completely to the acid-aldehyde, m.p. 132°C, mixed m.p. with the pure acid-aldehyde 132°C.

Action of acetic anhydride on diphenic acid monophenylsulphonhydrazide.

The sulphonhydrazide was treated exactly as in the above experiment and the compound obtained crystallised from acetic acid, m.p. 216°C. It was insoluble in alkali. (Found: C, 63.3; H, 3.9; N, 6.5%. $C_{22}H_{16}O_5N_2S$ requires C, 62.9; H, 3.8; N, 6.7%).

The sulphonhydrazide (0.5 g.) was dissolved in pyridine (10 cc.) and acetic anhydride (2.5 cc.) added. After standing overnight the solution was poured into dilute hydrochloric acid and the solid obtained crystallised from acetic acid, m.p. 215°C. This was the same compound as that obtained by the previous treatment; mixed m.p. 216°C.

Action of thio-p-cresol on phthalic anhydride.

1. In pyridine.

Phthalic anhydride (1 g.; 1 mole) was dissolved in pyridine (6 cc.) and treated with thio-p-cresol (1.4 g.; 1½ moles). After standing overnight the solution was poured into dilute hydrochloric acid and extracted with ether. From the ether solution on drying and concentration thio-p-cresol was obtained. From the aqueous layer crystals of phthalic acid were slowly deposited. No condensation product was obtained from the reaction.

The experiment was repeated, heating the pyridine solution at 70°C for 45 minutes instead of leaving it overnight at room temperature. The phthalic anhydride and thio-p-cresol were recovered unchanged on pouring the solution into dilute hydrochloric acid.

2. Under Schotten-Baumann Conditions.

Equimolecular proportions of phthalic anhydride and thio-p-cresol were shaken up with an excess of 20% sodium hydroxide for 90 minutes. The solution was then filtered from a little unchanged phthalic anhydride and the filtrate acidified with dilute hydrochloric acid. The precipitate contained only phthalic acid and thio-p-cresol.

3. By fusing the reactants together (cf. Wertheim[17]).

One mole (0.5 g.) of phthalic anhydride was treated in a test tube with 1½ moles (0.65 g.) of thio-p-cresol. After heating with a free flame for about a minute the tube was allowed to cool. The mixture was kept cool while 20 drops of 10% sodium hydroxide were added in several portions with vigorous shaking. The solid which did not go into solution during this treatment was found to be unchanged phthalic anhydride. The filtrate was treated with about 10 drops of 5% hydrochloric acid and the precipitate obtained was found to be thio-p-cresol.

o-carbomethoxy benzoyl chloride (cf. H. Meyer[18].

Mono methylphthalate (3 g.) was heated at 40°C with an excess of thionyl chloride till evolution of sulphur dioxide and hydrochloric acid had ceased (45 minutes). Care was taken not to allow the temperature to rise above 40°C owing to the rapidity with which the product is decomposed at higher temperatures. After the reaction had ceased the excess thionyl chloride was removed under reduced pressure. The resulting, faintly yellow coloured oil, was used immediately in the preparation of the thiol ester.

p-tolyl-o-carbomethoxythiolbenzoate (XXXVI).

To the o-carbomethoxy benzoyl chloride prepared in the above experiment was added 1 mole of thio-p-cresol and sufficient pyridine to dissolve the reagents which were cooled in an ice bath during the addition. After standing overnight the solution was poured into a mixture of dilute hydrochloric acid and ice. The oil which separated was extracted with ether, the ether extract washed with alkali, dried (sodium sulphate), and concentrated. The solid obtained was crystallised from methanol, m.p. 58-59°C. Yield, 1.7 g. (36% based on the monomethyl phthalate). (Found: C, 67.3; H, 4.9%. $C_{16}H_{14}O_3S$ requires C, 67.1; H, 4.9%).

p-thiotolyl hydrogen diphenate (XXXV).

One mole of diphenic anhydride (0.5 g.) and 1.2 moles thio-p-cresol (0.34 g.) were heated at 70°C in pyridine (6 cc.) for 90 minutes. On pouring the cooled solution into dilute hydrochloric acid an oil separated which solidified on rubbing. It was crystallised from dilute methanol, m.p. 147°C. Yield, 0.57 g. (73%). (Found: C, 72.8; H, 4.6%. $C_{21}H_{16}O_3S$ requires C, 72.4; H, 4.6%).

This compound should therefore be a carboxylic acid but, though it is acidic to litmus and phenol phthalein, it is

insoluble in cold alkali. On heating with alkali the ester-acid dissolved and there crystallised on cooling a compound, m.p. 88°C, which on treatment with dilute acid in the cold was reconverted to the ester-acid. The solid obtained from the alkali solution must therefore be the sodium salt of p-thiotolyl hydrogen diphenate. (Found: C, 51.6; H, 5.5%. $C_{21}H_{15}O_3S.Na.7H_2O$ requires C, 51.6; H, 5.8%).

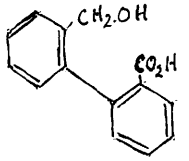
Raney Nickel hydrogenolysis of p-tolyl-o-carbomethoxythiol-benzoate.

The Raney nickel employed was prepared by the method of Mozingo[32].

To the thiol ester (1.5 g.) was added Raney nickel (7.5 g.) in 70% ethanol (30 cc.). The mixture was refluxed for 90 minutes and the Raney nickel filtered from the cooled solution. The ethanol was removed from the filtrate by distillation and an oil separated from the aqueous residue. Sufficient ether was added to dissolve this oil and the solution was then thoroughly shaken with a bisulphite solution. After three hours no bisulphite addition compound had been deposited, the ether solution was therefore separated, dried and concentrated. The residual oil crystallised on standing and cooling, m.p. 71-72°C, mixed m.p. with phthalide 71-72°C. Yield, 0.12 g. (17%).

Raney Nickel Hydrogenolysis of p-thiotolyl hydrogen diphenate.

To the thiol ester (1.5 g.) was added Raney nickel (7 g.) in 70% ethanol (30 cc.). The solution was refluxed for 40 minutes and the Raney nickel filtered from the cooled solution. The ethanol was removed from the filtrate by distillation and the aqueous residue extracted with ether. The ether extract was dried and concentrated and the solid obtained crystallised from ether and petroleum ether (40-60°) in the latter of which it was sparingly soluble. This compound had m.p. 145-146°C and when heated at 110°C for one hour was converted into a crystalline solid, m.p. 132°C which did not depress the m.p. of diphenide. (cf. Kenner[6], p.2113).

The product is therefore 2-hydroxymethyldiphenyl-2'-carboxylic acid 

Yield, 0.2 g. (20%).

Reduction of Diphenimide (cf.[23]).

The diphenimide was obtained by heating diphenic anhydride with urea[33].

Zinc dust (1.05 g.) was stirred to a thick paste with a solution of copper sulphate (0.1 g.) in water (3.5 cc.) and 20% sodium hydroxide (3 cc.) added. The mixture was cooled to 5°C in an ice bath and diphenimide (1.2 g.) was

added slowly in small portions so that the temperature did not rise above 8°C, the mixture being shaken during the addition. The mixture was diluted with water and warmed on a steam bath till evolution of ammonia ceased (5 - 6 hours). The solution was then filtered, the filtrate concentrated to a small volume and treated with concentrated hydrochloric acid till it was acid to Congo Red. The solution was heated to boiling and on cooling a colourless solid was deposited, m.p. 182-184°. On crystallisation from ethanol the m.p. rose to 192°, mixed m.p. with diphenamic acid 192°. Yield, 0.72 g. (60%).

Reaction of diphenic anhydride with acetic anhydride (cf.[27]).

Diphenic anhydride (2.24 g.) was suspended in acetic anhydride (8 cc.) and warmed to a clear solution. To this solution there was added in one lot 1 g. potassium acetate (freshly fused, powdered and weighed hot). The whole was heated in an oil bath at 145-155° for 15 minutes. During the reaction the solution became yellow and a yellow solid was deposited on cooling. This solid was filtered and washed with warm water to remove potassium salts. On cooling some diphenic acid crystallised from the washings. The solid was therefore suspended in boiling water for three hours and filtered hot. From the filtrate there was obtained 1.75 g. diphenic acid, m.p. 226°C. The insoluble

portion melted at 132-135°C with previous softening ca 80°C. It dissolved in warm alkali and on acidification a solid was obtained, m.p. 90-92°C. It was soluble in alcohol, ethyl acetate, acetic acid and benzene, but could not be obtained crystalline.

Condensation of 2'-formyldiphenyl-2-carboxylic acid (XXXI), with malonic acid.

The aldehyde (1.2 g.) and malonic acid (0.55 g.) were dissolved in pyridine (6 cc.) and eight drops of piperidine added. The solution was heated on the steam bath for one hour then refluxed for 15 minutes. This heating was accompanied by evolution of a gas and the solution became deep red in colour. The solution was cooled and poured into dilute hydrochloric acid. The resulting oil slowly solidified and was crystallised from dilute acetic acid, m.p. 228°C. Yield, 0.877 g. (60%). (Found: C, 72.1; H, 4.5%. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%). cf. Rapoport and Williams[13] record a m.p. of 230-231°C for β-2'-carboxy-2-diphenylylacrylic acid.

Titration of the above acid.

180 mg. of the acid were dissolved in methanol and titrated with 0.1 N sodium hydroxide with phenol phthalein as indicator. The acid titrated as a dibasic acid.

Equivalent weight = 130. Equivalent weight calculated for β -2'-carboxy-2-diphenylylacrylic acid (XLV) = 134.

In a previous titration carried out on 8 mg. of the acid with 0.01 N sodium hydroxide an end-point corresponding to the acid being monobasic was obtained when the titration was carried out in the cold, the dibasic end-point being obtained on warming the solution. This result, which would favour the lactonic structure (XLIII) for the acid, was not reproducible.

Catalytic hydrogenation of β -2'-carboxy-2-diphenylyl-acrylic acid (XLV).

For preparation of catalyst see[34].

84 mg. of palladium black were shaken in glacial acetic acid in an atmosphere of hydrogen till adsorption of hydrogen ceased. A solution of 100 mg. of the acid (XLV) in glacial acetic acid was then added to the catalyst which was again shaken in an atmosphere of hydrogen. There was initially a fairly rapid uptake of hydrogen (6 cc.) and eventually 9 cc. were absorbed. This volume is in agreement with the addition of two atoms of hydrogen to a compound of formula $C_{16}H_{12}O_4$. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. The solid obtained was crystallised from dilute acetic acid, m.p. 185°C. (cf. Rapoport and Williams[13]

record a m.p. of 171-173°C for β -2'-carboxy-2-diphenylyl-propionic ~~acrylic~~ acid).

(Found: C, 71.1; H, 4.8%. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%).

Sublimation of the Barium salt of β -2'-carboxy-2-diphenylyl-propionic acid (XLVI).

100 mg. of the acid were titrated with baryta using one drop of phenol phthalein as indicator. The solution was evaporated and the barium salt dried. This barium salt did not sublime or show any change on heating to 360°C under a pressure of 1 mm. The temperature was raised above 360°C under the vacuum of a water pump whereby a brown oil sublimed. The sublimate could not be crystallised even after distillation under a pressure of 0.2 mm. It was treated with 2:4-dinitrophenylhydrazine and the dinitrophenylhydrazone obtained crystallised from glacial acetic acid, micro m.p. 218-220°C. The melting point did not rise above 220°C after two further crystallisations. A mixed micro m.p. of this hydrazone with the 2:4-dinitrophenylhydrazone of 3:4:5:6-dibenzcyclohepta-1:3:5-triene-7-one (micro m.p. 237°C) melted at 219-220°C.

Treatment of the disodium salt of β -2'-carboxy-2-diphenylyl-propionic acid (XLVI) with acetic anhydride.

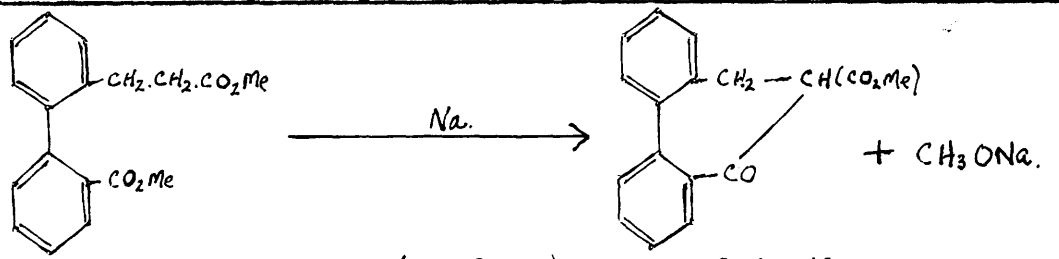
100 milligrams of the acid were neutralised with the theoretical quantity of standard sodium hydroxide. The solution was evaporated to dryness and the dry sodium salt refluxed for one hour with acetic anhydride (2 cc.). The acetic anhydride was removed under reduced pressure and the residue treated with very dilute alkali. The alkaline solution was extracted with ether. From the aqueous portion on acidification 8 mgs. of the acid were recovered. The ether extract was dried and concentrated and the residue distilled under a pressure of 0.2 mm. The distillate could not be crystallised but on treatment with 2:4-dinitrophenyl-hydrazine yielded a crystalline phenylhydrazone, micro m.p. 195-220°C. After several crystallisations from glacial acetic acid the melting point rose to 233-234°C. Mixed micro m.p. with the 2:4-dinitrophenylhydrazone of 3:4:5:6-dibenzcyclohepta-1:3:5-triene-7-one (micro m.p. 237°C) melted at 234-235°C.

Esterification of β -2'-carboxy-2-diphenylylpropionic acid (XLVI).

To a suspension of the acid (280 mg.) in a little ether was added slowly an ethereal solution of diazomethane

(0.54 g.). The addition was accompanied by gas evolution. After standing overnight the ether and excess diazomethane were removed and the residual oil dissolved in benzene and filtered from the flocculent precipitate resulting from the action of diazomethane on the glass sides of the container.

3:4:5:6-dibenzcyclohepta-3:5-diene-2-one-1-carboxylic ester.



Sodium powder (0.06 g.) prepared in the presence of xylene in the usual manner was covered with dry benzene and a solution of the di-ester in benzene, obtained as described above, was then added. The solution was raised to its boiling point and refluxed for one hour. By this time most of the sodium had gone into solution which was now reddish brown in colour. The solution was decanted from the sodium into dilute sulphuric acid and the benzene layer separated, washed, dried and concentrated. The residual oil gave a purple colouration with ferric chloride solution.

Hydrolysis of 3:4:5:6-dibenzcyclohepta-3:5-diene-2-one-1-carboxylic ester.

The ester obtained in the above experiment was refluxed with dilute sulphuric acid (1:2) for three hours.

The cooled solution was extracted with ether and the ether extract washed with alkali, dried and concentrated. The oil obtained could not be induced to crystallise and was therefore subjected to a vacuum distillation. The distillate, b.p. 150-155°/0.2 mm., could not be crystallised. It was found that this material still gave a ferric chloride colouration and the sulphuric acid treatment was therefore repeated. Ether extraction again yielded a gummy material which could not be crystallised but yielded a crystalline 2:4-dinitrophenylhydrazone.

1-(o-carbomethoxyphenyl)-3:3-dimethyltriazen (XLVIII).

Methyl anthranilate (50 g.) in concentrated hydrochloric acid (120 g.) and water (130 cc.) was diazotised with a concentrated solution of sodium nitrite (23 g.) in water. The diazo solution was added from a cooled dropping funnel to a cooled stirred mixture of aqueous dimethylamine (30%; 120 cc.) and an excess of 30% aqueous sodium carbonate (330 cc.) over that required for the neutralisation of the acid. Stirring was continued for 30 minutes and the separated triazen extracted with benzene. The extract was dried over caustic potash and after removal of the benzene the residual triazen was distilled under reduced pressure and obtained as a pale yellow oil, b.p. 172-176°/12 mm. Yield, 50 g.; 72%.

3:6-dimethoxy-2'-carbomethoxydiphenyl (XLIX).

Hydroquinone dimethyl ether was prepared by the method of Bogert and Howells[35].

The triazen obtained above (50 g.) was dissolved in molten hydroquinone dimethyl ether (160 g.) and heated on a steam bath with slow addition of glacial acetic acid (60 cc.). Heating was continued overnight. The resulting dark coloured liquid was dissolved in chloroform, washed with dilute hydrochloric acid, with water, with dilute sodium hydroxide and again with water. The chloroform solution was dried over anhydrous sodium sulphate and concentrated. Distillation then yielded 135 g. of hydroquinone dimethyl ether, b.p. 110-112°C/20 mm. The residue was distilled from a smaller distilling flask and the following fractions were obtained:-

1). A small amount of hydroquinone dimethyl ether, b.p. 95-100°C/10 mm.

2). An intermediate oily fraction, pale yellow in colour, b.p. 127-132°C/10 mm. Weight ~ 3 g.

3). The main oily fraction, b.p. 196-204°C/10 mm. Weight ~ 7 g.

4). A very viscous orange coloured gum, b.p. 205-215°C/10 mm., with much decomposition. Weight ~ 1 g.

Fraction 2) was hydrolysed by the addition of

potassium hydroxide (1.5 cc. 50% per g.) and sufficient methanol to give a clear solution. This solution was refluxed for one hour and the methanol removed. The cold solution was extracted with ether to remove any unsaponifiable material and the aqueous portion acidified with dilute hydrochloric acid. The pale brown solid obtained was dissolved in methanol and treated with charcoal. A colourless crystalline solid, 3:6-dimethoxy-2'-carboxydiphenyl, was thus obtained, m.p. 155°C.
(Found: C, 69.9; H, 5.4%. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%).

When fraction 3) was rubbed with half its volume of methanol and kept for several days in a refrigerator crystals were slowly formed. These were purified by crystallisation from methanol, m.p. 65°C. This was 3:6-dimethoxy-2'-carbomethoxy diphenyl (XLIX).
(Found: C, 70.6; H, 6.0%. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%).
This ester was hydrolysed with aqueous alcoholic potassium hydroxide and yielded, as expected, the same acid as that obtained from fraction 2) by hydrolysis. Further amounts of this acid were also obtained by the hydrolysis of the concentrated mother liquors from fractions 3) and 4).

An unidentified solid was obtained from fraction 4)

by rubbing with methanol and was crystallised as pale yellow needles from glacial acetic acid, m.p. 291-293°C.

The residue left in the distilling flask was dissolved in chloroform, washed free of decomposition products with dilute hydrochloric acid and, combined with the residues from later runs, concentrated and redistilled.

In later runs, where the distillation was carried out at lower pressures, 3-5 mm. no decomposition product corresponding to the solid obtained from fraction 4) above was formed.

Yield of ester 10% based on the triazen.

Treatment of 3:6-dimethoxy-2'-carbomethoxy diphenyl (XLIX) with hydrazine hydrate.

a). The ester (1.5 g.) was treated with hydrazine hydrate (4.5 cc., 90%) and sufficient methanol to make the solution homogeneous at its boiling point. The solution was refluxed on a water bath for 7 hours and most of the methanol distilled off. On cooling an oil separated and solidified on standing, m.p. 64°C. It did not depress the m.p. of the ester.

b). The ester (1 g.) was treated with hydrazine hydrate (2.5 cc., 90%) and ethylene glycol (5 cc.). The ester did not go into solution completely and after refluxing the mixture for four hours there was no noticeable

change in the amount of undissolved ester. A little dioxan was added to facilitate solution of the ester and the mixture refluxed for a further three hours. On cooling an oil separated and did not solidify on standing. By hydrolysis with potassium hydroxide the acid was recovered.

c). The ester (1 g.) was dissolved in ethanol and treated with hydrazine hydrate (2.5 cc., 99%). The solution was refluxed for a week. On concentrating the solution after this time the ester was recovered unchanged.

Treatment of 3,6-dimethoxy-2'-carboxy diphenyl with thionyl chloride.

The acid (0.5 gm.) was dissolved in dry benzene (~ 5 cc.) and thionyl chloride (1.2 cc.) added. The solution was left overnight at room temperature, the flask being corked with a calcium chloride guard tube. The benzene together with the excess thionyl chloride was removed by distillation under reduced pressure; bath temperature 20 - 25°C. A slightly yellow coloured solid remained, m.p. 114°C. When purified by crystallisation from benzene the solid was almost colourless, m.p. 119-120°C. The compound contained no chlorine, it gave no colouration with ferric chloride solution and no precipitate with 2:4-dinitrophenylhydrazine reagent. The compound is insoluble in cold alkali but dissolves on heating and is precipitated

unchanged on acidification.

(Found: C, 73.7; H, 4.4%; OMe, 13.4%. $C_{14}H_{10}O_3$ requires C, 74.3; H, 4.4; OMe, 13.7%).

When the acid is refluxed with thionyl chloride the same compound is obtained.

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Part II.

Stereochemistry of Two Metabolic Diols.

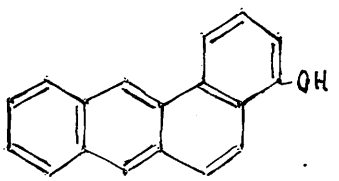
Introduction.

The fate of polycyclic aromatic hydrocarbons, especially those which possess carcinogenic activity, has received considerable attention in recent years.

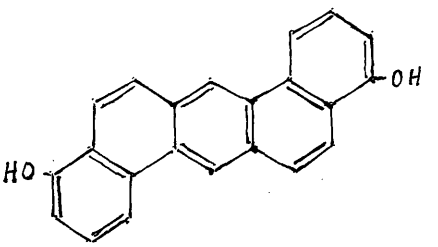
In general it has been found that the metabolic products from such hydrocarbons are phenols, excreted either as conjugated sulphates or glucuronides or in the free state, or diols. In many cases mercapturic acids have also been isolated[38]. Such diols as have been obtained are readily converted to phenols by treatment with dilute acid and, as we shall see later, are considered to be intermediates in the metabolic process leading to the production of phenols, although the mechanism of phenol formation is not necessarily the same in all cases. No essential difference in the metabolism of carcinogenic and non-carcinogenic hydrocarbons has been detected. Furthermore, investigation has shown the phenolic metabolites to be either non-carcinogenic or distinctly less active than the parent hydrocarbon. In the light of these facts the original supposition that carcinogenic activity is dependent on the formation of an active metabolite rather than on the direct action of the hydrocarbon itself becomes untenable. It appears rather that the metabolic process represents a

means of detoxification of biologically active material.

This process of detoxification, if indeed it may be so regarded, involves an attack on the molecule at a position which is frequently different from that attacked by purely chemical reagents. Thus Boyland and Levi[1] showed that anthracene was attacked, not at the reactive meso positions, but at the 1:2- positions with the production of 1:2-dihydroxy-1:2-dihydroanthracene. 1:2-Benzanthracene and 1:2:5:6-dibenzanthracene are also subject to substitution and oxidation at one or both of the reactive 9- and 10-positions of the anthracene system. Biochemical oxidation of these hydrocarbons on the other hand gives rise to 4'-hydroxy-1:2-benzanthracene (I) and 4':8'-dihydroxy-1:2:5:6-dibenzanthracene (II) respectively[2,3].



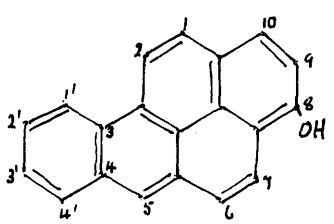
(I)

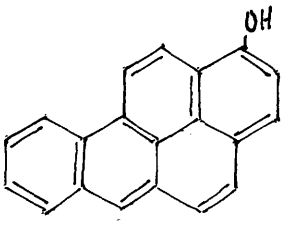


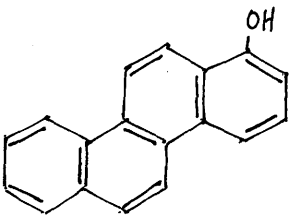
(II)

Another example of this phenomenon is provided by 3:4-benzpyrene. The reactive position in this molecule, as demonstrated in a variety of substitution reactions, is position 5. When, however, the hydrocarbon is injected into rabbits, it is excreted as 8- and 10-benzpyrenols[4]

(III) and (IV).



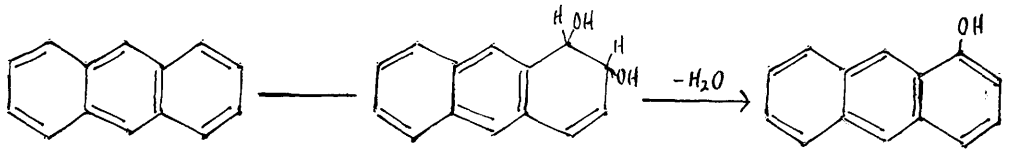




(III) (IV) (V)

In this respect it is interesting to note that, whereas nitration of benzpyrene takes place at position 5[5], nitration of 5-acetoxy-3:4-benzpyrene takes place at position 10[6], one of the centres attacked in the biochemical oxidation of the hydrocarbon.

A mechanism which took into consideration all these facts was postulated by Fieser[7]. It suggested that the metabolic process involved primarily the addition of the elements of hydrogen peroxide to the hydrocarbon and frequently a subsequent dehydration of the diol so formed. Such a process is illustrated below for the case of anthracene.



The isolation of the dihydroxydihydro compound postulated by Fieser has been effected in three cases. As already stated, 1:2-dihydroxy-1:2-dihydroanthracene has been obtained by Boyland and Levi from the urine of rats and

rabbits fed on a diet containing anthracene. It has been reported in a later communication by one of these authors[9] that the diol obtained from both rats and rabbits is a mixture of optically inactive and optically active material and that the laevo-rotatory form predominates in the case of rats, the dextro-rotatory in the case of rabbits.

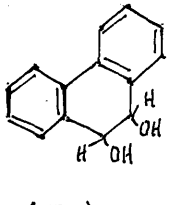
Young[8] has isolated l-1:2-dihydroxy-1:2-dihydronaphthalene from the urine of rats dosed with naphthalene and in similar experiments with rats and rabbits Booth and Boyland[9] have obtained a dl-1:2-dihydro diol mixed with laevo- and dextro-rotatory forms respectively. In the case of phenanthrene also it has been reported by Young (loc. cit.) and Boyland and Wolf[10] that dihydro diols are obtained. The latter authors formulate the diol obtained from rats as 9:10-dihydroxy-9:10-dihydrophenanthrene and that obtained from rabbits as a mixture of the above and 1:2-dihydroxy-1:2-dihydrophenanthrene. These diols are all readily dehydrated to phenols by mild treatment with dilute mineral acid.

No dihydroxydihydro compounds have been isolated from experiments with more complex hydrocarbons but this by no means precludes the possibility that diols have been formed and dehydrated either in the organism or during the processing of the urine. Weigert and Mottram[11] indeed

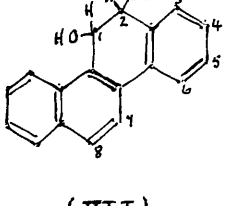
have deduced, from spectroscopic data, that such a diol may be present in the products of metabolism of 3:4-benzpyrene.

Typical polycyclic hydrocarbons which have been investigated include 1:2-benzanthracene, 1:2:5:6-dibenzanthracene, 3:4-benzpyrene and chrysene[12] which give rise to the phenolic products (I), (II), (III) and (IV) and (V) respectively. The position at which the molecule has been attacked is, in all these cases, favourable to Fieser's view that the mechanism of phenol formation involves the preliminary addition of two hydroxyl groups to adjacent carbon atoms. Fieser does not specify how this addition of two hydroxyl groups is effected and an insight into this question may be gained from the recent experiments of Cook and Schoental[13] on the oxidation of polycyclic aromatic hydrocarbons with osmium tetroxide.

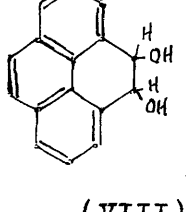
When phenanthrene is treated with osmium tetroxide in the presence of pyridine a crystalline complex is formed and may be hydrolysed to 9:10-dihydroxy-9:10-dihydrophenanthrene (VI).



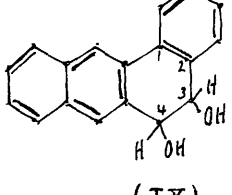
(VI)



(VII)



(VIII)



(IX)

This diol is dehydrated by treatment with dilute acid to 9-phenanthrol. This has been found to be a general reaction for polycyclic hydrocarbons containing a phenanthrene system. By use of this reagent chrysene was converted into 1:2-dihydroxy-1:2-dihydrochrysene (VII) which was dehydrated to 2-chrysenol; pyrene was converted into 1:2-dihydroxy-1:2-dihydropyrene (VIII), dehydrated to 1-pyrenol; and 1:2-benzanthracene was coverted into 3:4-dihydroxy-3:4-dihydro-1:2-benzanthracene (IX), dehydrated to 3-hydroxy-1:2-benzanthracene. This oxidation, involving the production of a phenol from the hydrocarbon through the intermediate formation of a dihydrodiol, is plainly analogous to the biochemical oxidation of the hydrocarbons. The analogy is heightened by the fact that in both cases the hydrocarbon molecule is attacked at a centre other than that most liable to attack by ordinary chemical reagents. As may be seen from the examples quoted, however, the position of attack by osmium tetroxide is not the same as that attacked in the biochemical oxidation. Hydrocarbons which do not contain a phenanthroid 9:10-double bond are also attacked by osmium tetroxide. For example, anthracene is oxidised to 1:2:3:4-tetrahydroxy-1:2:3:4-tetrahydroanthracene[14]. Here too the reagent has added to a double bond rather than to the reactive meso-positions but the product is not identical

with the anthracene metabolite.

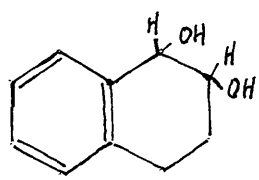
Biochemical oxidation therefore may involve the formation of a metallic complex similar to that formed in osmium tetroxide oxidations but it has still to be explained why the oxidation does not take place at one of the more reactive centres of the molecule.

It has been suggested by Boyland and Weigert[35] that in the body the hydrocarbons are combined with an enzyme, or with some other tissue constituent such as ascorbic acid[36] or a purine[37], through the most reactive positions which are therefore protected from attack by the biochemical oxidising agents. Meantime this remains a hypothesis unconfirmed by positive experimental evidence.

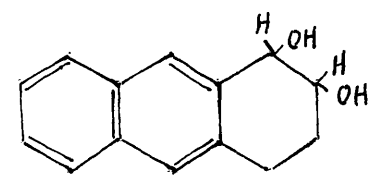
Another important difference between osmium tetroxide and biochemical oxidation is that the diols obtained by use of the former reagent invariably possess the *cis* configuration whereas those obtained by biochemical oxidation all appear to be *trans*.

In seeking to explain the mechanism of carcinogenesis by means of metabolic experiments it should be borne in mind that in these experiments the metabolic products isolated represent only a small fraction of the amount of hydrocarbon administered. The greater part of the hydrocarbon appears to be broken down into simple products which

escape isolation. The diols that have been obtained from naphthalene and anthracene can exist in four optically active isomeric forms, comprising a pair of cis-enantiomorphs and a pair of trans-enantiomorphs. A knowledge of the configuration of these metabolic products might be of value in elucidating further the mechanism by which they are formed. By catalytic hydrogenation the naphthalene and anthracene metabolites have been converted into 1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (X) and - anthracene (XI) respectively.



(X)

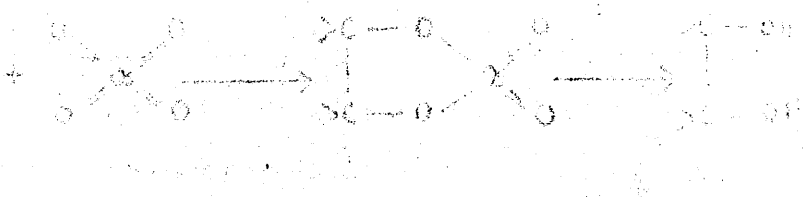


(XI)

The present work was undertaken with a view to obtaining synthetically specimens of the six isomers of (X) and (XI), the configuration of which would be fixed by the method of synthesis. By comparison with these synthetic products the hydrogenated metabolite could then be identified stereochemically.

Since this work was undertaken Booth and Boyland[9] have investigated the configuration of the naphthalene metabolites and, by comparison of the dihydro compounds with synthetically prepared specimens of dl-cis- and

dl-trans- 1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene, have shown they have the trans structure. These authors suggest that the anthracene diol also has the trans configuration since it does not react with Criegee's triacetyl osmiate reagent, in spite of the fact that Boyland and Shoppee[30] had previously concluded that the diol had the cis configuration owing to its rapid rate of oxidation by lead tetra-acetate.

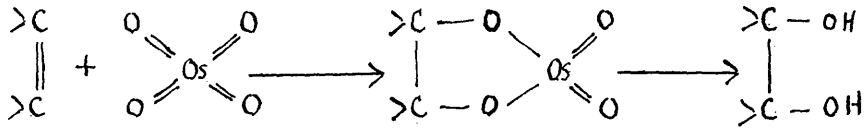


Discussion.

The starting material employed in the synthesis of the naphthalene diols was 1:2-dihydronaphthalene obtained from a.c.-tetrahydro-β-naphthol by the method of Bamberger and Lodter[15].

Several methods for obtaining dl-cis- and dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene from 1:2-dihydronaphthalene were studied.

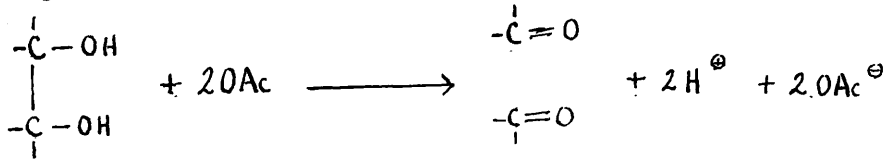
Criegee[16] has described a method for synthesising cis-diols from unsaturated hydrocarbons by the formation of osmic acid esters and their subsequent hydrolysis.



The application of this method to 1:2-dihydronaphthalene gave a hydroxy compound which was assumed to be dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene. The same compound was obtained by treating the dihydronaphthalene with hydrogen peroxide in tertiary butyl alcohol in the presence of osmium tetroxide (compare Milas and Sussman[17]). Neither of these methods however was suitable for the preparation of the large quantity of diol required for the ultimate resolution into the two optically active forms:

the former because of the relatively large amount of costly osmium tetroxide required; the latter because of the low yield obtained. The experiments of Straus and Rohrbacher[18], who claimed to obtain from 1:2-dihydronaphthalene the cis-diol by potassium permanganate oxidation and the trans-diol by stepwise hydrolysis of the dibromo compound, were therefore repeated and proved to be suitable preparative methods. The diol obtained by potassium permanganate oxidation was identical with the cis-diol already obtained and therefore the different compound obtained by hydrolysis of the dibromide was assumed to be trans-diol. The latter compound was also obtained by treating dihydronaphthalene with hydrogen peroxide in tertiary butyl alcohol in the presence of selenium dioxide, a method claimed by Seguin[19] to yield the trans configuration.

The configuration assigned to these diols was confirmed by a study of their rate of oxidation with lead tetra-acetate, since Criegee[20] has shown that lead tetra-acetate invariably oxidises cyclic cis-1:2-diols much more rapidly than the trans-isomerides by a reaction which may be symbolised thus:-



RATE OF OXIDATION OF (1) CIS- AND (2) TRANS-1:2-DIHYDROXY-1:2:3:4-TETRAHYDRONAPHTHALENE WITH LEAD TETRA-ACETATE.

(CONCENTRATION OF DIOL — (A) 0·0125
(B) 0·0031 GM. MOLES / LITRE.)

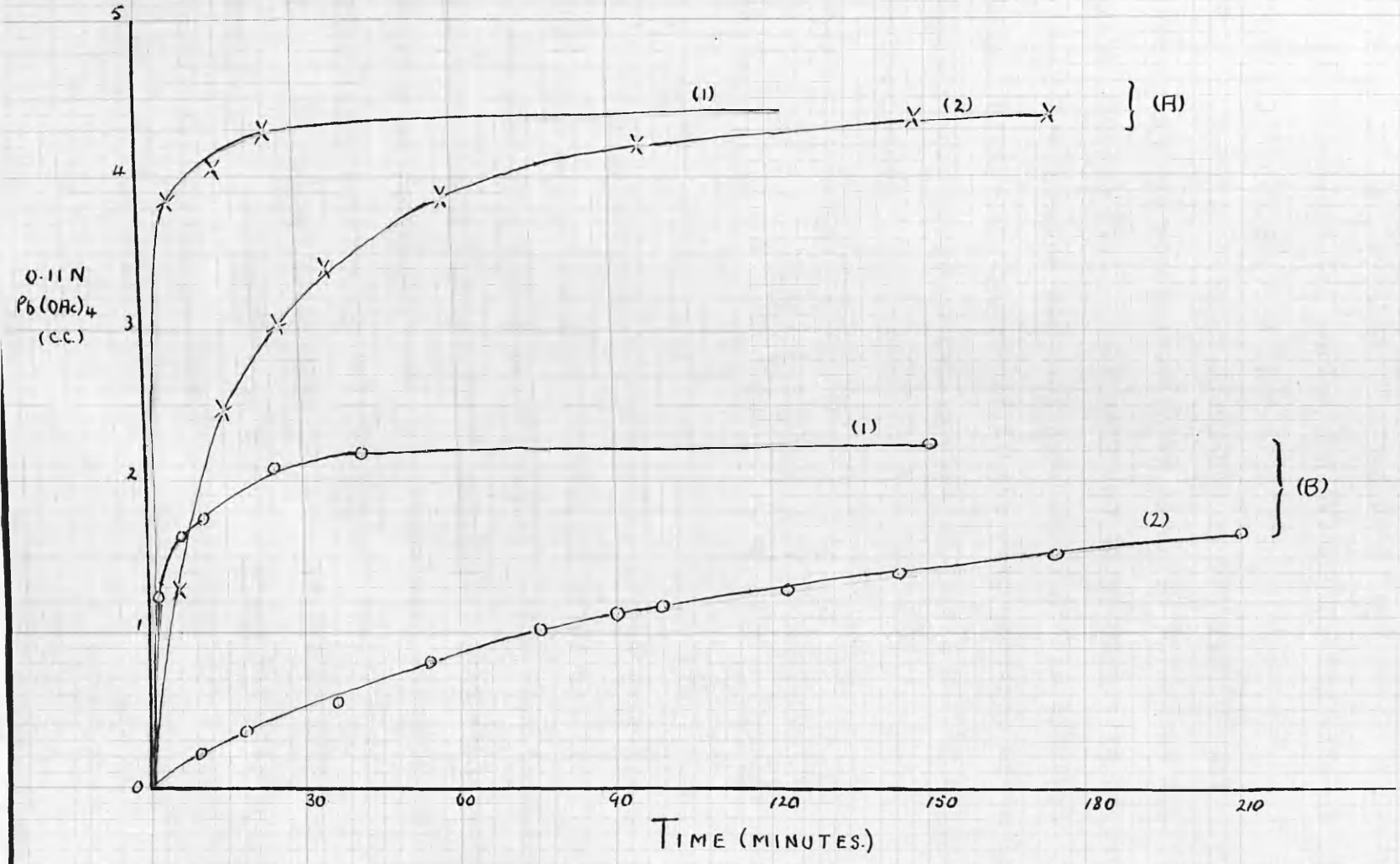
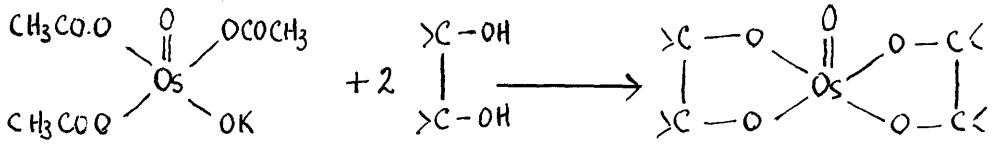


FIG. 1.

The graph of the results obtained here (see Fig.1) illustrates the usefulness of the method for distinguishing between cis- and trans-diols of this type.

Another reagent described by Criegee[21] for determining the configuration of diols is potassium tri-acetyl osmiate (X). This compound forms di-esters of the type (XI) with such diols as have two suitable hydroxyl groups, spatially favourable to the ring closure, at their disposal and therefore mainly with α-diols having a cis-configuration.



(X) (XI)

A solution of the reagent in acetic acid has a royal blue colour and the formation of di-esters is accompanied by a marked colour change. The test is therefore very simply carried out by addition of the diol to the solution of the reagent and is particularly valuable in being capable of application on a micro scale.

It is of particular interest in the present connection that Criegee[21] has reported trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene to be exceptional (like trans-cyclohexane-1:2-diol) in forming a di-ester with

potassium triacetyl osmiate. Booth and Boyland[9], however, without comment on Criegee's finding, state that the reagent provides the usual distinction between the cis- and trans-forms. Re-examination of this point showed that there is in fact a marked difference in the behaviour of the two forms; the cis-form giving an immediate colour change whereas the trans-form induces only a slow and less pronounced modification of the colour. Criegee[29], like Booth and Boyland, prepared the trans-diol by lead tetra-acetate oxidation of 1:2-dihydronaphthalene and it may be noted that in the anthracene series (cf. p.12) this procedure has been found to afford a mixture of cis- and trans-diols. Possibly, therefore, contamination with the cis-isomer in part accounts for Criegee's conclusion that the above-mentioned trans-diol shows exceptional behaviour.

Not all the methods which have been applied to the resolution of alcohols are applicable to diols, and not many examples of the successful resolution of diols are recorded in the literature.

For the resolution of the naphthalene diols a new resolving agent, l-menthoxy acetic acid, introduced by Read and his associates and successfully employed for the resolution of dl-trans-1:2-cyclohexane-diol[22] was considered to be the most promising. The basis of this

method of resolution is the formation of a solid ester and its subsequent separation by fractional crystallisation into the two diastereoisomeric forms from which the active diol and resolving agent are recovered by hydrolysis. It was necessary therefore to ascertain that the l-menthoxyacetic acid would form a solid ester with the diol.

Wilson and Read[22] found that in the reaction between dl-trans-1:2-cyclohexane-diol and l-menthoxyacetyl chloride only the mono-ester was formed even when two equivalents of the acid chloride were employed.

When dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene was treated in dry pyridine with either 1 or 1.5 equivalents of acid chloride a solid ester was obtained which was however contaminated with unesterified diol. An attempt was therefore made to obtain a di-ester by treating the mono-ester obtained above with a further 1.5 equivalents of acid chloride. The crystalline ester obtained in this way was shown to be a di-ester by an examination of its saponification value. It is not possible to distinguish the mono-ester from the di-ester analytically: the mono-ester, $C_{22}H_{32}O_4$, requires C, 73.33; H, 8.89% and the di-ester, $C_{34}H_{52}O_6$, requires C, 73.38; H, 9.35%.

The di-ester was separated into its diastereoisomeric forms by long fractional crystallisation from petroleum

ether. Approximately equal amounts of the two diastereoisomerides were ultimately obtained; the less soluble had m.p. 116-117°C $[\alpha]_D^{21}$ -21° (c, 1 in chloroform) and the more soluble, m.p. 101-102°C $[\alpha]_D^{21}$ -170° (c, 1 in chloroform). The ester of m.p. 116-117° when hydrolysed with alcoholic potassium hydroxide yielded l-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene $[\alpha]_D^{21}$ -134° (c, 1 in chloroform). The ester of m.p. 101-102°C similarly yielded d-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene $[\alpha]_D^{21}$ 132° (c, 1 in chloroform).

The metabolic product is a dihydronaphthalene derivative and on catalytic hydrogenation with a platinum catalyst yields a dextrorotatory 1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene. A specimen of this hydrogenated metabolite, kindly supplied by Professor Young, was found to be identical with d-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene, mixed melting point and specific rotation, and mixed melting point of the diacetates. This is in agreement with the conclusion of Booth and Boyland[9], that the naphthalene metabolites have the trans-configuration.

A preliminary investigation of the esterification of dl-cis-1:2:dihydroxy-1:2:3:4-tetrahydronaphthalene with l-menthoxyacetyl chloride indicated that a solid ester could be obtained by treating the diol with one equivalent of acid

chloride. When, however, it was discovered that the trans-diol could be resolved by fractionation of its di-ester it was decided to form a di-ester from the cis-diol also. Treatment of the diol with 2.5 equivalents of acid chloride gave rise to an oily product which could not be solidified. The original experiment yielding a solid ester by treatment with one equivalent of acid chloride could not be repeated and accordingly a search was made for another reagent with which to effect the resolution of the cis-diol.

Clark and Read[24] have reported a successful resolution of dl-menthol by means of a new resolving agent, l-menthylglycine. Esters of this acid are obtained by esterifying the racemic alcohol with chloracetyl chloride and treating the chloroacetate with l-menthylamine

$$R.OH \xrightarrow{ClCH_2COCl} R.O\,CO\,CH_2Cl \xrightarrow{C_{10}H_{19}NH_2} R.O.CO\,CH_2.NH\,C_{10}H_{19}.$$

The resulting diastereoisomeric l-menthylglycine esters are separated by crystallisation and the active alcohol is recovered from each form by hydrolysis. The majority of these esters are crystalline solids and they yield crystalline salts with acids and crystalline N-acyl derivatives.

Treatment of the dl-cis-diol with chloracetyl chloride led to an oily product which was assumed to be the desired di-chloroacetate. Treatment of this oil with

l-menthylamine either under the conditions described by Read[24] or in the cold yielded only a gummy material. No resolution therefore could be achieved by this means.

Failure to resolve the cis-diol may be due to a steric effect which would hinder the formation of a di-ester with the resolving agents employed. The required starting material for the preparation of cis- and trans-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene was 1:2-dihydroanthracene which it was hoped to obtain from 1:2:3:4-tetrahydro-2-anthrol.

2-anthrol was obtained from anthraquinone-2-sodium sulphonate by reduction with zinc dust and ammonia to anthracene-2-sodium sulphonate[26] and fusion with potassium hydroxide[27]. The 2-anthrol was purified by sublimation under reduced pressure and crystallisation of the sublimate from benzene.

Chemical reduction of 2-anthrol leads to the 9:10-dihydro derivative but v. Braun and Bayer[25] have reported that the 1:2:3:4-tetrahydro derivative is also formed when 2-anthrol is subjected to high pressure hydrogenation in the presence of nickel salts. The use of copper chromite as a catalyst in the high pressure hydrogenation of 2-naphthol leads to an 80% yield of 1:2:3:4-tetrahydro-2-naphthol[28].

2-Anthrol was therefore hydrogenated under pressure in the presence of copper chromite and was converted in 60% yield to 1:2:3:4-tetrahydro-2-anthrol together with a small amount of 9:10-dihydro-2-anthrol. v. Braun reported that the dehydration of 1:2:3:4-tetrahydro-2-anthrol to 1:2-dihydroanthracene did not take place readily but could be achieved by distillation of its phenylurethane. This method of dehydration was examined but found to be unsatisfactory. Better results were obtained by heating the tetrahydroanthrol with freshly fused potassium hydroxide.

The 1:2-dihydroanthracene was treated with osmium tetroxide in an ether solution containing pyridine according to Criegee's[21] modification of his earlier procedure. Hydrolysis of the osmium-pyridine adduct yielded dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene.

In order to obtain the trans-diol the method found to be successful in the naphthalene series; viz., the stepwise hydrolysis of the dibromide, was applied to 1:2-dihydroanthracene. The dibromide was readily obtained and converted to 1(2)-bromo-2(1)-hydroxy-1:2:3:4-tetrahydroanthracene in satisfactory yield. The hydrolysis of this hydroxybromide gave the desired trans-diol but in rather poor yield.

Treatment of unsaturated hydrocarbons with lead

tetra-acetate affords, generally, the diacetate of the trans-diol but in some cases the cis-diol diacetate is also formed[29]. A small amount of 1:2-dihydro anthracene was treated with lead tetraacetate and the oily product obtained was hydrolysed with alcoholic potassium hydroxide. dl-trans-1:2-Dihydroxy-1:2:3:4-tetrahydroanthracene was thereby obtained in 64% yield from the dihydroanthracene. The method was therefore applied to the bulk of the dihydro-anthracene but in this case the product after hydrolysis was a mixture of cis- and trans-diols. A partial separation of this mixture was effected by fractional crystallisation from benzene. During the separation a small amount of a high melting compound of unknown constitution was isolated.

The correctness of the configuration assigned to these diols was confirmed by a study of their rate of oxidation by lead tetra-acetate and their colour change on treatment with potassium triacetyl osmiate reagent[21].

It was found that, as in the case of the naphthalene diols, the cis-diol was oxidised much more rapidly than the trans-diol by lead tetra-acetate (see Fig.2).

Boyland and Shoppee[30] have measured the rate of oxidation of the metabolic 1:2-dihydroxy-1:2-dihydroanthracene with lead tetra-acetate. In doing so they took into consideration the reactivity of the meso positions of the

RATE OF OXIDATION OF (1) CIS - AND (2) TRANS - 1:2 - DIHYDROXY - 1:2:3:4 - TETRAHYDROANTHRACENE WITH LEAD TETRA - ACETATE.

(CONCENTRATION OF DIOL - 0·0125 GM. MOLES | LITRE.)

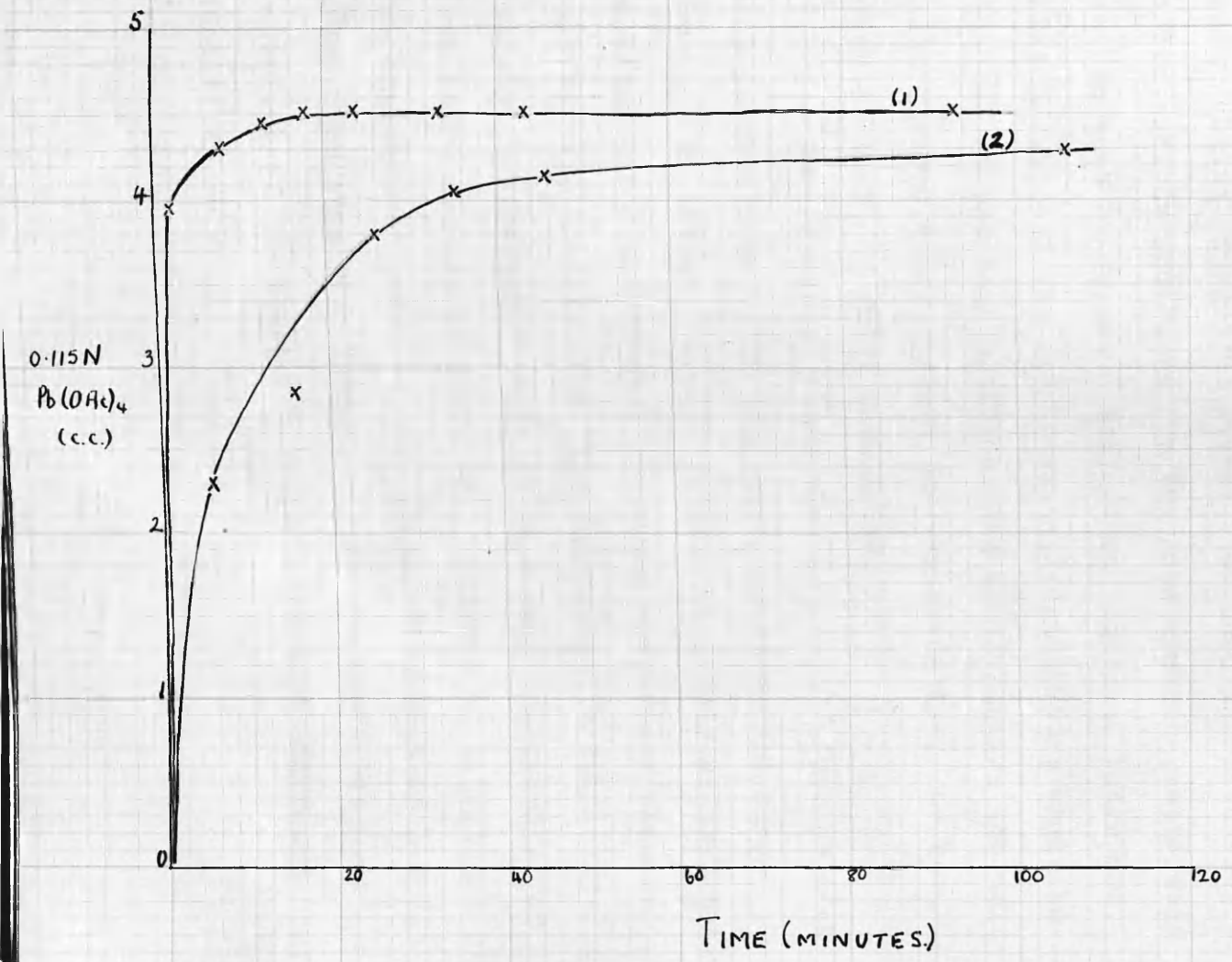


FIG. 2.

anthracene system towards this reagent. Thus Meyer[31] had found that anthracene was oxidised by a solution of lead dioxide in acetic acid; the product being anthranyl acetate when one molecule of lead dioxide was emphyed and meso-hydroxyanthranylacetate when two molecules of reagent are used. Later Fieser[32] showed that lead tetra-acetate in acetic acid is equivalent to the lead dioxide-acetic acid mixture used by Meyer. Boyland and Shoppee, therefore, anticipated that the dihydroxydihydroanthracene would be attacked at the meso positions and would require two molecules of lead tetra-acetate for its oxidation, and have reported that, in fact, this is so.

Nevertheless, their figures, viz. $^{1}/_{4000}$ mole of diol require 5 cc. $^{N}/_{10}$ lead tetra-acetate (and hence 1 mole ≡ 20 litres $^{N}/_{10}$ ≡ 2 litres N ≡ 1 mole of lead tetra-acetate) which are in good agreement with those obtained here for the oxidation of <u>cis</u>- and <u>trans</u>-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene, indicate that only one molecule of lead tetra-acetate is required. This is in accordance with the experiments recorded here on the treatment of 1:2-dihydroanthracene with lead tetra-acetate where the meso positions of the hydrocarbon are unattacked after one hour's heating at 90°C.

That the meso positions in these hydrogenated anthracene derivatives are unattacked by lead tetra-acetate is not contrary to theoretical expectations since it is a false analogy to compare them with the meso positions of anthracene itself.

When the potassium triacetyl osmiate reagent was applied to the anthracene diols the previous determination of their configuration was confirmed.

The resolution of the anthracene diols was attempted using as resolving agent l-menthoxyacetic acid. The dl-trans-diol on treatment with four molecules of l-menthoxyacetyl chloride yielded a reddish coloured oil. Attempts to induce this oil to solidify by sublimation, chromatography and renewed acylation, as well as by the usual methods, all failed. The purity of the diol was checked by converting it to a crystalline diacetate which was purified and hydrolysed to regenerate the diol. The diol obtained in this way showed no change in melting point and still gave an oil on treatment with l-menthoxyacetyl chloride. The dl-cis-diol similarly failed to yield a solid ester, though it is noteworthy that in this case there was a much less marked colour production on addition of the acid chloride to the diol solution and the oil obtained was almost colourless.

The dihydride of the optically inactive anthracene metabolite has been described by Boyland and Levi[1] and its physical properties, melting point and melting point of its diacetate, are in concordance with those of dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene. It appears therefore that the anthracene metabolite also has the trans-configuration although it has not been possible to obtain a specimen of the dihydro metabolite for direct comparison with the synthetic diol.

Experimental.

1:2-Dihydronaphthalene.

1:2-Dihydronaphthalene was obtained from a.c-tetrahydro-β-naphthol as a colourless oil, b.p. 98-100°C/14 mm., in 80% yield by the method of Bamberger and Lodter[15].

dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene.

A). Oxidation of 1:2-dihydronaphthalene with osmium tetroxide (cf. Criegee[16]).

Osmium tetroxide (2 g.) was dissolved in dry ether (40 cc.) and 1:2-dihydronaphthalene (1.04 g.) added. The solution darkened immediately. After standing for seven days the ether was removed and the black osmic ester refluxed for three hours with a solution of sodium sulphite heptahydrate (8 g.) in water (40 cc.) and ethanol (20 cc.). The solution was filtered hot and the sodium osmium sulphite refluxed for 30 minutes with ethanol. The solution was again filtered and most of the alcohol removed from the combined filtrates on the water bath. The solution was then extracted three times with 50 cc. chloroform and the chloroform extracts dried and concentrated. The solid obtained was purple in colour, but after refluxing in benzene with a little charcoal it was obtained by crystallisation from benzene as colourless lamellae, m.p. 101°C. Yield, 0.76 g. (65%).

B). Oxidation of 1:2-dihydronaphthalene with potassium permanganate.

By the method of Straus and Rohrbacher[18] the diol was obtained in 20% yield, m.p. 100-101°C.

C). Oxidation of 1:2-dihydronaphthalene with hydrogen peroxide in the presence of osmium tetroxide (cf. Milas and Sussman[17]).

The hydrogen peroxide reagent.

Hydrogen peroxide (5 cc., 90% by weight) was dissolved in tertiary butyl alcohol (50 cc.) and the solution dried over anhydrous sodium sulphate.

1:2-Dihydronaphthalene (1 g.) was mixed with an equimolecular quantity of the peroxide reagent (3.25 cc.; 0.26 g.) and the mixture cooled to 0°C in an ice bath. To the cooled solution was then added the catalyst; a solution of osmium tetroxide (0.1 g.) in tertiary butyl alcohol (10 cc.). The mixture was kept at 0°C for eight days. The solution was then evaporated to dryness under reduced pressure and the residual dark blue tar extracted several times with boiling water. The aqueous extraction concentration yielded a dark brown oil which was dissolved in benzene and refluxed with charcoal. Petroleum ether (60-80°C) was added to the filtered benzene solution till a

permanent turbidity was produced and the solution kept overnight. The solid material which was deposited was washed free of the oil still adhering to it and crystallised from benzene, m.p. 99-100°C. It did not depress the melting point of pure cis-diol. Yield of diol 40 mgs.

dl-cis-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene.

dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene was acetylated by treatment with acetic anhydride in pyridine in the cold. The diacetate was purified by crystallisation from petroleum ether (> 120°), m.p. 78°C. Straus and Rohrbacher[18] record a m.p. 78.6-79.2°C for cis-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene.

dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene.

A). Hydrolysis of 1:2-dibromo-1:2:3:4-tetrahydronaphthalene.

The dibromide was prepared from 1:2-dihydronaphthalene by the method of Bamberger and Lodter[15]. The dibromide was first partially hydrolysed, to yield 1(2)-bromo-2(1)-hydroxy-1:2:3:4-tetrahydronaphthalene which was then hydrolysed to dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene[18].

B). Oxidation of 1:2-dihydronaphthalene with hydrogen peroxide in the presence of selenium dioxide (cf. Seguin[19]).

The hydrogen peroxide reagent was prepared as

described above and concentrated to the desired strength by distillation under reduced pressure at room temperature in an all glass apparatus. 1:2-Dihydronaphthalene (2 g.) was treated with an equimolecular proportion of hydrogen peroxide (0.52 g. in ~ 2 cc. tertiary butyl alcohol). To this solution, cooled to 0°C, was added a solution of selenium dioxide (0.06 g.) in the minimum quantity of tertiary butyl alcohol. The solution, after standing for eight days, yielded on concentration a deep red, oily material. The solid obtained by treating this oil with a little benzene was slightly purple in colour and by repeated crystallisation from benzene was obtained as colourless needles, m.p. 112°C. It did not depress the melting point of the diol obtained by method A) above. Yield, 0.41 g. (16%).

dl-trans-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene.

dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene was acetylated with acetic anhydride in pyridine in the usual manner. The diacetate was crystallised from petroleum ether (60-80°C), m.p. 84°C. Straus and Rohrbacher[18] record a melting point of 84°C for trans-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene.

Rate of oxidation of cis- and trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene with lead tetra-acetate.

Lead tetra-acetate was prepared by the method of

Dimroth and Schweizer[33]. It was dried over concentrated sulphuric acid and a solution of approximately the desired strength prepared by weighing the dry material rapidly and dissolving it in acetic acid distilled over chromium trioxide. This solution was standardised by titration with standard sodium thiosulphate.

Determination of the rate of oxidation.

A known weight of the diol (~ 0.25 moles.) was dissolved in 10 cc. of acetic acid (distilled over chromium trioxide). These solutions were maintained at a constant temperature by immersion in a water bath. To each of the solutions 10 cc. of 0.112 N lead tetra-acetate was rapidly added with swirling, the time of addition being noted. A flask containing 10 cc. acetic acid (distilled over chromium trioxide) was treated in the same way in order to obtain a measure of the rate of consumption of lead tetra-acetate in the absence of diol. At intervals from the time of mixing, aliquots of 1 cc. were withdrawn, run into a potassium iodide-sodium acetate buffer solution and the iodine liberated titrated against standard sodium thiosulphate. In this way a measure of the amount of lead tetra-acetate consumed at any stage of the oxidation was obtained.

Thus it was found that at 20-21°C and with a diol

concentration of 0.0125 gm. moles/litre the cis-diol is completely oxidised after 30 minutes, while the trans-diol is only oxidised to the extent of 95% after 90 minutes.

Similarly at 17°C and a diol concentration of 0.003 gm. moles/litre the cis-diol is completely oxidised after 40 minutes, whereas the trans-diol is only 80% oxidised after 180 minutes.

These results, which are illustrated graphically in Fig.1, (p.65) are in agreement with those of Criegee[20].

Tests with potassium triacetyl osmiate. (See page 103).

Mono-esterification of dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene with l-menthoxyacetyl chloride.

dl-trans-diol (1.99 g.; 1 mole) was dissolved in dry pyridine (40 cc.) and treated with freshly distilled l-menthoxyacetyl chloride (2.8 g.; 1 mole). The solution after standing overnight was poured into water and the oil which separated extracted with ether. The ether solution was thoroughly washed with dilute hydrochloric acid, dilute sodium hydroxide and water; dried over anhydrous sodium sulphate and concentrated. A yellow viscous oil was obtained which solidified on rubbing with petroleum ether (60-80°). An attempted fractionation of this solid by crystallisation from petroleum ether showed the presence of unchanged diol

which could not readily be removed completely from the ester. A sample of the diol was therefore treated with 1.4 equivalents of menthoxyacetyl chloride in pyridine and the product isolated as above. Crystallisation from petroleum ether yielded a fraction of m.p. 122°C., $[\alpha]_D^{21}$ -68.1 and fractions of unchanged diol.

Di-esterification of dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene with l-menthoxyacetyl chloride.

dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (2.1 g.) and mono-ester (4 g.) were dissolved in pyridine (80 cc.) and treated with freshly distilled l-menthoxyacetyl chloride (11.7 g.; 2.5 moles per mole of diol and 1.5 moles per mole of mone-ester). After standing for 60 hours the solution was worked up in the usual way, yielding 10.3 g. of solid. By fractional crystallisation of this solid from petroleum ether there were obtained two pure compounds:- (A) m.p. 116-117°C $[\alpha]_D^{21}$ -22.0° (c, 1 in chloroform). Found: C, 73.6; H, 9.2%. $C_{34}H_{52}O_6$ requires C, 73.4; H, 9.3%. And (B) m.p. 100-101°C $[\alpha]_D^{21}$ -170.0° (c, 1 in chloroform). Found: C, 73.4; H, 9.3%. $C_{34}H_{52}O_6$ requires C, 73.4; H, 9.3%.

Saponification value of the ester (A).

The ester (A) (0.9679 g.) was refluxed with

0.4095 N methanolic potassium hydroxide (11 cc.) for three hours. The addition of a few drops of water after this time caused no precipitation, and esterification was therefore assumed to be complete. One drop of methyl red was added and the solution titrated with a standard hydrochloric acid solution. 12.65 cc. of 0.0837 N hydrochloric acid were required for neutralisation, so that 8.41 cc of 0.4095 N potassium hydroxide were used up in the hydrolysis of the ester. This corresponds to 0.9581 g. of di-ester and the compound (A) must therefore be 98.8% di-ester: i.e., pure di-ester within the limits of experimental error.

Resolution of dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene.

Mono-ester (20.5 g.; 1 mole) was dissolved in dry pyridine (100 cc.) and treated with freshly distilled l-menthoxyacetyl chloride (24.9 g.; 1.8 moles). The solution was cooled during the addition of the acid chloride which was accompanied by the precipitation of a solid and the production of a deep orange colour. After standing at room temperature for 40 hours the solution was worked up in the usual way. The product (27.2 g.) was an oily solid, deep red in colour. By refluxing this solid in petroleum ether with animal charcoal and recrystallising the product

twice from petroleum ether 16.6 g. of almost colourless solid were obtained. Repeated crystallisation from petroleum ether yielded a less soluble fraction, m.p. 116-117°C. $[\alpha]_D^{21}$ -21° (C, 1 in chloroform) and a more soluble fraction, m.p. 101-102°C $[\alpha]_D^{21}$ -170° (C, 1 in chloroform).

1-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene.

The ester of $[\alpha]_D^{21}$ -21° (6.89 g.) was refluxed for three hours with 2.5% methanolic potassium hydroxide (76 cc.). The methanol was removed by distillation and the residue extracted with ether. The ether extract was washed with dilute alkali, dried over anhydrous sodium sulphate and concentrated, yielding 1.61 g. diol (85%). The diol was optically pure after two crystallisations from benzene, m.p. 114-115°C $[\alpha]_D^{21}$ -134.0° (C, 1 in chloroform). Found: C, 73.4; H, 7.4%. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.3%.

l(+) -trans-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene.

l-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (213 mg.) was dissolved in dry pyridine (4 cc.) and acetic anhydride (1 cc.) added with cooling. After standing overnight at room temperature the solution was poured into a mixture of dilute sulphuric acid and ice. The oil that separated rapidly solidified and was filtered and dried.

It was purified by two crystallisations from petroleum ether ($>120^{\circ}C$), m.p. 66-67° $[\alpha]_D^{21}$ 126° (C, 1 in chloroform). Found: C, 67.8; H, 6.3%. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.4%.

d-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene.

The ester of $[\alpha]_D^{21}$ -170° (6.36 g.) was refluxed for three hours with 2.5% methanolic potassium hydroxide (70 cc.). By working up in the same manner as above there was obtained 1.55 g. (83%) diol, which was purified by two crystallisations from benzene, m.p. 114-115°C $[\alpha]_D^{21}$ 132° (C, 1 in chloroform) $[\alpha]_D^{21}$ 64° (C, 0.5 in ethanol) $[\alpha]_{5461}^{21}$ 44° (C, 0.5 in ethanol.

Found: C, 73.2; H, 7.1%. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.3%.

Mixed m.p. of d- and l-isomers, 104-108°C. The melt was allowed to re-solidify and its melting point redetermined. It was then found to melt at 112°C, i.e., the melting point of the dl-diol.

d(-)-trans-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene.

d-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (198 mg.) was dissolved in dry pyridine (4 cc.) and treated with acetic anhydride (1 cc.). On working up as in the above case there was obtained 284 mg. of diacetate which

was purified by two crystallisations from petroleum ether (>120°C), m.p. 66-67°C. $[\alpha]_D^{20}$ -125° (C, 1 in chloroform). Mixed m.p. of the two diacetates 40-42°C.

Found: C, 67.7; H, 6.3%. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.4%.

Comparison of the dextrorotatory dihydro metabolic naphthalene diol with the synthetic diols obtained above.

A sample of the dihydride of the metabolic product was kindly supplied by Professor Young. A sample of the diacetate was prepared from it by treatment with acetic anhydride in pyridine.

The identity of the dihydro metabolite with d-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene is shown in the following table;

	m.p. °C	$[\alpha]_D$ (C, 0.5 in ethanol)
Dihydro metabolite	114°	62°
d-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene	114-115	64°
mixed m.p. 114-115°		

	micro m.p. °C
Diacetate of dihydro metabolite	63-65
d(+)-trans-1:2-diacetoxy-1:2:3:4-tetrahydronaphthalene	65-66
mixed micro m.p. 63-65	

Esterification of dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene with l-menthoxyacetyl chloride.

1). dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (0.5 g.; 1 mole) dissolved in dry pyridine (15 cc.) was treated with freshly distilled l-menthoxyacetyl chloride (0.78 g.; 1.1 moles). After standing for 24 hours the solution was poured into water and the oil which separated extracted with ether. The ether extract was washed with dilute hydrochloric acid, dilute sodium hydroxide and water, dried and concentrated. The oily residue solidified on standing. Yield, 0.765 g. (70%). m.p., after crystallisation from petroleum ether, 130-132°C.

This presumed mono-ester was retreated with l-menthoxyacetyl chloride in an attempted di-esterification.

2). dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (8 g.; 1 mole) dissolved in dry pyridine (100 cc.) was treated with freshly distilled l-menthoxyacetyl chloride (27.8 g.; 2.4 moles), the solution being cooled during the addition of the acid chloride, which was accompanied by the precipitation of a solid and the production of a reddish colour. After standing at room temperature for 40 hours the solution was poured into a mixture of dilute sulphuric acid and ice and the oil which separated extracted with

ether. The ether extract was washed with dilute sodium hydroxide and water, dried over potassium carbonate and concentrated. 18 gm. of a reddish oil was obtained and did not solidify. A portion of this oil in benzene solution was passed through a column of alkali free alumina and the colourless band of adsorption eluted with benzene. Concentration of the eluate yielded a yellow oil which did not solidify on rubbing with the usual solvents or on retreatment with a further 2 moles of l-menthoxyacetyl chloride. A further portion (1 g.) of the oil resulting from the original treatment with the acid chloride was dissolved in dry pyridine and warmed with l-menthoxyacetyl chloride (1.8 g.) for one hour at 90-100°C. The yellow solution did not darken during this treatment and when it was worked up in the usual manner a yellow viscous oil was obtained.

A small amount of the oil was then subjected to distillation under reduced pressure. A few drops of a yellow coloured oil distilled at 140-145°C/3 mm. The distillate became deep red on standing and could not be solidified. The residue did not distil even when heated quite strongly in an open flame at 2 mm. pressure.

Cis-1:2-di-chloroacetoxy-1:2:3:4-tetrahydronaphthalene.

Chloracetyl chloride was prepared by Boescken's[12] procedure. B.p. of product 102-104°C. c.f. literature b.p. 105°C.

A). A solution of dl-dis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene (1.13 g.; 1 mole) and chloracetyl chloride (1.6 g.; 1.02 moles) in dry benzene (35 cc.) was boiled under reflux in an apparatus closed with a calcium chloride tube until hydrogen chloride ceased to be evolved (seven hours). The benzene solution was washed with water, sodium hydroxide and again with water, dried over anhydrous sodium sulphate and concentrated. 1.75 g. of a yellow mobile oil was obtained.

B). The diol (150 mg.; 1 mole) was dissolved in dry benzene (3 cc.) and treated with chloracetyl chloride (250 mg.; 1.2 moles). The solution was stoppered with a calcium chloride tube and allowed to stand at room temperature for 48 hours. After this time the benzene solution, which had turned yellow in colour, was thoroughly washed with water, dilute sodium hydroxide and water, dried and concentrated. An orange coloured oil (250 mg.) was obtained.

C). The diol (0.2 g.; 1 mole) was treated with chloracetyl chloride (2.6 g.; 10 moles). The solution, which became yellow in colour almost immediately, was allowed to

stand at room temperature for 48 hours. It was then poured into a large excess of ice-cold water and stirred for twenty minutes to destroy the excess chloracetyl chloride. The yellow oil which separated during this treatment was extracted with ether and the ether solution washed with dilute sodium hydroxide, dried and concentrated. A yellow mobile oil (400 mg.) was obtained.

l-menthylamine.

l-menthol was oxidised to l-menthone[13]. The ketone was converted to its oxime[14] and the latter reduced with sodium in alcohol[15]. The menthylamine obtained in this way is a mixture of four isomers of which the desired isomer is present in the largest amount. It is freed from the other isomers by repeated crystallisation of the mixed hydrochlorides from water. The pure l-menthylamine hydrochloride has m.p. 294-295°C. $[\alpha]_D^{20}$ -36.8° (C, 0.25 in water).

Cis-1:2-dimenthylaminoacetoxy-1:2:3:4-tetrahydronaphthalene.

1). A solution of l-menthylamine was prepared by dissolving l-menthylamine hydrochloride (9.45 g.; 3.6 moles) in water and treating with the theoretical amount of potassium hydroxide (2.76 g.). The aqueous solution of the amine was extracted with benzene and the benzene solution

dried over anhydrous sodium sulphate. The solution was protected by a soda lime tube throughout this operation. To this solution was added the di-chloroacetate obtained in (A) above, the benzene was removed by distillation and the residue heated at 140°C for six hours in an apparatus closed by a soda lime tube. The mixture, almost black in colour, was cooled, poured into an excess of dilute sulphuric acid and extracted twice with chloroform. The chloroform solution was washed six times with water to remove all retained l-menthylamine sulphate, once with sodium carbonate solution to ensure that no sulphuric acid remained in combination with the ester and finally with water. From the acid liquor and the water washings l-menthylamine was recovered as the hydrochloride. The dried chloroform solution on concentration yielded an almost black gum from which no solid could be obtained.

2). The di-chloroacetate (250 mg.) obtained by method (B) above was treated with a solution of l-menthylamine (1.1 g.; 3 moles) in dry benzene in a flask closed with a soda lime tube. The solution became purple on the addition of the l-menthylamine and after standing at room temperature for 48 hours was worked up as described above. Again a very dark coloured gum was obtained.

An attempt was made to see whether a sulphate could

be formed from this gum. A portion of the gum dissolved in chloroform was shaken with an excess of dilute sulphuric acid. The residue obtained by concentrating the chloroform solution was a black gum. No solid was obtained from the aqueous layer on concentration to a small volume.

Purification of 2-anthrol.

To a solution of crude 2-anthrol in benzene was added a solution of picric acid in benzene. Long needle-shaped crystals, deep red in colour, separated on standing. They were purified by crystallisation from benzene, m.p. 155-156°C.

Found: C, 57.0; H, 3.1; N, 10.0%. $C_{20}H_{13}O_8N_3$ requires C, 56.7; H, 3.1; N, 9.9%.

The decomposition of the picrate was effected with sodium carbonate solution but the separation of the 2-anthrol from the picric acid was tedious. The crude anthrol was sublimed at 200°C/1 mm. and the sublimate crystallised from benzene. The pure product was light green in colour. It softened at ~ 220°C and melted with decomposition at 247-250°C.

1:2:3:4-tetrahydro-2-anthrol.

Pure 2-anthrol (10 g.) in ethyl alcohol (100 cc.) was hydrogenated over copper chromite (1 g.) at 200°C under

122 atmospheres for seven hours. After filtration from the copper chromite the alcohol was removed on the water bath and a slightly yellow crystalline material obtained. Yield, 11 g. m.p. 125-130°C. This solid was dissolved in ether and thoroughly washed with 20% sodium hydroxide solution. The alkali extract was acidified with dilute hydrochloric acid and the cloudy solution obtained extracted with ether. There was thus obtained, by concentration of the respective ether solutions, an alkali insoluble and an alkali soluble portion of the hydrogenation product. The alkali soluble product (0.8 g.; 8%) was yellow-brown in colour. It was purified by repeated crystallisation from petroleum ether (80-100°C) but the final product was still coloured. M.p. 129°C.

Found: C, 85.3; H, 6.2%. $C_{14}H_{12}O$ requires C, 85.7; H, 6.1%

V.Braun[25] records a m.p. of 129°C for 9:10-dihydro-2-anthrol.

The alkali insoluble portion (6.1 g.; 60%) was purified by three crystallisations from benzene followed by two crystallisations from ethanol. M.p. 140-142°C.

Found: C, 85.1; H, 6.8%. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%.

V. Braun[25] records a m.p. of 148°C for 1:2:3:4-tetrahydro-2-anthrol.

1:2:3:4-tetrahydro-2-acetoxy-anthracene.

1:2:3:4-tetrahydro-2-anthrol (150 mg.) was treated with acetic anhydride (0.5 cc.) and the mixture heated on a steam bath for one hour. The solution, after cooling, was poured into water and the oil which separated extracted with ether. The ether solution was dried and concentrated, yielding a solid residue, m.p. 66-70°C. (cf. v. Braun[25], m.p. 75-76°C).

Picrate of 1:2:3:4-tetrahydro-2-anthrol.

1:2:3:4-tetrahydro-2-anthrol (100 mg.) was dissolved in hot benzene and a solution of picric acid (120 mg.; 1 mole) in hot benzene added. The solution immediately darkened and on cooling deposited needle-shaped yellow crystals. They were purified by crystallisation from benzene, m.p. 142-143°C. (Cf. v. Braun[25], m.p. 142°C) Found: C, 56.6; H, 3.9; N, 10.0%. $C_{20}H_{17}O_8N_3$ requires C, 56.2; H, 4.0; N, 9.8%).

1:2:3:4-tetrahydro-2-anthrol phenyl iso-cyanate.

1:2:3:4-tetrahydro-2-anthrol (0.6 g.) was heated on a steam bath for one hour with an equimolecular proportion of phenyl iso-cyanate (0.36 g.). On cooling a brown gummy solid was obtained. It crystallised from ethanol in glistening white plates, m.p. 145-146°C. (Cf. v. Braun[25] m.p. 150°C).

Found: C, 78.5; H, 6.2; N, 4.9%. $C_{21}H_{19}O_2N$ requires C, 78.8; H, 6.2; N, 4.6%.

1:2-dihydroanthracene.

1). 1:2:3:4-tetrahydro-2-anthrol phenyl iso-cyanate (375 mg.) was heated in a small distilling flask in a metal bath. Decomposition began at 240°C and the temperature was maintained at 260°C for thirty minutes. Distillation was very slow and it was assumed that decomposition was complete after this time. The small amount of distillate that had collected together with the residue in the flask was treated with 5 cc. boiling benzene and filtered. The white insoluble residue melted at 238-241°C and did not depress the melting point of diphenylurea. The filtrate, which was dark brown in colour, was passed through a column of alkali free alumina, eluted with 120 cc. of benzene and finally with 50 cc. of a benzene-chloroform mixture (1:1). The first fraction of the benzene eluate yielded on concentration a light brown solid (50 mg.), m.p. 143-145°C which depressed the m.p. of 1:2:3:4-tetrahydro-2-anthrol and was the desired 1:2-dihydroanthracene. The later fractions of the benzene eluate contained undecomposed 1:2:3:4-tetrahydro-2-anthrol phenyl iso-cyanate (100 mg.) and the benzene-chloroform eluate yielded a trace of 1:2:3:4-tetrahydro-2-anthrol.

The yield of crude 1:2-dihydroanthracene was increased to 80% by heating at a higher temperature, 280-300°C, for one hour.

2). 1:2:3:4-tetrahydro-2-anthrol (4 g.) was heated with freshly fused potassium hydroxide (4 g.) for one hour at 180-210°C. The product was extracted with ether and weighed 3.55 g. (92%). It was purified by sublimation at 100-120°C/2 mm. and crystallisation of the sublimate from ethanol. Yield of pure product 1.53 g. (42%), m.p. 147-148°C.

(Found: C, 93.4; H, 6.7%. $C_{14}H_{12}$ requires C, 93.3; H, 6.7%)

The dihydroanthracene in ethanol treated with a solution of picric acid in ethanol yielded long brick red needles of picrate. M.p. 112-115°C.

(v. Braun[25] reports a m.p. of 150°C for 1:2-dihydroanthracene and 115°C for its picrate.)

dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene (cf. Criegee[21])

1:2-dihydroanthracene (1.418 g.; 1 mole.) in dry ether (10 cc.) was added to a solution of osmium tetroxide (2 g.; 1 mole) and dry pyridine (1.37 cc.; 2.2 moles) in dry ether (100 cc.). A brown precipitate of the pyridine complex of the osmic ester was deposited immediately and was filtered after standing overnight.

Hydrolysis of the pyridine compound of the osmic ester.

A solution of the dihydroanthracene-osmium-pyridine adduct (3.8 g.) in methylene chloride (80 cc.) was shaken for six hours with a solution of mannitol (19 g.) and potassium hydroxide (1.9 g.) in water (190 cc.). The methylene chloride layer was still deeply coloured after this treatment, nor was this colour removed by separation of the methylene chloride layer and further prolonged shaking with a fresh potassium hydroxide-mannitol aqueous solution. Since complete hydrolysis could not be effected in this manner, recourse was had to the hydrolytic technique described by Criegee[10] in an earlier paper.

The methylene chloride layer was separated and concentrated. The concentrate, an oily partly crystalline solid, was refluxed for one hour with a solution of sodium sulphite teptahydrate (8.1 g.) in water (40 cc.) and alcohol (20 cc.). The solution was filtered hot and on cooling a crystalline solid was deposited. Most of the alcohol was removed from the filtrate on the water bath and a further crop of crystals obtained from the aqueous solution. The dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene was purified by crystallisation from benzene. M.p. 133-135°C.

Found: C, 78.7; H, 6.6%. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.5%.

dl-cis-1:2-diacetoxy-1:2:3:4-tetrahydroanthracene.

The diol (125 mg.) dissolved in dry pyridine (2 cc.) was treated in the cold with acetic anhydride (0.5 cc.). After standing overnight the solution was poured into ice cold water and the precipitate, which solidified on rubbing with a glass rod, filtered. It was crystallised three times from petroleum ether (60-80°C), m.p. 122°C.
Found: C, 72.1; H, 6.2%. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.0%.

1:2-dibromo-1:2:3:4-tetrahydroanthracene.

1:2-dihydroanthracene (0.5 g.; 1 mole) dissolved in dry carbon disulphide (10 cc.) was treated dropwise with a solution of bromine (0.14 cc.; 1 mole) in carbon disulphide in the cold. On removal of the carbon disulphide an oily solid remained and was crystallised from petroleum ether (60-80°C), m.p. 105-106°C. Yield, 750 mg. (80%).
Found: C, 49.4; H, 3.7; Br, 47.3%. $C_{14}H_{12}Br_2$ requires C, 49.4; H, 3.5; Br, 47.1%.
(v. Braun[25] records a m.p. of 102°C for this dibromide).

1(2)-bromo-2(1)-hydroxy-1:2:3:4-tetrahydroanthracene.

1:2-dibromo-1:2:3:4-tetrahydroanthracene (200 mg.) was dissolved in acetone and as much water added as would not cause a permanent turbidity. The solution was maintained at 50-60°C while magnesium carbonate (100 mg.) was

added over a period of two and a half hours. The solution was filtered hot and the acetone distilled from the filtrate. The brown oil which separated from the aqueous solution was extracted with ether and the ether extract dried and concentrated. The solid obtained (140 mg., 85%) was crystallised from petroleum ether (60-80°C), m.p. 102-103°C.

Found: C, 60.6; H, 4.8%. $C_{14}H_{13}OBr$ requires C, 60.6; H, 4.7%.

dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene.

The hydroxybromide (0.456 g.) was refluxed for four hours with a solution of potassium hydroxide (0.145 g.) in water (8.5 cc.). The cooled solution was saturated with sodium sulphate, acidified and extracted with ether. The ether solution on concentration yielded a reddish oil which partly solidified on rubbing with benzene, m.p. 154-158°C. Yield, 158 mg. (45%). Purified by crystallisation from benzene, m.p. 162-163°C.

Reaction of 1:2-dihydroanthracene with lead tetra-acetate.

Lead tetra-acetate was prepared by the method of Dimroth and Schweizer[33] and crystallised from acetic acid, distilled over chromium trioxide. To a mixture of lead tetra-acetate (1.2 g.; 1 mole) in acetic acid (20 cc.,

distilled over chromium trioxide) was added 1:2-dihydro-anthracene (0.5 g.; 1 mole). The mixture was maintained at 80-90°C for one hour, by which time all the lead tetra-acetate had been used up (tested with water). The mixture was allowed to cool, poured into a large volume of water and extracted with ether. The ether extract was washed four times with water and once with bicarbonate solution. The combined water washings were neutralised with sodium bicarbonate and extracted with ether. The combined ether extracts were dried and concentrated, yielding a reddish oil (0.65 g.; 78%). The oil was readily soluble in benzene, chloroform and carbon tetrachloride and insoluble in petroleum ether. It did not solidify on rubbing with any of these solvents, nor did sublimation at 1 mm. pressure yield any solid. The oil (560 mg.) was therefore hydrolysed by heating for 15 minutes on a boiling water bath with 0.7 N methanolic potassium hydroxide (33.5 cc.). Most of the alcohol was removed under reduced pressure and a large volume of water was added to the residue, which was then extracted with ether. The ether extract was dried and concentrated and the oily residue solidified by rubbing with benzene. Yield, 320 mg. (80%). The solid was crystallised from benzene, m.p. 160-162°C and it did not depress the m.p. of the diol obtained by hydrolysis of the dibromide.

Found: C, 78.4; H, 6.8%. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.5%.

A repeat of this experiment on 10 g. of 1:2-dihydroanthracene yielded, after hydrolysis, 4.5 g. of a mixture of cis- and trans-diols. By repeated crystallisation from benzene a partial separation of the cis- and trans-isomers was effected and a third product isolated. This latter compound crystallised from benzene as fine yellow needles, m.p. 281-284°C. Found: C, 80.4; H, 4.0%.

dl-trans-1:2-diacetoxy-1:2:3:4-tetrahydroanthracene.

The diol (118 mg.) dissolved in pyridine (2 cc.) was treated with acetic anhydride (0.6 cc.). The solution after standing overnight was poured into ice-cold water and the oil, which did not solidify on rubbing, extracted with ether. The ether extract was washed with dilute hydrochloric acid, dried and concentrated, yielding an oil from which a solid, m.p. 80-82°C, was obtained on rubbing with petroleum ether (60-80°C). The diacetate was purified by crystallisation from petroleum ether, m.p. 85-87°C. Found: C, 72.5; H, 6.2%. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.0%.

Hydrolysis of the diacetate.

The above purified diacetate (42 mg.) was refluxed

for three hours with 2.5% methanolic potassium hydroxide (0.9 cc.). The solution was poured into water, extracted with ether and the ether extract washed with dilute alkali, dried and concentrated. A colourless solid was obtained, m.p. 159-162°. Yield, 26 mg. (theoretical).

Rate of oxidation of cis- and trans-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene with lead tetra-acetate.

The preparation of a standard lead tetra-acetate solution and the determination of the rate of oxidation was carried out in the same way as that already described for the case of the naphthalene diols (see page 80).

The lead tetra-acetate solution was 0.115 N. The oxidation was carried out on 53 mg. of the diol. Assuming that one molecule of diol requires one molecule of lead tetra-acetate for complete oxidation, 53 mg. of diol will require 109.7 mg. of lead tetra-acetate, i.e., 4.3 cc. of 0.115 N lead tetra-acetate.

The results obtained (see Fig.2, page 72) are in agreement with this assumption and also with Criegee's rule that cis-diols are more rapidly oxidised than their trans isomerides.

Thus at 18-19°C and a diol concentration of 0.0125 g.moles/litre the oxidation of cis-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene by lead tetra-acetate is complete in 15 minutes, while at the same temperature and concentration

the trans-diol requires 40 minutes for complete oxidation.

Tests with potassium triacetyl osmiate.

Potassium triacetyl osmiate was obtained in solution by dissolving dipotassium tetramethyl osmiate in acetic acid[21]. The colour of the solution is royal blue. The test was carried out by adding the solution of the reagent in acetic acid to a small amount of the diol in acetic acid. The results obtained are shown in the following table:-

Compound	Colour change in potassium triacetyl osmiate.	Rate of Change
dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene	Blue-green-red-brown	Immediate
dl-, d- and l-trans-1:2-dihydroxy-1:2:3:4-tetrahydronaphthalene	Blue - purple	30 minutes
dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene	Blue - green	Immediate
dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene	No change	—

The reagent itself on exposure to air very slowly (> 6 hours) turns purple.

Esterification of dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene with l-menthoxyacetyl chloride.

The diol (135 mg.; 1 mole) was dissolved in dry pyridine (5 cc.) and treated with freshly distilled l-menthoxyacetyl chloride (1 g.; 4 moles). The solution turned purple and a solid was precipitated when the acid chloride was added. Heat was generated during the addition, the solution being cooled by immersion in cold water. The solution was kept in a stoppered flask at room temperature for 40 hours and then poured into water. An oil was precipitated and extracted with ether. The ether extract was washed thoroughly with dilute hydrochloric acid, dilute sodium hydroxide and water; dried and concentrated. The residue was a red, rather viscous oil which was very soluble in benzene, petroleum ether, ether, chloroform, carbon tetrachloride, ethyl acetate, cyclohexane and dioxan, somewhat less soluble in alcohol. No solid material was obtained by treatment with any of these solvents. Neither the oil nor a petroleum ether solution of the oil yielded any solid on cooling in an ethanol-cardice cooling mixture.

The oil, dissolved in benzene, was passed through a column of alkali free alumina and eluted with benzene. The residue obtained by concentrating the eluate was still an oil from which, however, much of the colour had been removed.

This oil was retreated with 3 moles. of l-menthoxyacetyl chloride in the same manner as before. On addition of the acid chloride the solution turned green then red. As before, heat was generated and a precipitate formed. After standing for 40 hours the solution was worked up and yielded a red oil from which no solid material could be obtained.

A fraction of this oil was submitted to sublimation. At 200-210°C/1 mm. a yellow oil sublimed but could not be solidified. A portion (800 mg.) of the oil was refluxed for three hours with 2.5% methanolic potassium hydroxide (9 cc.; 40% excess). The methanol was removed by distillation under reduced pressure and the residue extracted with ether. The ether extract was washed with dilute sodium hydroxide, dried and concentrated. The oily residue (250 mg.) smelt strongly of menthol. By rubbing with benzene a solid was obtained, m.p. 161-162°C, which did not depress the melting point of the trans-diol.

Esterification of dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydroanthracene with l-menthoxyacetyl chloride.

The diol (150 mg.; 1 mole) was dissolved in dry pyridine (10 cc.) and treated with freshly distilled l-menthoxyacetyl chloride (525 mg.; 2.9 moles). The solution

became slightly warm and was cooled in cold water. There was no colour production on addition of the acid chloride, a white solid being precipitated. After standing at room temperature for 48 hours the solution was worked up in the usual manner and a slightly yellow coloured oil obtained. This oil was soluble in all the usual organic solvents and could not be induced to solidify. On cooling in a mixture of cardice and ethanol it became hard and glassy but did not solidify.

Comparison of the dihydride of the optically inactive metabolic anthracene diol with the synthetic diols obtained above.

Compound	m.p. °C	m.p. of diacetate °C
Optically inactive dihydro metabolite[1]	162	84
dl-trans-1:2-dihydroxy-1:2:3:4-tetrahydro-anthracene	162-163	85-87
dl-cis-1:2-dihydroxy-1:2:3:4-tetrahydro-anthracene	133-135	122

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