THE DEGRADATION OF QUATERNARY AMMONIUM SALTS

AND RELATED COMPOUNDS.

with

AN ADDITIONAL PAPER : THE ERGOSTADIENETRIOLS.

A Thesis presented by
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C O N T E N T S.

SECTION I.

SECTION II.

SECTION I.

THE DEGRADATION OF QUATERNARY AMMONIUM SALTS AND RELATED COMPOUNDS.

THE DEGRADATION OF QUATERNARY AMMONIUM SALTS

INTRODUCTION

When an aqueous solution of phenacylbenzyldimethylammonium bromide (I) is treated with sodium amalgam, the reaction does not take the normal course with elimination of the phenacyl radical, but yields a solid base, $C_{17}H_{19}ON$, to which the structure Ph.CO.CH.$N(Me)_2$.CH_2Ph. has unequivocally been assigned. The same product is also obtained in good yield when the salt I. is heated with dilute aqueous alkali (1).

$$\mathrm{Ph.CO.CH_2N\,Me_2Br.\ (CH_2Ph)} \xrightarrow{\text{alkali}} \mathrm{Ph.CO.CH(CH_2Ph).NMe_2}$$

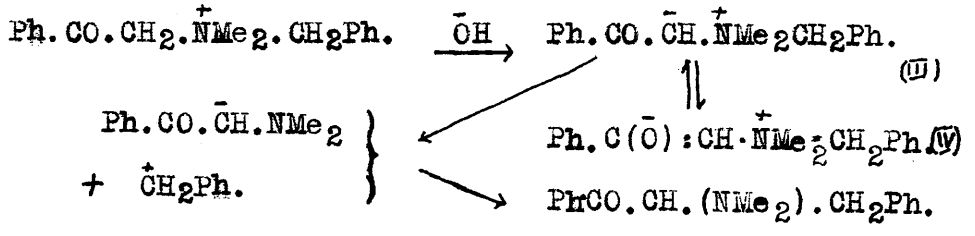
I. II.

Following on this it was shown (2) that the replacement of the benzyl by substituted benzyl radicals such as m-bromobenzyl, α-phenylethyl, benzhydryl, or 9-fluorenyl, of the phenacyl groups by p-bromophenacyl or acetonyl (3) or of the dimethylammonium system by piperidinium (2) does not prevent migration, in fact, the benzhydryl and fluorenyl radicals wander so readily as to prevent isolation of their quaternary salts. Alkaline conditions are, however, essential (dilute sodium or potassium hydroxides, sodium ethoxide or ammonia), no

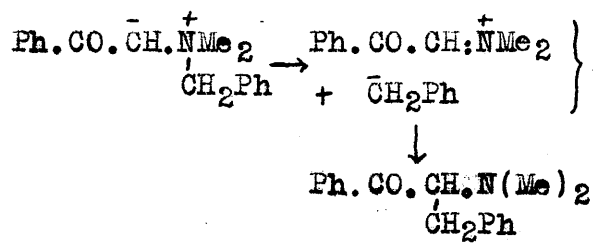
transformation taking place in neutral or acid solution.

The rearrangement was shown to be an intramolecular one (2), by acting on a mixture of phenacyl-m-bromobenzyldimethylammonium and p-bromophenacylbenzyldimethylammonium bromides with sodium ethoxide solution. Under similar conditions the rates of transformation of these two salts are of the same order of magnitude, but the mixture yielded only the rearrangement products corresponding to the individual salts: neither ω-dimethylamino-ω-benzylacetophenone nor ω-dimethylamino-ω-m-bromobenzyl-p-bromoacetophenone could be detected.

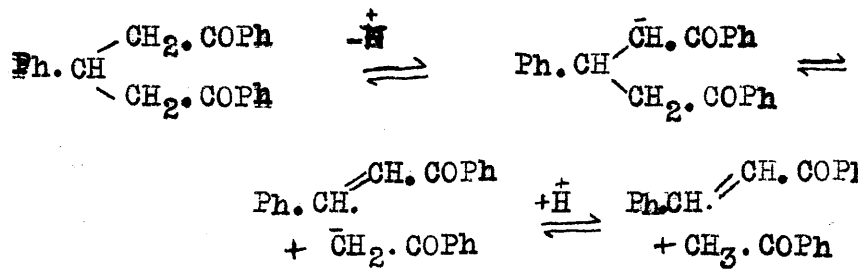
The first suggestion (2) as to the mechanism of the rearrangement was that the salt is converted by the action of alkali into the keto-enolic betaine (III)⇄(IV) followed by the detachment of the benzyl radical as a kation and its reattachment at the original methylene carbon atom. Such a process would be analogous to the conversion of betaine into dimethylaminoacetate (14) or of the anhydride of N-trimethyl-o-aminophenol into dimethyl-o-anisidine. (15)



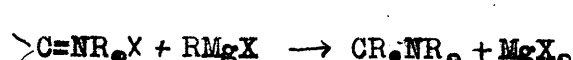
A series of preliminary measurements of the relative migratory tendencies of substituted benzyl groups however, showed that this theory was untenable, for by the introduction of "negative" groups into the benzene nucleus of the benzyl radical, the reaction velocity was increased, while "positive" groups led to a decrease. These results suggested that the benzyl radical is detached as an anion and is then "captured" by the ω-carbon atom of the phenacylidene group before it can escape into the bulk of the reaction mixture viz.,



The first stage is formally analogous to the reversed Michael and similar reactions, e.g., (16)



And the second to the energetic action of the Grignard reagent on salts of the pseudo-bases (17)



An exhaustive study of the effect of substitution of halogens, NO_2, Me, or OMe in the o-, m-, and p-positions in the benzyl group by a more exact method confirmed these previous results (4). As a necessary preliminary to this study Stevens and Thomson investigated the rearrangement of the unsubstituted compound in considerable detail. They found, (a), that the reaction (I)→(II) does not proceed quantitatively, but gives rise to some 12-15% by-product, isolated as a neutral gum from which no definite compound could be extracted: (b), that the by-product is formed principally in the early stages of the reaction: (c), that the use of two molecules of alkali in place of one caused an appreciable, but not proportional increase in velocity: and (d), that the quaternary iodide or chloride corresponding to (I) is rearranged at the same rate as the bromide.

These same authors later extended this reaction which so far had involved only the migration of a substituted benzyl group to the methylene carbon atom of an acetonyl or substituted phenacyl radical, to systems in which the migrating radical is phenacyl (III→IV), or the recipient methylene carbon atom is that of a benzyl group. (V→VI)

$$\underset{\text{(III).}}{\mathrm{Ph.CO.CH_2NMe_2Br}\ (\mathrm{CH_2.CO.Ph})} \xrightarrow{\text{alkali}} \underset{\text{(IV).}}{\mathrm{Ph.CO.CH(CH_2.CO.Ph).NMe_2}}$$

$$\underset{\text{(V)}}{\mathrm{PhCH_2NMe_2Br}\ (\mathrm{CH_2Ph})} \xrightarrow{\text{alkali}} \underset{\text{(VI)}}{\mathrm{PhCH(CH_2Ph)NMe_2}}$$

The first of these rearrangements (III→IV) takes place under conditions similar to those emplpyed in the original (I→II) viz., dilute aqueous alkali, but the second (V→VI) demands more drastic treatment, necessitating fusion with sodamide.

From this interchangeability of function of the migrating and acceptor radicals, it would appear that that characteristic of a group which enables it to lose a hydrogen ion and act as recipient of the migrating group, is the same as that which enables it to migrate, and is probably as previously suggested, some form of anionic stability.

DEGRADATION OF QUATERNARY AMMONIUM SALTS

PART I.

THE INFLUENCE OF SUBSTITUTION IN THE PHENACYL RADICAL ON THE VELOCITY OF INTRAMOLECULAR REARRANGEMENT.

It was hoped that a study of the effect of substitution in the phenacyl radical on the velocity of migration of the benzyl group in the rearrangement (I)→(II) would throw further light on the mechanism of the reaction.

$$\underset{\text{(I).}}{\mathrm{Ph.CO.CH_2.NMe_2Br}\ (\mathrm{CH_2Ph})} \xrightarrow{\text{alkali}} \underset{\text{(II).}}{\mathrm{Ph.CO.CH.NMe_2}\ (\mathrm{CH_2Ph})}$$

The salts with the following substituents in the phenacyl group, o-, m-Bromo, o-, m-NO_2, p-Cl, p-I, p-MeO, p-Me, were accordingly prepared and their degradation studied.

Since, as shown previously (4), the rearrangement does not proceed quantitatively, the course of the reaction was followed by isolation of (II) as such and of (I) as picrate. The quantity k defined by the equation,

$$x = k \int_0^t y \cdot dt.$$

where x and y are the concentrations of (II) and (I) respectively at time t, was arbitrarily taken as a measure of the progress of the reaction. This is equivalent to the assumption that the main reaction is of the first order

with respect to (I) and of zero order with respect to the alkali, and that the side reaction is simultaneous with the rate determining stage of the main process. Since we have no information as to the nature of the side reaction however, this proceedure must be regarded as empirical and justified as a method of comparison by the facts that the values of k found during the reaction, did indeed show satisfactory constancy, and that the ratios of the migratory velocities of a series of substituted benzyl radicals were the same whether the radicals were associated with phenacyl or with p-bromophenacyl (4).

The measurements were carried out at 37.7°C. in dry methylalcoholic solutions, 0.05 N. with respect to the salts and 0.1 N. with respect to sodium methoxide. In general the quaternary bromides were used, but in the cases of the o- and m-bromo-compounds, the iodides and in that of the p-nitro- the chloride was employed, the previous investigation (4) having shown this to be admissible. The velocity constants are recorded in Table I.; the value for the o-nitro compound may have no other significance than that of the maximum value (see experimental part). The errors of manipulation probably do not exceed ± 2%, but the existence of the side reaction introduces an uncertainty which is difficult to assess, and the errors may be greater. The unequality p-Me > (H) is here considered established, but not the smaller differences.

TABLE I.

Substituent.	$k.10^4$	K_a10^5	Substituent.	$k.10^4$	K_a10^5
p-OMe	31.9.	3.2.	m-Br	34.2.	13.7.
p-Me	46.1.	4.3.	m-NO_2 ###	22.5.	34.8.
(H)	# 41.9.	6.6.	o-Br ###	8.	145.
p-Cl	33.9.	9.3.	o-NO_2	(8).	630.
p-Br	# 33.6.	##			
p-I	32.8.	##			

\# Thomson and Stevens (4).

The dissociation constants of these acids have not been measured in aqueous solution, but in 50% methyl alcohol they are practically the same as that of p-chlorobenzoic acid (18).

Derived by slightly modified methods (compare experimental part).

On account of the comparitively slight effect of substitution on the reaction velocity, and of experimental difficulties (see experimental part) the scope of the investigation was not extended.

The results obtained may be summarised independently of any theory of the reaction mechanism by the statement that the presence of the so-called "negative" substituents in the benzene nucleus of the phenacyl radical retards the reaction, whereas their presence in the benzyl radical causes marked acceleration (4). It was suggested (2) that the alkaline medium first converts the salts nearly completely into neutral ions of the type $Ph.CO.\bar{C}H.\overset{+}{N}Me_2CH_2Ph.$, and that the velocity of rearrangement is then determined by that of the detachment of the migratory radical from the nitrogen atom. If now the instability of the anionic carbon atom in the neutral ion is regarded as supplying the driving force of the reaction, the velocity of rearrangement would increase with diminishing acidity of the phenacyl methylene group in the original salt and substitution in the phenacyl radical would be expected to influence the velocity of rearrangement mainly by its effect on this acidity. Previous experiments by Mr.T.Thomson to determine the acid dissociation constants of such salts did not give encouraging results. The similarly substituted benzoic acids are therefore the most legitimate analogues for which data are available, and their dissociation constants K_α are recorded along with the

velocity constants in Table I. The two sets of values show a fair degree of parallelism in the inverse sense except in the case of p-OMe, but the experimental data are not sufficiently extensive to justify great stress being laid on the fact.

EXPERIMENTAL

As previously explained, the reaction (I) → (II) does not proceed quantitatively, and therefore, any volumetric process dependent upon the estimation of the alkali remaining at any stage of the reaction is not satisfactory. The following gravimetric process in which both the rearrangement product II. and the unaltered quaternary salt are estimated was accordingly devised. (4).

The reaction was carried out in a flask (frequently 15 c.c.) filled to the neck by the solution under investigation (to prevent atmospheric oxidation of the rearrangement product; it is not, however, necessary to use boiled-out reagents), and the process effectively checked by pouring into water (40 c.c.) containing ammonium chloride equivalent to the alkali used. The product II. was extracted with ether (3 x 20 c.c.) ~~and~~ and the united extracts were washed once with water. The aqueous layer and washings were acidified with acetic acid, warmed to 30 - 40°, freed from ether by a current of air, and treated gradually with 0.2 N sodium picrate solution (2 c.c. excess; larger quantities of sodium picrate or of ammonium chloride may cause separation of ammonium picrate).

The precipitate of quaternary picrate crystallised readily on scratching; after remaining overnight it was collected and dried at 100°. The tertiary base was extracted from the ethereal solution by hydrochloric acid (3 x 10 c.c. of 0.1 N): and the acid solution heated on the water bath to expel ether; cooled in ice, and treated with ammonia; the precipitated base then crystallised readily on agitation. After some hours it was collected and brought to constant weight in a current of dry air.

On the basis of control experiments with known quantities of material, the manipulatory losses were estimated at 5 m.g. for the tertiary base and for the picrate, 1 m.g. + (1 m.g. per 5 c.c. of alcohol used). These corrections raised the reaction co-efficients by some 4%.

The methyl alcohol used was lime dried and distilled over sodium.

The quaternary salts are not extracted from their aqueous solutions by ether, nor are they affected by 0.1 N ammonia in several days at room temperature.(4)

In general the tertiary bases are but little affected by caustic alkali in the absence of air, or by air in the absence of caustic alkali, but in the

case of the degradation of the m - nitro - salt a series of values of $k.10^4$ were obtained which showed a progressive diminution from 21 to 15. This can be accounted for by the destruction of the normal degradation product by the alkali, for when 0.3 g. of that base was subjected for four hours to conditions similar to those used in the degradation less than 0.1 g. could be recovered.

t.	90.	180.	270.	360.	450.
Recovered quat. salt.	70.5.	52.8.	40.3.	31.4.	24.3.
Tertiary Base.	17.5.	24.8.	30.0.	33.4.	38.5.
$k.10^4$	21.0.	19.7.	17.8.	16.4.	15.4.

The figure given in Table I. is the value arrived at by extrapolating these values to zero time.

The o - and p. nitro salts were destroyed by alkali, but under no conditions could any tertiary base be recovered. On treatment in aqueous solution both substances gave tarry material, but in sodium methoxide solution the o - nitro-salt gave water soluble products only. The half-life period of the o - nitro - compound was about 900 and that of the p - nitro- about 150 minutes; the maximum value for the o - compound given in Table I. is based on these figures.

p - Iodo -ω - dimethylamino -ω- benzyl-

acetophenone gave a hydrochloride rather sparingly soluble in water making it necessary to precipitate the free base with ammonia from the hot aqueous solution.

As the ϕ - bromo - analogue was an oil, the normal proceedure could not be adopted. Attempts to isolate it quantitatively as picrate proving unsuccessful, the bromine content of the total basic material formed after 8 hours was estimated, and some 90% of the original material thus accounted for, a figure which agrees well with the usual side - reaction losses. Runs of 2, 4 and 6 hours in which only the quaternary salt was recovered as picrate were made and from these and the above, a figure for k was deduced which is probably comparable in accuracy with the other values in Table I.

The data for p - methylphenacylbenzyldimethylammonium bromide (0.05 N) in sodium methoxide (0.1 N) at 37.7° are given in full as a specimen. The definite integral in the expression for k (page 6.) is evaluated by Simpson's Rules; x and y are expressed in mols.% on the initial material and t in minutes.

Interval. (t).	Unchanged quat. salt (y).	Tertiary base. (x)	Total.	k x 10^4.
60.	70.1.	23.6.	93.6.	46.9.
120.	52.9.	39.6.	92.5.	45.7.
180.	38.7.	52.8.	91.5.	46.3.
240.	31.1.	61.8.	92.9.	46.0.
300.	24.0.	68.2.	92.2.	45.5.

Table II. shows the values of kx10^4 for the salts together with the mean deviations from the average. Column B contains the percentages of by-product formed when 60% of the initial material has disappeared, very little being formed subsequently. In general five determinations were made.

TABLE II.

Substituent.	B%	k x 10^4.	
o-Br.	12	8	
m-Br.	7	34.2.	1.3
p-Cl.	11	33.9	1.5
p-I.	10	32.8	0.6
p-Me.	8	46.1	0.8
p-OMe.	11	31.9	1.2

Preparation and Characterisation of Materials - The p - methyl-, methoxy-, -chloro-, and -iodo-acetophenones prepared by the Friedal-Crafts reaction were converted into the ω - bromo - derivatives by bromination in glacial acetic acid.(8). The substituted phenacyl bromides so obtained had the properties attributed to them in the literature. The quaternary salts were formed in cold benzene or ether from the bromo-ketones and benzyldimethylamine.

p - Methylphenacylbenzyldimethylammonium bromide separated from the components in ether in almost quantitative yield and crystallised from alcohol-ether in small prismatic needles, m.p. 185 - 186° (Found: Br, 23.1. $C_{18}H_{22}ONBr$ requires Br. 23.0%); its picrate crystallised from methyl alcohol in yellow needles, m.p. 149 - 150°. (Found: $C_6H_2O_7N_3$, 45.9. $C_{18}H_{22}ON.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$ 46.0%).

ω - Dimethylamino -ω- benzyl -p- methylaceto-phenone, obtained by the degradation of the quaternary ammonium salt, gave prismatic needles, m.p. 62° from methyl alcohol; it rapidly decomposed even in a sealed tube. (Found: N. 5.4. $C_{18}H_{21}ON$ requires N, 5.2%).

p - Methoxyphenacylbenzyldimethylammonium bromide was obtained in good yield from the components in cold benzene. It crystallised from alcohol-ether in

colourless prismatic needles, m.p. 202 - 203°. (Found: Br.21.7. $C_{18}H_{22}O_2N$ Br. requires Br.,22.0%), and its picrate, yellow needles, m.p. 144-145°, from methyl alcohol. (Found: $C_6H_2O_7N_3$, 44.7. $C_{18}H_{22}O_2N$. $C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$, 44.6%). ω - Dimethylamino - p - methoxy - ω - benzylacetophenone crystallised from methyl (alcohol) in clusters of colourless needles, m.p.57-58°. (Found: N, 4.7. $C_{18}H_{21}O_2N$ requires N, 4.9%)

p - Iodophenacylbenzyldimethylammonium bromide was formed in benzene from the components and crystallised from absolute alcohol in small plates, m.p. 179-180°. (Found: Br.16.9. $C_{17}H_{19}ONBrI$, H_2O requires Br.16.7%.). On heating at 105-110° decomposition set in. Its picrate crystallised from methyl alcohol in yellow prismatic needles, m.p. 151-152°. (Found: $C_6H_2O_7N_3$, 37.4. $C_{17}H_{19}ONI.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$, 37.6%.). p - Iodo- ω - dimethylamino - ω - benzylacetophenone obtained by degradation of the above quaternary salt crystallised from methyl alcohol in clusters of yellow needles m.p. 119-120°. (Found: I, 33.6. $C_{17}H_{18}ONI$ requires I,33.5%.) It gives a hydrochloride very sparingly soluble in water.

p - Chlorophenacylbenzyldimethylammonium bromide was obtained in good yield from the constituents in benzene. It crystallised from alcohol-ether in small

microcrystalline masses, m.p. 175-176°. (Found: Br. 20.8; loss at a 100°, 4.5. $C_{17}H_{19}ONClBr, H_2O$ requires Br. 20.7; loss, 4.7%.). Its picrate separated from methyl alcohol in yellow prismatic needles, m.p. 155-156°. (Found: $C_6H_2O_7N_3$, 44.1. $C_{17}H_{19}ONCl.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$, 44.3%.). p - Chloro - ω - dimethylamino - ω - benzyl acetophenone obtained by degradation of the above salt, gave yellow prisms, m.p. 91-92°, from methyl alcohol. (Found: Cl, 12.5. $C_{17}H_{18}ONCl$ requires Cl, 12.3%.).

o - Nitroacetophenone was prepared by the hydrolysis of o - nitrobenzoylacetoacetic ester (9) (10), and brominated in glacial acetic acid (11). From the bromide and benzyldimethylamine in cold benzene there separated o - nitrophenacylbenzyldimethylammonium bromide in good yield, which crystallised from absolute alcohol in small, slightly yellow rhombs, m.p. 168-169°. (decomp.) (Found: Br. 21.1. $C_{17}H_{19}O_3N_2Br$. requires Br. 21.1%.). Its picrate crystallised from acetone-methyl alcohol (1:1) in stout yellow needles m.p. 167-168° (Found: $C_6H_2O_7N_3$ 43.5. $C_{17}H_{19}O_3N_2.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$, 43.6%.).

m - Nitrophenacylbenzyldimethylammonium bromide, prepared from ω - bromo - m - nitroacetophenone (12) and benzyldimethylamine in cold benzene, crystallised from alcohol - ether in yellow cubes, m.p. 153 - 154°.

(Found: Br, 20.1. $C_{17}H_{19}O_3N_2Br,H_2O$ requires Br, 20.1% Heating at 100° leads to decomposition.). The picrate crystallised from methyl alcohol in slender brown needles m.p. 134-135° (Found: $C_6H_2O_7N_3'$, 43.9). Its degradation product m - nitro - ω - dimethylamino - ω - benzylacetophenone separated from methyl alcohol in yellow prismatic needles, m.p. 77-78° (Found: N, 9.5. $C_{17}H_{18}O_3N_2$ requires N, 9.4%.).

p - Nitrophenacylbenzyldimethylammonium chloride, obtained as a slowly crystallising oil from ω - chloro - p - nitroacetophenone (13) and benzyldimethylamine in cold benzene, separated from absolute alcohol in small, slightly yellow needles, m.p. 176° (Found: Cl, 10.7. $C_{17}H_{19}O_3N_2Cl$ requires Cl, 10.6%.). Its picrate, stout almost brown cubes from methyl alcohol melted at 164-165° (Found: $C_6H_2O_7N_3'$, 43.7%).

ω - Chloro - m - bromoacetophenone, prepared in good yield from diazo-methane and m - bromobenzoyl chloride (13) crystallised from ligroin (b.p. 40-60°.) in small plates m.p. 47-48°. {0.1034 g. required 23.4c.c. 0.0382 N - $AgNO_3$ (Robertson) C_8H_6OClBr. requires 23.3c.c.} The quaternary chloride separated very slowly from cold benzene as an oil and was converted by treatment with potassium iodide into m - bromophenacylbenzyldimethyl-

ammonium iodide, which crystallised from absolute alcohol in fine needles m.p. 180-181.° (Found: I, 27.5. $C_{17}H_{19}ONBrI$ requires I, 27.9%.). Its picrate, separated in stout yellow needles m.p.149-150° from methyl alcohol (Found: $C_6H_2O_7N_3$ 41.2. $C_{17}H_{19}ONBr.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$, 40.9%.).

m - Bromo - ω - dimethylamino - ω - benzylacetophenone, obtained by the degradation of the above salt, crystallised in slightly yellow needles m.p. 99-100°, from methyl alcohol. (Found: Br.24.3. $C_{17}H_{18}ONBr$ requires Br, 24.1%.)

ω - Chloro - o - bromoacetophenone was prepared by the action of diazomethane on o - bromobenzoyl chloride. Owing to the small difference in b.p. between it (164°/10 m.m.) and o - bromobenzoyl chloride (158°/49m.m.) and to the small quantities used, it could not be obtained sufficiently pure for analysis and was accordingly converted directly in benzene solution into the quaternary chloride, a non-crystallising oil which by treatment with potassium iodide gave o - bromophenacylbenzyldimethyl-ammonium iodide: this crystallised from absolute alcohol in small white cubes, m.p. 134-135° (Found: I, 27.6.) Its picrate crystallised from absolute alcohol in yellow needles m.p. 125-126°. (Found: $C_6H_2O_7N_3$, 41.1%.) Its

degradation product o - bromo - ω - dimethylamino - ω - benzylacetophenone was obtained as an oil which could not be crystallised. Its picrate, however, separated from methyl alcohol in yellow needle clusters m.p.126-127° (Found: Br,14.9. $C_{17}H_{18}ONBr$. $C_6H_3O_7N_3$ requires Br.14.6%.).

DEGRADATION OF QUATERNARY AMMONIUM SALTS

PART II.

NECESSARY STRUCTURAL CONDITIONS FOR MIGRATION IN RADICALS.

The investigations described in the introduction have shown that the rearrangement (I→II) takes place when R is a substituted benzyl or phenacyl radical, and the effect of substitution on the velocity of the rearrangement is such as to suggest that the tendency of a radical to migrate can be correlated with its anionic stability, which however need not be very pronounced.

$$Ph.CO.CH_2.\underset{\dot{R}}{N}Me_2X \xrightarrow{Alkali} Ph.CO.\underset{\dot{R}}{C}H.NMe_2$$

(I). (II).

It was therefore anticipated that the radicals allyl, propargyl, nitroisopropyl ($-CMe_2NO_2$), or phenylisopropyl ($-CMe_2Ph$) could replace R in the rearrangement. The choice of radical in the third case was influenced by the known instability of primary and secondary nitro-compounds towards alkali: and the fourth was chosen as another example of a group with no α-hydrogen atom. Groups such as $-CH_2CN$, and $-CH_2SO_2R$ also suggest themselves, but the former can be excessively susceptible to alkaline hydrolysis, When attached to quaternary nitrogen (compare Stevens, Snedden, Stiller and Thomson.(3)), and salts containing the latter radical/

would probably be difficult to obtain (5).

Phenacylallyldimethylammonium sulphate (I; R=-CH_2.CH:CH_2) underwent rearrangement easily on warming with alkali. The corresponding propargyl compound could not be obtained, however, owing to the difficulties attending the preparation of propargyl bromide, or propargyldimethylamine, but the analogous salt (III) was prepared by taking the advantage of the recent elegant synthesis of phenylpropargylpiperidine by Mannich and Chang. (19)

$$\mathrm{Ph.CO.CH_2.N(C_5H_{10})Br} \longrightarrow \mathrm{Ph.CO.CH.N<C_5H_{10}>}$$
$$\mathrm{CH_2.C{:}CPh} \qquad\qquad \mathrm{CH_2.C{:}CPh}$$

(III) (IV)

This with caustic alkali was decomposed to tarry material, but on warming with sodium carbonate readily gave (IV). The third salt (I: R=-CMe_2NO_2) could not be prepared, since β-bromo-β-nitropropane did not combine with phenacyldimethylamine, and with the dimethylamine gave only dimethylamine hydrobromide. An attempt to prepare the fourth from phenacyl bromide and phenylisopropyldimethylamine gave only the hydrobromide of the tertiary base.

Attention was next directed to the behaviour of a number of radicals not fulfilling the conditions considered necessary for facile migration. Modification of the benzyl group in (I: R=-CH_2Ph) by the interposition of further methylene groups between the aromatic nucleus and the nitrogen atom inhibited the

rearrangement. Thus on vigorous treatment with alkali, Phenacyl-β-phenylethyldimethylammonium bromide lost the phenacyl group, and phenacyl-γ-phenylpropyldimethylammonium bromide lost the phenacyl or the phenylpropyl radical according to the conditions used, neither salt giving evidence of rearrangement. The latter case was chosen to disclose any possible "alternation" in the relation between the effect of a phenacyl group and its position. In order to test the possibility that increase in the number of phenyl groups might compensate for their remoteness, it was proposed to study the salt (I: R=$-CH_2.CPh_3$) β:β:β-Triphenylethyldimethylamine, however, could not be made to combine with phenacyl bromide, for on long standing in the cold in benzene solution, or refluxing for 24 hours, the only product obtained was the tertiary base hydrobromide.

Phenacylphenyldiethylammonium bromide (V), in which there is no methylene group interposed between the aromatic nucleus and the nitrogen atom, yielded phenacylethylaniline (VI) and ethyl alcohol, and gave no evidence of migration, either of phenyl or ethyl. This decomposition, though facile, is much less so than the rearrangement of (I; R=$-CH_2Ph$). Previous experience suggests that the replacement in this case of the two methyl groups in (I) by ethyl is not of major importance.

(V) $Ph.CO.CH_2NPhEt_2Br \xrightarrow{NaOH} Ph.CO.CH_2NPhEt + EtOH$ (VI)

Several saturated radicals were also investigated. Phenacyltrimethylammoniumbromide (I; R= Me) gave only trimethylamine, as found by Rumpel (20). Phenacylhexahydrobenzyldimethylammonium bromide (I: R= $-CH_2.C_6H_{11}$), containing the nearest possible saturated analogue of the mobile benzyl group, was unaffected by moderate, and completely decomposed by violent treatment with alkali. The observation that the α-phenylethyl radical migrates with enormously greater facility than benzyl suggested that phenacyl tert. butyldimethylammonium bromide (I: R=-CMe_3) might be capable of rearrangement. This salt could not be prepared as tert. butyl bromide gave only dimethylaminehydrobromide with dimethylamine and did not react with phenacyldimethylamine.

The results obtained, though less complete than could be desired, are in agreement with the view that migratory aptitude is correlated with anionic stability:- migration of phenacyl, benzyl, allyl and phenylpropargyl; non-migration of methyl, ethyl, phenyl, hexahydrobenzyl, β-phenylethyl, and γ-phenylpropyl. The migrating radicals, however, with the possible exception of phenacyl, could be regarded as possessing both cationic a nd anionic stability in virtue of the $\beta\gamma$-multiple linkage, and it was therefore considered important to study the extreme case of

phenacylmethoxydimethylammonium bromide (I: R=OMe), containing a radical of the most unambiguous electrochemical character. But ONN-trimethylhydroxylamine and phenacyl bromide yielded phenacyldimethylamine hydrobromide in place of the expected product, a surprising reaction, for the mechanism of which, some form of internal oxidation-reduction analogous to the Cannizzaro reaction of aldehydes is tentatively suggested. In order to prepare the O-benzyl-NN-dimethylhydroxylamine, which would have been as suitable as the rather inaccessible trimethyl analogue, the rearrangement of benzyldimethylamine oxide was attempted (compare Meisenheimer's conversion of allylmethylaniline oxide into O-allyl-N-phenyl-N-methylhydroxylamine(21)) but there resulted only dimethylamine and the products of the Cannizzaro dismutation of benzaldehyde. The amine oxide rearrangement is formally analogous to the one at present under discussion and further reference will be made to it at a later stage.

Emphasis is laid on the fact that the negative results obtained in this work are not absolute; in general they merely show that the migration of the radical concerned is less facile than the destruction of the phenacyl radical, which as a rule proceeds slowly on boiling with concentrated alkali. Hughes and Ingold (22) record a case in which a more robustly constituted salt appears to exhibit migration of methyl.

$$CHPh_2.NMe_3OH \longrightarrow CMePh_2.NMe_2$$

Although not strictly within the scope of this study, two modifications of the "recipient" radical were investigated. In parallel with the modifications of the benzyl group which have been described the attempt was made to interpose a second methylene group between the benzoyl groups of the phenacyl radical and the ammonium nitrogen atom (VII), but interaction of ω-dimethylamino-propiophenone and benzylchloride yielded only dibenzyldimethylammonium chloride, possibly by the mechanism indicated:

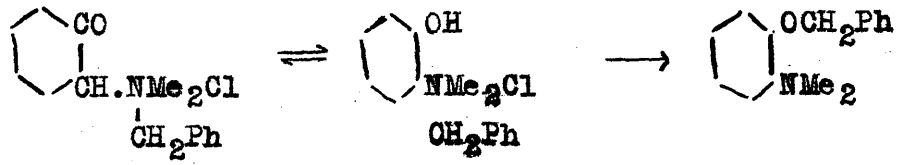
$$\underset{\text{(VII)}}{Ph.CO.CH_2.CH_2.\underset{\substack{|\\CH_2Ph}}{N}Me_2Cl} + Ph.CO.CH_2.CH_2.NMe_2 \longrightarrow$$

$$Ph.CO.CH{=}CH_2 + CH_2Ph.NMe_2 + Ph.CO.CH_2.CH_2.NMe_2,HCl$$

$$CH_2Ph.NMe_2 + CH_2PhCl \rightarrow (CH_2Ph)_2NMe_2Cl$$

o-Hydroxyphenylbenzyldimethylammonium chloride (VIII) is of peculiar interest from the analogy between is ketonic form (IX) and (I). When the salt was fused with sodamide, however, the benzyl group migrated, not to carbon, but, to oxygen, yielding (X). The mechanism which seems best able to explain this, is that under the conditions of the reaction an anhydride is formed which splits to give (X). (Compare the formation of dimethyl-<u>o</u>-anisidine from the anhydride of N-trimethyl-<u>o</u>-

aminophenol. Griess (15))



(IX) (VIII) (X)

Constitutions of the Rearrangement Products.

The products (II; R=$CH_2.CH=CH_2$) and (IV) were converted into the methosulphate and reduced with zinc and sulphuric acid. The former yielded ω-allylacetophenone, and the latter an oil which was hydrated by sulphuric acid to αγ-dibenzoylpropane $Ph.CO[CH_2]_3.CO.Ph$. Attempts to prepare (IV) from ω-piperidino-acetophenone, formaldehyde and phenylacetylene were unsuccessful. The methiodide of (X) was identical with a specimen prepared by successive reduction and methylation of o-nitrophenyl-/benzyl ether.

EXPERIMENTAL

Allyldimethylamine (23), was added to phenacyl bromide (1 mol.) in ether. Considerable heat was evolved, and an oil separated, from the aqueous solution of which sodium picrate and acetic acid precipitated phenacylallyldimethylammonium picrate, m.p. 78-79°, after recrystallisation from methyl alcohol. (Found: $C_6H_2O_7N_2$', 52.7. $C_{13}H_{18}ON.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$',52.8%). The picrate was treated with dilute sulphuric acid, the picric acid extracted with benzene, and sufficient sodium hydroxide added to give a final alkaline concentration of 10%. After 2 hours' refluxing, the basic material was isolated in dry ethereal solution in the usual way. Ethereal picric acid precipitated ω-dimethylamino-ω-allyacetophenone picrate as a slowly solidifying oil, which formed stout needles, m.p. 97-99°, after crystallisation once from methyl alcohol and twice from benzene (Found: C, 52.8; H, 4.7. $C_{13}H_{17}ON,C_6H_3O_7N_3$ requires 52.8: H,4.6%.). The methosulphate was prepared in ether as small plates which on steam distillation from zinc and sulphuric acid gave allylacetophenone, identified as semicarbazone, m.p.158-159°(Helferich and Lecher (24) give 156-157°) (Found: C, 66.5; H, 7.0. $C_{12}H_{13}ON_3$ requires C, 66.4; H, 6.9%).

Thomson and Stevens (25) obtained no propargyldimethylamine from acetylenylmagnesium bromide

and dimethylaminoacetonitrile. $\alpha\beta\gamma$-Tribromopropane, on distillation over solid potash, yielded β-bromoallyl bromide, but none of the propargyl bromide reported by Henry (26). β-Bromoallyldimethylamine was obtained by heating a mixture of β-bromoallyl bromide (1 mol.) with dimethylamine (2 mols.) in 70% alcohol at 60-70° for a week. The solution was acidified, steam distilled, basified, and again steam distilled, when a heavy oil came over which, after drying with potassium carbonate, boiled at 132-134°. Yield 80%. The picrate, stout yellow prisms, from methyl alcohol, melted at 94-95°. (Found: $C_6H_3O_7N_3$, 58.6. $C_5H_{10}NBr.C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 58.4%). The base was unaltered by heating with solid potash at 120° followed by distillation from alkali; or by refluxing for several hours with 25% aqueous alcoholic potash. Heating with alcoholic sodium ethoxide solution at 130-150° (sealed tube) led to total decomposition, the only basic material obtained being dimethylamine (identified as picrate).

ω-Bromostyrene (27) was converted to phenacylacetylene (28) and then to phenylpropargylpiperidene (yielded 60%) (19). Phenacylphenylpropargyldimethylammonium bromide separated from a benzene solution of its generators, on standing a few days, as a viscous oil which crystallised from alcohol-ether in cubes, m.p. 162°. (Found: Br, 20.3. $C_{22}H_{24}ONBr$ requires Br, 20.1%.).

The addition of excess of 8% sodium hydroxide or carbonate solution to an aqueous solution of the salt resulted in an immediate turbidity. The mixture was heated on the water bath for a few minutes and worked up for basic material in the usual way, experiments with caustic alkali yielding traces, and those with carbonate giving about 50% of a gummy solid which could not be crystallised. From its ethereal solution hydrogen chloride precipitated ω-dimethylamino-ω-phenylpropargylacetophenone hydrochloride, white needles from alcohol-ether m.p. 167-168°. (Found: HCl, 10.1. $C_{22}H_{23}ON$,HCl requires HCl, 10.2%). The hydrobromide similarly obtained, crystallised from alcohol-ether in needles which darkened from 130° and melted at 182-183° (with complete decomposition). (Found: C, 64.6; H, 6.2; Br,19.5.. $C_{22}H_{23}ON$,HBr.$\frac{1}{2}H_2O$ requires C, 64.6: H, 6.1, Br 19.7.). An ethereal solution of the free base and methylsulphate, kept for a week, deposited an oil which was reduced with zinc dust and sulphuric acid. The oil so formed was extracted with ether, dried over sodium sulphate, the ether evaporated, and the residue heated for a few minutes on the water bath with 77% sulphuric acid. Dilution of the acid yielded a solid which, after recrystallisation from light petroleum, melted at 66-67°, alone, or mixed with a specimen of αγ-dibenzoyl propane prepared by the method of Japp and Michie (29). Attempts to reduce the above hydrochloride with hydrogen and

platinum black in glacial acetic acid failed, no hydrogen being absorbed even after 6 hours' shaking. Attempts were also made to synthesise the rearrangement product by heating ω-piperidinoacetophenone, phenylacetylene, and paraformaldehyde in dioxan, or in boiling alcohol with and without a trace of pyridine. In all cases the piperidinoacetophenone was recovered unchanged. ω-Piperidinoacetophenone hydrobromide was prepared by adding piperidine (1 mol.) to phenacyl bromide (1 mol.) in three times its weight of alcohol (heat evolved) and warming for half an hour on the water bath. On cooling the required hydrobromide crystallised, and after one crystallisation from alcohol melted at 227-228°. (Yield 65%) Van Ark. (30) gives 220°. (Found: HBr, 28.4. Calc. for $C_{13}H_{17}ON$,HBr: HBr, 28.2%).

β-Nitropropane (31) was converted to β-bromo-β-nitropropane (32) and the latter heated with dimethylamine in dry xylene at temperatures ranging from 60-130° (sealed tube). In every case dimethylamine hydrobromide was formed, but no tertiary base. The bromide would not combine with phenacyldimethylamine nor with phenacylpiperidine on long standing in ether.

α-Dimethylaminoisobutyronitrile (33) was added to phenylmagnesium bromide (2 mols.) and after 12 hours the product was decomposed with ammonium chloride

and water and the crude basic material distilled in steam. The main product was non-volatile tar, and the distillate appeared to consist mainly of phenylisopropyldimethylamine isolated as picrate, yellow laminae from alcohol m.p. 205°. (Found: $C_6H_3O_7N_3$, 59.0. $C_{11}H_{17}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 58.4%). A benzene solution of the free base and phenacyl bromide kept for several months in a warm place, deposited only the hydrobromide of the tertiary base, identified as picrate.

Phenacyl-β-phenylethyldimethylammonium bromide (1) was heated to 150-160° (oil-bath) with two equivalents of powdered sodamide. The only basic product obtained was 40% of β-phenylethyldimethylamine as picrate (m.p. and mixed m.p.). No unchanged quaternary salt was recovered, and an odour like that of styrene was noted. Similar results were obtained when the salt was boiled for some hours with concentrated sodium hydroxide solution.

β-phenylpropionitrile (34) was reduced with sodium (20 atoms) and boiling alcohol. The mixture was acidified with concentrated hydrochloric acid, filtered from sodium chloride, the alcohol evaporated and the γ-phenylpropylamine extracted from the basified residue with ether. It was isolated in 30-40% yield, as the hydrochloride, m.p. 218° (compare Tafel.(35)), which on Eschweiler methylation in the usual manner gave γ-phenylpropyldimethylamine, isolated in good yield as the picrate

m.p. 99°, as found by Senfter and Tafel (36).

Phenacyl-γ-phenylpropyldimethylamine bromide was rapidly produced from the tertiary base and phenacyl bromide in benzene, and crystallised from alcohol-ether in nodules, m.p. 124-125°. (Found: Br, 21.8. $C_{19}H_{24}ONBr$ requires Br, 22.1%.). Boiled for 4 hours with excess of 25% sodium hydroxide solution, it gave 60-70% of phenylpropyldimethylamine as picrate (m.p. and mixed m.p.) and on one occasion a small quantity of a picrate, yellow prisms from ether, m.p. 103-104°, depressed below 90° by admixture with the foregoing. (Found: $C_6H_3O_7N_3$, 58.4%. The picrate of II, R=-$(CH_2)_3$Ph i.e. $C_{19}H_{23}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 45.3%). No unaltered material could be detected as the highly insoluble ferrocyanide. Each experiment gave traces of a neutral substance insoluble in water, acid, alkali, ether or benzene, which crystallised from much alcohol in colourless needles m.p. 210°, and was not further investigated. The violent interaction of the quaternary salt and sodamide at a 130-140° gave a small yield of phenacyldimethylamine; picrate, m.p. and mixed m.p. 140-143°; the methopicrate, m.p. and mixed m.p. 137-139° (prepared via the methiodide) crystallised from methyl or ethyl alcohol in stout deep yellow prisms or in pale yellow needles, which were interconvertible and had the same m.p. Steam distillation of the neutral products gave a small quantity of oil, which on bromination in carbon tetra-chloride, evaporation of the

solvent, and crystallisation from methyl alcohol, yielded fine needles, m.p. 63-65° not depressed by admixture with authentic propenylbenzene dibromide. This was prepared by distillation of phenylethylcarbinol over potassium bisulphate, followed by bromination (compare Hell and Bauer.(37).). Allylbenzene the normal product of Hofman degradation of the quaternary salt, is known to yield propenylbenzene on heating with alkali. One experiment gave, not phenacyldimethylamine picrate, but the picrate m.p. 103-104° already described. This substance is not identical with the β-hydroxy-β-phenylethyldimethylamine picrate described by Tiffeneau and Fourneau (38), nor with the picrate of either of the possible products of addition of dimethylamine to propenylbenzene. α-Phenyl-β-dimethylaminopropane (7) yielded a picrate, yellow prisms from methyl alcohol, m.p. 135-139°. The isomeric α-Phenyl-α-dimethylaminopropane was prepared from dimethylaminophenylacetonitrile (39) and ethylmagnesium bromide (2 mols): the mixture was decomposed with ice and ammonium chloride and the product distilled b.p. 100-105/22 mm. The picrate after several recrystallisations from methyl alcohol and from acetone-ligroin, formed stout yellow prisms, m.p. 161-164°. (Found: $C_6H_3O_7N_3$, 58.7. $C_{11}H_{17}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 58.4%.).

βββTriphenylpropionic acid (40) was converted via the benzoylhydroxamic acid to βββtriphenylethylamine, (41) which on Eschweiler methylation gave triphenylethyldimethylamine,

cubes from light petroleum, m.p. 110-112°. The hydrochloride prepared in ether, separated from absolute alcohol as a crystalline mass of cubes, m.p. 207-209° (Found: HCl, 10.7. $C_{22}H_{23}N$,HCl requires HCl, 10.8%). A benzene solution of the free base with phenacyl bromide (slight excess) deposited a few crystals of triphenylethyldimethylamine hydrobromide after two months, but gave no quaternary salt even on subsequent refluxing for several days.

Phenacylphenyldimethylammonium bromide slowly crystallised from a solution of phenacyl bromide and diethylaniline in a little acetone; it separated from alcohol-ether in irregular prisms, m.p. 150-152° (Found: Br, 22.7. $C_{18}H_{22}ONBr$ requires Br, 23.0%). Boiled with 10% potassium hydroxide solution, it yielded phenacylethylaniline (m.p. and mixed m.p.) together with alcohol (iodoform test) and a little diethylaniline. The salt was recovered unchanged after treatment with alcoholic sodium ethoxide solution for several weeks in the cold, and at 37° it yielded phenacylethylaniline in a few days.

Phenacyltrimethylammonium bromide (20) was heated for an hour with 25-30% sodium hydroxide solution in a slow current of steam, the volume of liquid being kept nearly constant, and the distillate collected in hydrochloric acid. The residue contained some benzoic acid (m.p. and mixed m.p.), but no basic material and no unchanged quatern-

ary salt could be identified as the highly insoluble ferrocyanide. The distillate contained a little acetophenone (identified as dinitrophenylhydrazone) and yielded 50-60% of pure trimethylamine picrate (m.p. and mixed m.p.), but no high boiling bases. The salt reacted explosively with sodamide at 170°, half of the material was recovered as ferrocyanide, and no high boiling basic material could be detected.

Hexahydrobenzyl bromide, prepared by refluxing the alcohol (42) with constant-boiling hydrobromic acid, distilled at 79-81°/30mm. The bromide (1 mol.) was heated with dimethylamine (2 mols.) in 70% alcohol on the water-bath for 24 hours. The ethereal solution of the basic material was dried over potassium carbonate, and about half the solvent distilled off through a column to remove dimethylamine. With ethereal picric acid the residue yielded 30% of hexahydrobenzyldimethylamine picrate, which on crystallisation from methyl alcohol showed dimorphism. There first separated yellow needles, and then, more slowly, stout, deep orange prisms; both melted at 136-137° and gave similar analyses, and the needles changed into the prismatic form when kept in a warm place in contact with a solvent for a few hours (Found: $C_6H_3O_7N_3$, 62.3:62.4. $C_9H_{19}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 62.0%). Phenacylhexahydrobenzyldimethylammonium bromide separated overnight in almost quantitative

yield from a benzene solution of its generators, and formed nodular aggregates of micro-crystals, m.p. 185-187°, from alcohol-ether (Found: Br, 23.7. $C_{17}H_{26}ONBr$ requires Br, 23.6%). The picrate crystallised from methyl alcohol in yellow prisms, m.p. 123-124° (Found: $C_6H_2O_7N_3'$, 46.5. $C_{17}H_{26}ON.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 46.8%). The bromide, refluxed for one hour with 10% alkali, was recovered unchanged as picrate; when boiled with 50% alkali, it slowly charred without dissolving, and from the residue no basic material or unchanged quaternary ammonium salt could be isolated. After heating the salt to 160° with sodamide, no basic material could be isolated even when precautions were taken to prevent loss of volatile products.

Tert.butyl bromide was treated with bases in the same way as β-bromo-β-nitropropane (above), and with similar results.

Hydroxyurethane (43) was converted into ONN-trimethylhydroxylamine (44) (45), which, on standing for several days with phenacyl bromide in ether gave fine white needles, m.p. 185-186°, Rumpel (loc.cit.) records m.p.184-186° for phenacyldimethylamine hydrobromide. (Found: HBr, 33.0 Calc. for $C_{10}H_{13}ONBr$: HBr, 33.2%).

Benzyldimethylamine oxide was obtained by shaking benzyldimethylamine (6 c.c.) with hydrogen peroxide (200 cc. of 3%) for 4 hours by which time the basic smell had completely gone. After standing overnight the solution was

concentrated in vacuo to 50cc. on the water-bath at 50-60°, with addition of a piece of platinum to assist decomposition of unchanged hydrogen peroxide. 8 Cc. of the residue yielded with aqueous picric acid benzyldimethylamine oxide picrate (1.8g.), which crystallised from methyl alcohol in needles, m.p. 153-154° (Found: $C_6H_3O_7N_3$, 60.2. $C_9H_{13}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 60.4%)% The remainder was steam-distilled with 100 cc. of 20% potassium hydroxide solution, but the distillate yielded nothing to ether or chloroform. When the residue was distilled from an oil-bath, the smell of dimethylamine was felt and benzyl alcohol came over, b.p. 200°, identified as p-nitrobenzoyl ester (m.p. and mixed m.p.). The final residue yielded benzoic acid (m.p. and mixed m.p.)

β-Dimethylaminopropionphenone (46) was added to benzyl chloride (1 mol.) in ether. An oil slowly separated which could not be crystallised, but yielded with picric acid dibenzyldimethylammonium picrate, m.p. and mixed m.p. 148-149°.

o-Hydroxydimethylaniline (47) was methylated according to Pinnow (48). The o-hydroxydimethylaniline left with benzyl chloride in benzene for several weeks yielded large crystals of o-hydroxyphenylbenzyldimethylammonium chloride, which, after recrystallisation from alcohol-ether, formed stout cubes, m.p.115-116° (Found: Cl, 13.3. $C_{15}H_{18}ONCl$ requires Cl, 13.5%). The salt, reacted violently with finely divided sodamide at 110°. The basic products, isolated in dry ether

in the usual manner, slowly combined with methyl iodide to give a mass of needles which, recrystallised twice from alcohol, melted at 157-158° after softening at 110°. The picrate, prepared in aqueous solution, formed orange-yellow prismatic needles from methyl alcohol, m.p. 155° (Found: N, 11.8. $C_{16}H_{20}ON.C_6H_2O_7N_3$ rquires N, 11.9%). These two compounds were identical (m.p. and mixed m.p.) with the corresponding o-benzyloxyphenyltrimethylammonium salts (below).

o-Nitrophenyl benzyl ether (compare Kumpf, (49) was prepared by boiling equimolecular quantities of o-nitrophenol, benzyl chloride, and sodium ethoxide in alcohol for 8 hours, by which time the red colour of sodium o-nitrophenoxide had disappeared. After removal of most of the alcohol, the neutral material was obtained in dry ethereal solution and distilled, when nitrophenyl benzyl ether boiled at 210°/12mm. This was reduced by West's method: the ether (11g.), methylated spirit (30 cc.) iron filings (9g.) and concentrated hydrochloric acid (1 cc.) were boiled on the water-bath for two hours. After filtration, the residue, and the concemtrated and basified filtrate, were separately extracted with ether. On addition of concentrated hydrochloric acid, the united extracts deposited white flakes of o-aminophenyl benzyl ether hydrochloride, m.p. after recrystallisation from alcohol-ether, 198-199° (Hochster, Farbwerke, D.R.-P. 141516, gives m.p. 198°). o-Benzyloxyphenyltrimethylammonium iodide was prepared by heating

the above hydrochloride with methyl iodide and sodium hydroxide solution on the water-bath for half-an-hour. On cooling large crystals separated, which after recrystallisation from alcohol melted at 158-159° (softening at 110°) (Found: I, 32.6; loss at 100°, 4.8. $C_{16}H_{20}ONI,H_2O$ requires I, 32.8: loss, 4.65%).

DEGRADATION OF QUATERNARY AMMONIUM SALTS.

PART III.

REARRANGEMENTS IN ANALOGOUS COMPOUNDS CONTAINING A COORDINATED LINKAGE.

On the theory previously suggested for the mechanism of the rearrangement (I)→(II), viz., that the alkali first converts (I) almost quantitatively into the neutral ion $Ph.CO.\bar{C}H.\overset{+}{N}(CH_2Ph)Me_2$, after which the benzyl group is

$$Ph.CO.CH_2.N(CH_2Ph)Me_2Br \longrightarrow Ph.CO.CH(CH_2Ph)NMe_2$$

(I). (II).

detached as an anion and subsequently reattached at the phenacylidene carbon atom, the reaction should be a general one and capable of extension to systems which do not contain quaternary nitrogen.

In support of this Thomson and Stevens (5) showed that the related compound phenacylbenzylmethylsulphonium bromide (III) readily yielded (IV) on treatment with alkali.

$$Ph.CO.CH_2S(CH_2Ph)MeBr \xrightarrow{\text{alkali}} Ph.CO.CH(CH_2Ph)S.Me$$

(III). (IV).

The generality of the reaction has now been further extended by obtaining evidence of rearrangement in compounds containing a coordinated linkage. Examples of such are found in the sulphilimines of which (V) may be taken as typical.

$$CH_3Ph.SO_2\bar{N}.\overset{+}{S}(CH_2Ph)Me$$

(V).

A comparison of the structure of this compound with that of the neutral ion $Ph.CO.\bar{C}H.\overset{+}{N}(CH_2Ph)\ Me_2$ postulated as the first effect of alkali on (I), shows them to be closely analogous and therefore under suitable conditions (V) might be expected to exhibit a similar tendency to rearrange, without however requiring the presence of alkali.

When (V) was boiled for 12 hours in p-cymene the only product isolated was p-toluenesulphonamide, but from its analogue (VI) in which a phenyl radical replaces the methyl of (V), under the same conditions, was obtained p-toluensulphonbenzamide, indicating that migration had taken place followed by decomposition of the rearrangement product, presumably (VII).

$$CH_3PhSO_2\bar{N}.\overset{+}{S}(CH_2Ph)Ph \longrightarrow CH_3PhSO_2N(CH_2Ph).SPh$$

(VI). (VII).

The earlier observation that the benzhydryl and fluorenyl radicals migrate with extraordinary rapidity, led to attempts being made to prepare the compounds in which one or other of these radicals replace the benzyl of (VI) in the hope that under the milder conditions there necessary for migration, the direct rearrangement products might be isolated as such. Fluorenyl-phenyl-sulphide however could not be prepared from thiophenol and 9, bromofluorene under a variety of conditions, while benzhydrylphenylsulphide would not combine with Chloramine-T even on long refluxing in alcohol.

Two interesting cases of rearrangement in similar compounds have previously been recorded. Meisenheimer

and Collaborators (21) (50) showed that allylphenylmethylamine oxide or its benzylphenylmethyl analogue on steam distillation from a strongly alkaline solution gave the corresponding substituted hydroxylamines in which the allyl or benzyl radicals were found attached to oxygen (VIII)→(IX). The presence

$$\underset{\text{(VIII).}}{Ph(CH_2Ph)(Me).\overset{+}{N}.\bar{O}} \longrightarrow \underset{\text{(IX).}}{Ph(Me)N.OCH_2Ph}$$

of the phenyl radical on the nitrogen is essential, for dimethylallylamine oxide or dimethylbenzylamine oxide (see part II.) under these conditions gave no sign of rearrangement, a result very similar to that observed in the case of the sulphilimines (above).

Fromm and Achert (51) and later Smythe (52) observed that by the distillation of dibenzyl sulphoxide there is obtained benzaldehyde and benzyl disulphide, suggesting that migration of the benzyl radical from sulphur to oxygen had taken place, followed by complete decomposition of the product. Thomson and Stevens (5) however were unable to find any trace of rearrangement in the closely analogous phenacylbenzylsulphone even on heating to 190° with benzyldimethylamine.

A case of the apparent reversal of a similar reaction is recorded by Neogi and Chowdhuri (53) who found that on heating aliphatic nitrites to 120°, there is produced small quantities of the isomeric nitrocompounds.

Unfortunately the case of benzylnitrite was not investigated.

The failure to isolate the direct rearrangement products of the sulphilimines or sulphoxides prevents undue stress being laid on these results, but they seem to indicate that the mechanism suggested for the original migration is the correct one.

EXPERIMENTAL.

Benzylmethylsulphine-p-toluenesulphonylimine was prepared by the general method of Mann and Pope (54). 3.2gms. benzylmethylsulphide in 20 cc. acetone were added to 8gms. Chloramine T in 45 cc. water. Considerable heat was evolved and crystals separated. After shaking for one hour the acetone was removed on the water bath, the crystal mass filtered and recrystallised from alcohol when it separated in stout cubes m.p. 161-162°. yield 6 gms. (Found: N, 4.7. $C_{15}H_{17}O_2NS_2$ requires N, 4.6%). On heating this compound to 165-170° for 4 hours, slight decomposition took place but the major portion was recovered unchanged, while a higher temperature (200°) led to complete decomposition. By heating to 170-175° while passing a stream of dry ammonia gas was obtained p-toluenesulphonamide, which was also isolated together with tetraphenylethane by boiling in diphenylmethane.

Benzylphenylsulphide (55) would not combine with Chloromine T in an acetone-water mixture on heating and shaking but on boiling in alcohol, combination readily took place. 10gms. sulphide and 15gms. Chloramine T were refluxed in alcohol for 2 hours during which time sodium chloride separated. After concentration the residue was poured into water and the solid filtered off and crystallised from alcohol from which it came out in stout cubes m.p. 145-146°

Yield 12gms. (Found: S, 17.1. $C_{20}H_{19}S_2O_2N$ requires S,17.3%) This on boiling with caustic soda solution for 3 hours gave p-toluenesulphonamide. To effect rearrangement it was boiled for 24 hours in p-cymene, the cymene steam distilled off, and the residue extracted with dilute caustic soda solution. On acidification there was obtained p-toluene-sulphonbenzylamide (m.p. and mixed m.p.) No trace of the intermediate product could be found.

Attempts to prepare fluorenylphenylsulphide.

9,Bromofluorene (one mol.) (56) in hot alcohol was added to thiophenol (one mol.) dissolved in alcohol containing one equivalent of sodium ethylate. The mixture was left overnight, then heated on the water bath for two hours, after which the alcohol was removed and the residue poured into water. An oil separated which was taken up in ether, the solution dried and left to evaporate when there separated a few crystals fluorenylphenylsulphide but the major portion of the residue was an oil which could not be crystallised and was probably fluorenyl ethyl ether.

To the theoretical quantity of alomised sodium in toluene was added thiophenol and the whole boiled for 2 hours, by which time a white solid had separated. The bromofluorene was then added and the mixture refluxed for 4 hours. Only unchanged material was recovered.

Similarly 9 bromofluorene and thiophenol heated at 110-120° did not combine.

Attempts to prepare a sulphilimine from benzhydrylphenylsulphide.

4.5gms. Benzhydrylphenylsulphide (57) with 6gms. Chloramine T were dissolved in boiling alcohol and refluxed for four hours. The alcohol was then concentrated somewhat and on cooling crystals of the original sulphide separated (m.p. and mixed m.p.) A similar result was obtained when the same quantities of these substances were refluxed for 6 hours in methyl alcoholic solution.

DEGRADATION OF QUATERNARY AMMONIUM SALTS .

PART IV.

A NEW REARRANGEMENT OF SULPHONHYDRAZIDES.

It was early realised by Stevens (2) that the presence of quaternary nitrogen is not essential for the rearrangement (I)→(II) and he has since shown (Private Communication) that under drastic alkaline conditions the tertiary base phenacylbenzylaniline undergoes a similar transformation (III)→(IV).

$$Ph.CO.CH_2NMe_2Br \xrightarrow{\text{alkali}} Ph.CO.CH(CH_2Ph).NMe$$

(I). (II).

$$Ph.CO.CH_2N(CH_2Ph).Ph \xrightarrow{\text{alkali}} Ph.CO.CH(CH_2Ph).NHPh$$

(III). (IV).

The well recognised acidity of the nitrogen atom of benzenesulphonamides suggested that the compound p-toluenesulphon-uns-benzylphenylhydrazide (V) in which the group $CH_3Ph.SO_2NH$ replaces the phenacyl group of (I) might exhibit similar properties. On boiling this substance for a few minutes in 7% aqueous alcoholic potash it was converted quantitatively to p-toluenesulphinic acid and benzaldehyde phenylhydrazone suggesting that the expected migration had taken place followed by the

elimination of the elements of the sulphinic acid and subsequent rearrangement of the benzeneazotoluene so formed, to the isomeric hydrazone (V)→(VI)→(VII)→(VIII).

$$CH_3PhSO_2NH.NPh(CH_2Ph) \xrightarrow{alkali} CH_3PhSO_2N(CH_2Ph).NHPh \xrightarrow{alkali}$$

(V). (VI).

$$CH_3PhSO_2H + PhCH_2N{=}NPh \longrightarrow PhCH{=}N.NHPh$$

(VII). (VIII).

This being so, the results recorded in Part I. would indicate that with decrease in acidity of the unsubstituted nitrogen atom, should come an increase in the facility of migration. The corresponding benzoylhydrazide, in which the degradation was expected to stop at the stage analogous to (VI) above, however, showed no tendency to exhibit a similar wandering of the benzyl group, either under the mild conditions used for the change (V→VIII) or on heating to 200° with sodium methoxide.

These results suggested that the <u>first</u> action of alkali on (V) is the elimination of the elements of *p*-toluenesulphinic acid followed by rearrangement of the unstable nitrogen compound so formed, a mechanism reminiscent of the Stieglitz and Jones theories of the Hofman degradation of amides and of the Lossen rearrangement of hydroxamic acids (58)(59) respectively viz.,

$$R.CONH_2 \xrightarrow{NaOBr} R.CONHBr \rightarrow [R.CON\lt] + HBr \rightarrow R.NH_2$$

$$R.CONHOAc \xrightarrow{alkali} [R.CON\lt] \rightarrow R.NH_2$$

or even more so of the formation of "nitroxyl" from benzenesulphonhydroxamic acid. (60)(61).

$$PhSO_2NHOH \xrightarrow{alkali} PhSO_2H + "NOH".$$

If this is the case then the benzyl radical is not essential, and a similar degradation might be expected in all unsymmetrical sulphonhydrazides. Benzenesulphon-uns-diphenylhydrazide, however, did not yield the expected azobenzene even on boiling with 30% potash, nor on alkaline fusion, being totally unaffected by the former and hydrolysed to diphenylamine by the latter. The corresponding phenylmethyl and phenylethyl compounds on treatment with 10% alkali gave black oils from which no crystalline material could be isolated, nor could methylamine or ethylamine be detected in the reduction products of these oils.

The phenylhydrazones of the simpler aliphatic aldehydes being in general unstable, ill-defined compounds, an attempt was made to test the validity of the above hypothesis by treating benzenesulphonbenzamide (IX) and benzenesulphonphenylacetamide (X)

$Ph.CO.NHSO_2Ph$ (IX). $Ph.CH_2CONHSO_2Ph$ (X).

with alkali in the hope that from these compounds aniline and benzylamine respectively might be isolated. In neither of these cases were these expectations realised, for aqueous alcoholic potash in concentrations up to 30% had little or

no effect upon them while fusion at 200° led to complete hydrolysis with formation of benzoic and phenylacetic acids.

Jones and his Collaborators (58)(59) have shown that the ease of rearrangement in the Lossen reaction is roughly proportional to "the tendency of the radical in the univalent nitrogen derivative to exist as a free radical" and assuming that this new reaction is analogous to the Lossen in this respect, it was hoped that a study of p.toluenesulphondiphenyleneacetamide (XI)

$$CH_3PhSO_2NCOCH\begin{matrix}C_6H_4\\|\\C_6H_4\end{matrix} \qquad (XI)$$

in which, according to the above, there should be a very great tendency to rearrange, would prove conclusively whether this reaction could take place or not. Unfortunately this compound could not be prepared owing to the instability of diphenyleneacetylchloride.

In the hope that alkaline hypobromite would bring about the conversion of uns, benzylphenylhydrazine to benzaldehyde phenylhydrazone and thus establish the relationship between this reaction and the Hofmann degradation of amides, this experiment was tried, but the only crystalline material obtained was 1,4 dibenzyl, 1,4 diphenyltetrazone i.e. the oxidation product of the hydrazine.

While the mechanism suggested, viz., that the alkali first splits off the elements of p.toluenesulphinic acid and the unstable nitrogen derivative so formed rearranges to give benzaldehyde phenylhydrazone is

attractive, the paucity of the positive results obtained and the lack of confirmation from the non-production of benzylamine from the treatment of benzenesulphonphenylacetamide with alkali, prevents great stress being laid upon it. The instability of benzoylbenzyl hydrazide to rearrange in manner analogous to its sulphonyl analogue indicates that the mechanism is not that of the original (I)→(II), and much more experimental data is required before any explanation can be given which will adequately cover the results obtained.

EXPERIMENTAL

Benzylphenylhydrazine was prepared by heating benzyl chloride with phenylhydrazine at 120° (62).

p-Toluenesulphon-uns-benzylphenylhydrazide was prepared by dissolving in the minimum quantity of benzene, benzylphenylhydrazine (2 mols.) and p-toluenesulphonyl chloride (1 mol.) and heating on the water bath for 36 hours. The precipitated material was filtered off, well washed with hot water, dissolved in very dilute alkali and after precipitation with dil. HCl crystallised from alcohol from which it separated in cubes m.p. 142-143° (Found : S, 9.3. $C_{10}H_{20}SO_2N_2$ requires S, 9.1%.).

Rearrangement of this compound.

The above hydrazide (1gm.) was taken up in 10 cc. of 10% caustic soda and 5 cc. alcohol, and boiled. After a few minutes a turbidity appeared and solid material separated, which after recrystallisation from ethyl alcohol melted at 158° , and did not depress the m.p. of a specimen of benzaldehyde phenylhydrazone prepared in the usual way. The alkaline filtrate made just acid to litmus and into it passed chlorine gas in the cold. The turbid solution was then extracted with benzene, the extract dried and partially evaporated when p-toluenesulphonyl chloride separated (m.p. and mixed m.p.).

The original hydrazine boiled up for some

with 10% alkali
hours/was recovered unchanged as picrate. Uns-phenylbenzylhydrazine picrate crystallised from benzene in long needles m.p. 143-145°. (Found: $C_6H_3O_7N_3$, 52.8. $C_{13}H_{14}N_2 \cdot C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 52.4%.).

Benzoyl-uns-benzylphenylhydrazide prepared by the method of Minunni (62) was heated with 25% aqueous alcoholic potash for several hours, but was recovered unchanged. Heating with sodium methoxide at 200° for half-an-hour had likewise no effect upon it.

Diphenylhydrazine (2 mols.) (prepared by the method of Fischer (63)) was heated with p-toluenesulphonyl chloride (1 mol.) in a little benzene for 8 hours on the water bath. During this time crystals of the hydrazine hydrochloride separated, after removal of which, the benzene was extracted with dil. HCl, dried over sodium sulphate and evaporated. On addition of petroleum ether to the residue a solid mass was obtained which was well extracted with dilute caustic soda. Acidification of this extract gave p-toluenesulphon-uns-benzylphenylhydrazide which crystallised from alcohol in stout cubes m.p. 139-141°. (Found: N, 8.4. $C_{19}H_{18}O_2SN_2$ requires N, 8.3%.).

This compound was boiled with various concentrations of alkali up to 25%, but in each case was recovered unchanged. Fusion with potash at 250° for one hour gave diphenylamine.

Benzenesulphonbenzamide from benzoyl chloride and benzenesulphonamide at 140-150° (64) was treated as in the previous instance with various concentrations of aqueous alcoholic potash, but in each case on acidification unchanged material was recovered. Kept at 220° for one hour with solid potash it yielded benzoic acid but no trace of aniline.

Benzenesulphonphenylacetamide was prepared by heating for an hour in an oil bath maintained at 140-150° equimolecular quantities of benzenesulphonamide and phenylacetyl chloride. After cooling, the mass was extracted with sodium carbonate, from which extract on acidification the above compound separated. It crystallised from alcohol in small hard cubes m.p. 75-76°. (Found: S, 11.7. $C_{14}H_{13}O_3NS$ requires S, 11.6%.). Boiling with various concentrations of alkali up to 30%, invariably gave unchanged material on acidification, while fusion with potash at 210° gave phenylacetic acid but no trace of basic material.

Diphenyleneacetyl chloride (65) on fusion with benzenesulphonamide at temperatures ranging from 100-250° invariably gave only diphenyleneacetic acid as the only sodium carbonate-soluble product of the reaction.

Benzenesulphonyl-uns-phenylmethylhydrazide (66), and Benzenesulphonyl-uns-phenylethylhydrazide (66) when boiled with 10% alkali gradually decomposed with

formation of dark coloured oils. From these oils on reduction with sodium and alcohol, no basic products could be obtained.

Action of hypobromite on benzylphenylhydrazine.

A solution of hypobromite was made in the usual way from 6gms. KOH in 60 cc. water and 1.3 cc. bromine. To this was added with cooling 5gms. benzylphenylhydrazine. After standing at room temperature for one hour the mixture was heated for one hour longer on the water bath. A quantity of tarry material separated which was purified by successive washings with a little hot alcohol, when a small quantity of light brown material was left which after crystallisation from benzene-ligroin melted at 143° and did not depress the m.p. of a specimem of 1,4,diphenyl-1,4,dibenzyl tetrazone prepared by oxidation of the hydrazine with yellow mecuric oxide (62). This experiment was repeated using 4 mols. of hypobromite instead of one in the hope that there might be isolated the tribromo-~~phenyl~~ benzaldehydephenylhydrazone obtained by Cuisa and Vecchiotti (67) from treatment of benzaldehydephenyl-hydrazone with bromine or hypobromite. As before the only crystalline product was the tetrazone.

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SECTION II.

AN ATTEMPT TO DEFINE THE POSITION OF THE HYDROXYL GROUP AND THE UNSATURATED CENTRES OF ERGOSTEROL.

THE ERGOSTADIENETRIOLS.

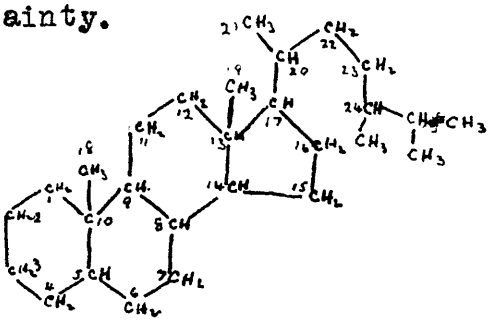
THE POSITION OF THE HYDROXYL GROUP AND OF THE UNSATURATED CENTRES IN ERGOSTEROL.

INTRODUCTION.

The yeast sterol, ergosterol has been shown during the last two years to have the molecular formula $C_{28}H_{44}O$ (1) (2) and not $C_{27}H_{42}O$ as previously suggested. (3).

Investigations extending over a long period of years and embracing cholesterol, ergosterol and the bile acids, the nuclear structure of all of which are closely related, have shown that this represents a tetracydic compound with a side chain, containing one hydroxyl group and three double bonds.

From ergosterol there can be obtained a fully saturated hydrocarbon ergostane, $C_{28}H_{50}$, in which the ring system of the original sterol is intact, and to this the structure I. can be assigned with almost complete certainty.



To convert this formula into that of ergosterol one hydroxyl group and three double bonds must

be introduced.

THE HYDROXYL GROUP. That the oxygen is present as a secondary alcohol grouping is proved by its conversion not only in ergosterol, but in its di-tetra- and hexahydro derivatives, to a ketonic group. Its position has for long been assumed to be on carbon atom 3 as in cholesterol, the only evidence for this, apart from possible biogenetic assumptions, being that ergostanol on oxidation yields a dicarboxylic acid, $C_{28}H_{48}O_4$, from which a pyroketone, $C_{27}H_{40}O$, can very easily be obtained. (5). Recent work, however, by Heilbron, Samant, and Simpson (6) on the acids obtained by oxidation of chlorergostane and chlorcholestane has thrown considerable doubt on this point, and at the moment there appears to be no definite evidence as to its position.

THE DOUBLE BONDS. Ergosterol reacts with three molecules of perbenzoic acid (4), indicating the presence of three double bonds. These vary enormously in reactivity. Hydrogenation with sodium and alcohol (8) gives dihydroergosterol, which can be further hydrogenated catalytically (palladium black in alcohol) to the singly unsaturated α-Ergostenol. Attempts to reduce this further, fail, but on treatment with hydrogen chloride in chloroform this compound yields the isomeric β-ergostenol, which can then be hydrogenated, using platinum oxide in glacial acetic acid, to the fully saturated ergostanol.

Ozonisation of ergosterol and of dihydroergosterol yields methylisopropylacetaldehyde (7) which is not obtained from α or β ergostenol under similar conditions, proving a), that one double bond of ergosterol is in the side chain between carbon atoms 22 and 23, and b), that this double bond is not reduced by sodium and alcohol. The extraordinary lability of the double bond which is saturated in the formation of dihydroergosterol suggests that it is part of a conjugated system, a hypothesis which is borne out by molecular refraction and dispersion measurements (9), and by the formation of a maleic anhydride condensation product of ergosterol (10). The product is somewhat abnormal, however, in that for its formation, the components have to be heated together to 135^{o} instead of the more usual 80^{o}, and that on high vacuum distillation it breaks down to ergosterol and maleic anhydride.

From its lack of reactivity and resistance to hydrogenation, it would appear that the third double bond in ergosterol is situated between two quaternary carbon atoms, and that hydrogen chloride displaces it to a more reactive position.

THE ERGOSTADIENETRIOLS.

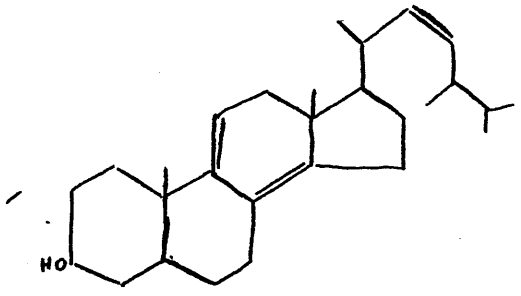
Two Ergostadienetriols are known. The first Ergostadienetriol I. is obtained by reduction of

ergosterol peroxide (prepared by photo-oxydation of an alcoholic solution of ergosterol in presence of eosin) with zinc and alcoholic potash.(11). This compound is characterised by the remarkable facility with which it loses the elements of water; thus, heating with acetic anhydride in pyridine gives not the expected acetate but a mixture of partially dehydrated products (12), and a similar result is obtained simply by dissolving the triol in acetic acid. Hydrogenation with sodium and alcohol gives an ergostenediol, while high vacuum distillation converts it completely to the tetraunsaturated compound dehydroergosterol (12).

The second triol, Ergostadienetriol II. is obtained by hydrolysis of its monobenzoate, which is produced when ergosterol is treated with one molecule of perbenzoic acid (4). This with the methoxyergostadienediol, obtained in a like manner from ergosterol methyl ether, has been very carefully studied by Heilbron, Morrison and Simpson (13) who find a) that ozonisation yields methylisopropyl-acetaldehyde, this proving that the side chain bond is intact and b) that oxidation with lead tetra-acetate (14) produces compounds presumably keto aldehydes, in which no degradation from a C_{28} molecule has taken place, thus indicating that direct 1,2 addition has taken place at a nuclear double bond. Furthermore, they have shown that complete hydrogenation to an ergostanetriol is not possible without first isomerising

with hydrogen chloride in chloroform, which leads them to conclude that triol formation has taken place at the "reactive" nuclear double bond.

From these results and from the fact that the triol gives only di-esters and its methyl ether only mono-esters, they consider that one introduced hydroxyl group is secondary and the other tertiary, and suggest the following structure for ergosterol.(II).



II.

Further work in the Liverpool laboratories (Private Communication) has shown that this triol is as stable to dehydrating influences as the other is labile, even phosphorus pertoxide in boiling toluene having no effect upon it. In view of this wide difference in reactivity, it was thought that the structure of Ergostadienetriol I. must differ considerably from that of its isomer, and we had turned our attention to it when a paper by Achtermann (15) appeared in which he showed that triol I. could be converted to triol II. simply by boiling with maleic anhydride in benzene for 8 hours, and furthermore that distillation of ergostadienetriol I.

monobenzoate in high vacuum gave dehydroergosterol, although the free triol distilled unchanged. On this evidence he suggested that these triols are cis-trans isomers. We have now repeated and fully confirmed this work, and have adduced further evidence in support of his suggestion as to the stereoisomeric nature of these compounds.

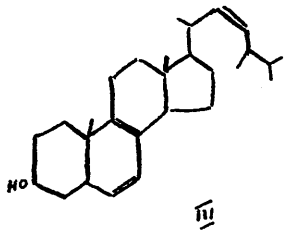
Previous to the appearance of Achtermann's paper we had sought to prove this possibility by treating Ergostadienetriol I. with lead tetra-acetate, in which case had these triols been stereoisomers, the same compound as obtained from the triol II. should have been obtained. An entirely different compound was, however, isolated but analysis figures showed that these compounds were not comparable, further degradation having presumably taken place in the case of triol I.

Heilbron, Morrison and Simpson, (13) obtained by oxidation of triol II. with chromic anhydride in acetic acid an ergostadienedionol, m.p. 249°, oxime m.p. 232°. By oxidation of triol I. under similar conditions there has now been obtained the same compound, proving definitely that these triols are stereoisomeric, and if the possibility of epimerisation of one hydroxyl group during oxidation is not considered, that the introduced secondary hydroxyl group is the seat of the stereoisomerism.

This diketone, on treatment with alcoholic potash, dissolves with an intense red colour, and is not precipitated from the alkaline solution by addition of water. On addition of acid, the deep red colour is discharged and a yellow solid is obtained, from which after repeated crystallisation from methyl alcohol a well defined yellow crystalline compound m.p. 146° can be isolated, which gives analytical figures consistent with only two atoms of oxygen for a molecular weight of about 400. This new compound is not now soluble in alkali. The exceedingly small yields (about 5%) obtained of this compound prevented its further investigation, but the fact that the corresponding methoxy-ergostadieneonol is recovered unchanged after similar alkaline treatment indicates that the ketonic group produced by oxidation of the original hydroxyl of ergosterol has taken part in this change, which is probably some form of benzilic acid rearrangement, followed by loss of carbon dioxide, and seems to suggest that the reactive double bond in ergosterol is situated very near to the hydroxyl group.

As previously explained, the oxidation of ergostadienetriol II. or its methyl ether with lead tetra-acetate yields compounds presumably keto aldehydes. The oxidation of one or other of these compounds to an acid under conditions known to be specific for the conversion of aldehydes to acids would throw considerable light on the structure of

ergosterol and such an acid would moreover form a convenient starting point for a further series of degradations. It has recently been suggested by Inhoffen (16) that formula III. represents the structure of ergosterol and the lead tetra-



III

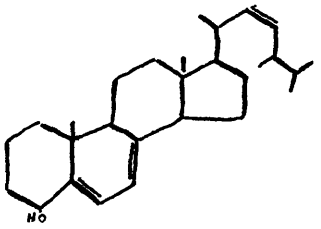
acetate oxidation product of triol II. should then be a dialdehyde and on further oxidation should yield a dibasic acid, instead of the keto acid expected on the formulation of Heilbron, Morrison and Simpson (13).

Previous attempts to oxidise the hydroxy keto aldehyde in the Liverpool laboratories (Private Communication) had failed. Small quantities of acidic products were obtained from comparitively large quantities of starting material, but under the normal conditions of working up these rapidly changed to a neutral form, suggesting the formation of a lactone. To obviate this difficulty the methoxyketoaldehyde was employed, and to decrease as far as possible the lability of the molecule to oxidising influences, it was proposed to hydrogenate the side chain double bond. Methoxyergostenediol was readily prepared but on treatment with lead tetra-acetate yielded only an oil from which no crystalline material could be isolated.

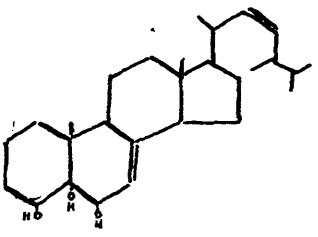
Attention was then turned to the more labile doubly unsaturated compound, methoxyergostadienediol, which on treatment with lead tetra-acetate yields a compound m.p.

105-106° (13). On repeating this work under conditions somewhat different to those employed by the earlier workers, there was obtained a compound m.p. 130-131°, identical with that obtained by them but in a much purer form. Attempts to oxidise with ammoniacal silver oxide under a variety of conditions uniformly failed, the only products obtained being dark oils. Potassium permanganate in acetone yielded oily neutral products, presumably by glycol formation at one or other of the double bonds, while chromic anhydride at 35° gave back unchanged material. At a higher temperature (70°) this reagent gave only oily acidic products and accordingly this investigation was discontinued.

Attention is drawn to one point in connection with these triols. Recently Rosenheim and King (17) have suggested formula IV. as being in best agreement with the known reactions of ergosterol and V. as that of ergostadiene-triol, in which case VI. is presumably that of the monobenzoate formed when ergosterol is treated with perbenzoic acid.



IV



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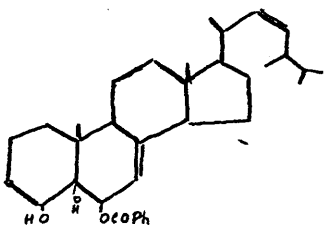
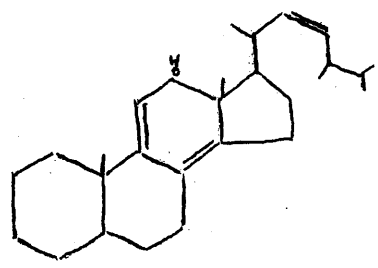


VI

If this is the case then VI. should undergo ring fission when treated with lead tetra-acetate under the normal conditions. Heilbron, Morrison and Simpson (13) have previously reported that this compound is unchanged under these conditions, and this work has now been repeated and fully confirmed, leading to the conclusion that VI. does not represent the formula of the monobenzoate, and hence that IV. cannot be that of ergosterol. These authors consider that the reactive double bond must be in the position to the hydroxyl group and if this is the case in order to agree with this observation of Heilbron, Morrison and Simpson (13), some formula must be found such that the introduced secondary hydroxyl group lies between the introduced tertiary and the original hydroxyl. Such a condition is satisfied by the formula (II) if the hydroxyl group is placed in position 12, (VII), but the ease of formation of a pyroketone from Reindel's dibasic acid (5) is against this location of the hydroxyl group.



VII

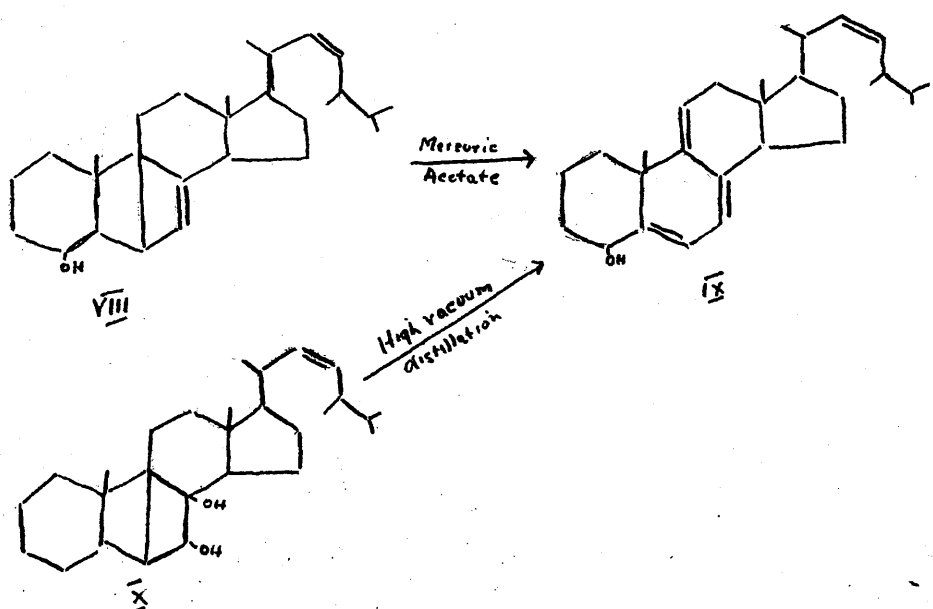
At the moment from the mass of often

conflicting experimental data it seems impossible to suggest a formula which will adequately account for all the known reactions of ergosterol. The two most recent formulations, those of Inhoffen (16) and of Rosenheim and King (17) both explain a few of its reactions, but fail when applied to others. Especially is this so when the oxidation of ergosterol with mercuric acetate to dehydroergosterol (11) is considered. This compound is also produced when ergostadienetriol I. or ergostadienetriol II. monobenzoate is distilled in high vacuum, and suggests that is formed by hydroxylation at a double bond followed by removal of two molecules of water. It is difficult to explain this if the double bond involved is one of a normal conjugated system, and suggests that ergosterol contains a bridge link, which is opened on treatment with mercuric acetate (compare the formation of sobrerol from α-pinene.) Further support is given to this suggestion from the recent reconsideration of Professor Sugden of his measurement of the parachor of ergostenol, which he now finds to be more in accordance with a bridged ring than an ethylenic double bond. (Private Communication). It is difficult to reconcile this, however, with the observation of Morrison and Simpson (20) that the α- and β-ergostenyl oxides, prepared by the action of perbenzoic acid on the corresponding ergostenols, both give α-ergostenol on hydrogenation, thus requiring the re-formation of a bridge

link during reduction.

The formation of a maleic anhydride addition compound is also against this idea, unless it is supposed that under the abnormal conditions required for the condensation (135°), isomerisation of the bridge link to an ethylenic double bond takes place.

In order to account for the formation of neoergosterol (21) and toluenetetracarboxylic acid (7) the bridge link and the double bond must be in the same ring and formula (VIII) seems to fit these conditions best. Dehydroergosterol would then be (IX)



while to explain the formation of this compound from the ergostadienetriols (X) a complete rearrangement of the

double bonds to postulated, which would appear to be quite feasible considering that distillation generally takes place about 200°.

On this formulation α-ergostenol contains the bridge link while β-ergostenol has an ethylenic double between carbon atoms 8 and 9.

In the absence of other evidence C_4 is suggested as the location of the hydroxyl group.

While it is emphasised that this structure is not in complete agreement with all the known reactions of ergosterol, yet it is suggested as giving a fairly reasonable explanation of some of the changes which could not be accounted for on the earlier formulations.

EXPERIMENTAL.

Preparation of Ergosterol Peroxide. For the preparation of this compound in large quantities the apparatus of Windaus and Brunken (18) was considerably modified. 30gms. of ergosterol and 50mgms. eosin were dissolved at 60°C. in 8 litres of 95% alcohol in a tank fitted with cooling coils and into which projected three electric lamps giving a total energy output of 400 watts. A stream of oxygen was passed through and the cooling current adjusted so that the temperature remained about 45°. At the end of 6 hours a test portion no longer gave an insoluble digitonide. The alcohol was removed under reduced pressure, and the residue crystallised from acetone (charcoal) when 22-25g. of a product m.p. 170-172° was obtained, which was pure enough for reduction.

The reduction was carried out practically as described by Windaus and Linsert (11), except that for each 10g. peroxide 750c.c 10% alcoholic potash and 100g. zinc dust were used. The whole was refluxed for 1-1½ hours and diluted with water as previously described, when the triol crystallised out. For recrystallisation a mixture of ethyl acetate and alcohol (3:1) was found to be more suitable than ethyl acetate itself in which the triol is very sparingly soluble. Yield 60%.

Action of Lead Tetra-acetate on Ergostadiene-

triol I. A suspension of the triol (2-5 g.) in benzene (200 c.c.) was shaken with lead tetracetate (5 g. nearly 2 mols.) at room temperature. At the end of 24 hours practically all the triol had dissolved and the solution had darkened considerably. Shaking was continued for a further 24 hours, at the end of which time no further change appeared to have taken place. The turbid brown mixture was then diluted with ether, sodium carbonate (aqueous) added and the whole shaken well together. The clear ether-benzene solution was then dried with Na_2SO_4 and evaporated. A yellow viscous gum was left which was taken up in methyl alcohol and left for several weeks at -10°. It slowly crystallised and the crystals were filtered off, recrystallised twice from methyl alcohol, from which they separated in large soft glistening plates, m.p. 183-184°. (Found; C, 73.8; 73.8; H, 10.0, 9.9%)

Oxidation of Triol I. 2 g. ergostadiene-triol I. in 150 c.c. acetic acid were stirred mechanically at room temperature while a solution of 1.6 g. chromic acid in 40 c.c. acetic acid and 3 c.c. water, was slowly added over a period of 5 hours. At the end of that period, the whole was poured into water, extracted with ether, the acetic acid washed out from the ether with water and Na_2CO_3 aq. and after drying the ether evaporated. The residue was taken up in ethyl acetate, from which it crystallised in plates m.p. 240-242°. One recrystallisation from ethyl

acetate-alcohol (1:1) brought the m.p. to 248-249° at which it remained constant. (Found: C, 79.0; H, 9.6. $C_{28}H_{40}O_3$ requires C, 78.6: H, 9.8%). This compound gave an oxime m.p. 233° after softening at 225°.

The melting points are the same as those recorded by Heilbron, Morrison and Simpson (13) for their ergostadiendioneol and oxime, and with these they gave respectively no depression. Yield 10%.

2 g. of ergostadienetriol I. were oxidised as above but after addition of CrO_3 left standing overnight. The ether on evaporation yielded a residue which after recrystallisation twice from ethyl acetate melted at 205-206°. (Found: C, 76.8, 77.C: H, 9.3, 9.2. $C_{28}H_{40}O_4$ requires C, 76.4 H, 9.1%). Its oxime prepared in the usual way separated in needles, m.p. 165-167°. from alcohol (Found: N, 3.2. $C_{28}H_{41}O_4N$ requires N, 3.1%).

Preparation of compound m.p. 146°.

200 mg. ergostadienedioneol were dissolved in 120 c.c. boiling alcohol. To this was added 25 c.c. 4N alcoholic potash, when a deep red colour appeared, and the whole heated on the water bath for a further 5 minutes. Water (500 c.c.) was then added and the whole filtered. The addition of acid discharged the red colour and a yellow precipitate was formed. This was filtered off, and after several recrystallisations from methyl alcohol yellow needles, m.p. 146° were obtained. (Found: C,81.6; H,10.2. $C_{28}H_{42}O_2$ requires C,81.9; H, 10.2%).

Oxidation of methoxyergostadiendiol. A solution of methoxyergostadienediol (19) in ACOH (60 c.c.) was stirred and maintained at 35° for 1 hour while a solution of CrO_3 (4g. in ACOH (10 c.c.)) was dropped in. After pouring into water the whole was extracted with ether, the ether washed with water and Na_2CO_3 (aq.) to remove ACOH, and after drying over Na_2SO_4, evaporated. The residue methoxyergostadieneonol crystallised from methyl alcohol in glistening plates m.p. 175-176°. Mixed with the starting material m.p. 174-175° a specimen melted at 150-155°. (Found: C, 78.8; H, 10.5, $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.4%). Boiled up for 6 hours with hydroxylamine acetate in alcohol this compound gave no oxime.

Treated with alcoholic potash as described for ergostadiendionol, it was recovered unchanged.

Conversion of Triol I. to Triol II.

2 gms. of Ergostadienetriol I. were dissolved in 750 c.c. of dry benzene and after the addition of 2 gms. maleic anhydride, the whole boiled for 8 hours. The benzene was then removed in vacuo, and the residue boiled for 2 hours with 200 c.c. 5% methyl alcoholic potash. This was then poured into water, and ether extracted. After drying and removal of the ether, the residue was taken up in a little ethyl acetate from which on cooling ~~in~~ it separated in glistening plates m.p. 240-241°, which did not depress the melting point of a specimen of Ergostadienetriol II. prepared in the usual way. Its acetate likewise gave no depression of melting point with a specimen of ergostadienetriol II. acetate, m.p. 179°.

Dehydroergosterol from Ergostadienetriol II. monobenzoate.

Ergostadienetriol II monobenzoate (1 gm.) was distilled at a pressure of about .0001 m.m. A light coloured oil came over, which was taken up in ether-methyl alcohol. On concentrating and cooling, crystals m.p. 146° separated, and these on treatment with acetic anhydride in pyridine gave an acetate m.p. 146°. These substances gave no depression in melting point with specimens of dehydroergosterol and its acetate respectively prepared by the action of mercuric acetate on ergosterol.

Methoxyergostatriene, prepared by the action of methyl iodide on potassium ergosterylate (19) was treated with perbenzoic acid (1 mol.) according to the method of Heilbron, Morrison and Simpson (13) and thereby gave methoxyergostadienediol monobenzoate in 15% yield which on hydrolysis readily yielded the free diol.

Methoxyergostadienediol monoacetate. The above diol (1 gm.) was heated in pyridine (10 c.c.) with acetic anhydride (5 c.c.) for 2 hours on the water bath. The whole was then poured into water, the solid filtered off and crystallised from methyl alcohol from which it separated in glistening plates m.p. 143-144° (Found: C, 77.0: H, 10.3. $C_{31}H_{50}O_4$ requires C, 76.5: H, 10.3%).

This acetate was hydrogenated with Adam's PtO_2 in glacial acetic acid-ethyl acetate (1:1) until hydrogen corresponding to one double bond had been absorbed. After removal of the solvent in vacuo the residue was crystallised from methyl alcohol, from which it separated in fine needles m.p. 152-153°. (Found: C, 76.2, H, 10.8. $C_{31}H_{52}O_4$ requires C, 76.2. H, 10.7%.). On hydrolysis with 2½ alcoholic potash this gave methoxyergostenediol, long prismatic needles m.p. 165-166°, from methyl alcohol. (Found: C, 78.3, H, 11.1. $C_{29}H_{50}O_3$ requires C,78.0, H, 11.2%).

Treatment of Methoxyergostadienediol and methoxyergostenediol with lead tetra acetate. The diol (1 gm.) was shaken for two hours with a solution of lead tetra-acetate in ACOH (75 c.c. of N/10). The solution was then poured into brine (which destroys the excess tetra-acetate by precipitation of the lead as chloride), and the whole extracted with ether. The ether layer was washed with water and Na_2CO_3 to remove ACOH, and after drying and evaporation, the residue crystallised from methyl alcohol, from which it is obtained in long prismatic needles m.p. 130-131°. (Found: C, 78.8. H, 10.3. $C_{29}H_{46}O_3$ requires C, 78.7, H, 10.4%).

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