# CCCCXXIII.—*Degradation of Quaternary Ammonium Salts. Part I.*

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In the course of synthetic work a method was required whereby the nitrogen atom of a secondary amine might be protected in such a way as to admit of quaternary salt formation and subsequent removal of the protecting group : the most obvious solution was the insertion of an alkyl radical which should be removed with special ease in a Hofmann degradation of the subsequently formed quaternary salt. Now quaternary salts derived from tetrahydro*iso*quinoline readily undergo such degradation with rupture of the bond between the nitrogen atom and carbon atom 3, but the conversion of narcotine methiodide (I) into narceïne (II) forms a notable exception. This fact suggested that the group $Ph \cdot CH(OH) \cdot CH_2 \cdot$ might prove suitable.
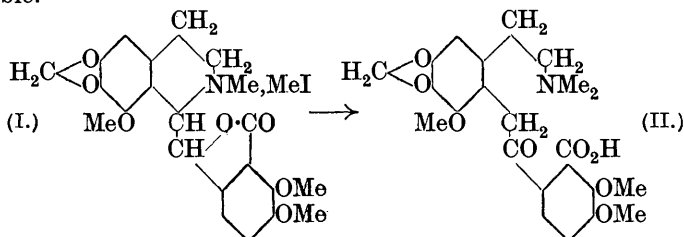
Preliminary experiments showed that styrene iodohydrin did not readily yield quaternary salts, and accordingly salts were prepared from ω-bromoacetophenone and tertiary bases, and submitted to reduction with sodium amalgam. It is probable, however, that the removal of the phenacyl group under these conditions is not due to its reduction to β-hydroxy-β-phenylethyl and subsequent Hofmann degradation, for it was found that *phenacylbenzyldimethylammonium bromide* yielded benzyldimethylamine on reduction in *acid* solution, and similar observations have been recorded by Schmidt and Rumpel (*Arch. Pharm.*, 1899, **237**, 222) and by Emde and Runne (*ibid.*, 1911, **249**, 354). Emde's systematic study of the reduction of ammonium salts has shown that of the commonly occurring radicals benzyl is most loosely held, but it was necessary for the present purpose to find a still more easily detachable group.
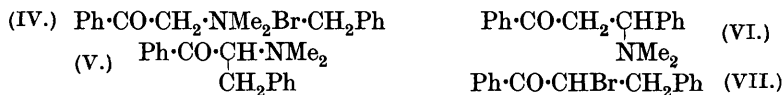
The phenacylo-bromides or -iodides of β-phenylethyldimethylamine, dimethylpiperazine, hydrohydrastinine (III), benzyldimethylamine, and α-phenylethyldimethylamine were investigated ;

the first three salts readily lost the phenacyl group on reduction with sodium amalgam, but the last two reacted abnormally (*vide*

$$H_2C{<}{^O_O}\diagdown\diagup\begin{array}{c}CH_2\\ CH_2\\ NMe\\ CH_2\end{array}\quad (III.)$$
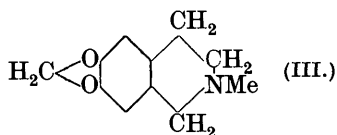
infra). The results show that the removal of the phenacyl group by reduction may leave intact structures which exhibit little stability towards other methods of degradation. The satisfactory results obtained with the salt derived from dimethylpiperazine are of particular interest, since the piperazine ring is opened with exceptional ease by Hofmann degradation (von Braun, Goll, and Zobel, *Ber.*, 1926, **59**, 936).

When an aqueous solution of phenacylbenzyldimethylammonium bromide (IV) is treated with sodium amalgam, the reaction does not proceed normally with elimination of the phenacyl radical, but yields a solid base, $C_{17}H_{19}ON$, which is also produced in excellent yield by heating the salt (IV) with dilute sodium hydroxide solution. The analytical data are not inconsistent with the formula $C_{16}H_{17}ON$ ($= Ph \cdot CO \cdot CH_2 \cdot NMe \cdot CH_2Ph$), but the degradation has not taken the unusual course of removing a methyl group preferentially to benzyl or phenacyl, since the *methobromide* of the new base is not identical with the salt (IV). Hot alkali converts this methobromide into phenyl styryl ketone, so that the solid base would appear to have the constitution (V) or (VI). The former alternative is favoured, and the presence of an $\alpha\gamma$-diphenylpropane skeleton confirmed, by the observation that the methobromide yields benzylacetophenone on reduction.

(IV.) $Ph \cdot CO \cdot CH_2 \cdot NMe_2Br \cdot CH_2Ph$ $Ph \cdot CO \cdot CH_2 \cdot \overset{|}{C}HPh$ (VI.)

(V.) $Ph \cdot CO \cdot \overset{|}{C}H \cdot NMe_2$ NMe_2

        CH_2Ph $Ph \cdot CO \cdot CHBr \cdot CH_2Ph$ (VII.)

The formula (V) was shown by synthesis to be the correct one. Benzylacetophenone yields the substance (VII) on bromination, the position of the bromine atom being confirmed by the non-identity of the compound with the known β-bromobenzylacetophenone (Rupe and Schneider, *Ber.*, 1895, **28**, 958; Vorländer and Tubandt, *Ber.*, 1904, **37**, 1652). By the action of dimethylamine, (VII) yields a product identical with the base $C_{17}H_{19}ON$. The synthesis might conceivably give rise to the isomeride (VI) by removal of hydrogen bromide from (VII), followed by addition of dimethylamine to the unsaturated ketone, but experiments on the addition of dimethylamine to phenyl styryl ketone have yielded only small quantities

of very unstable basic material, in general agreement with the observation of Georgi and Schwyzer (*J. pr. Chem.*, 1912, **86**, 273) that β-piperidinobenzylacetophenone is highly unstable.

Phenacyl-α-phenylethyldimethylammonium iodide yields with alkali a presumably similar solid base which will be described in a future communication.

This peculiar migration of the benzyl radical is probably due to the combined effect of the relative toleration of the benzyl group for a positive charge (compare Hanhart and Ingold, *J.*, 1927, 1003) and the reactivity of the methylene group in the phenacyl radical, but we prefer not to speculate further as to the mechanism of the reaction until more experimental data are forthcoming.

The fact that the substance (I) yields benzyldimethylamine on reduction in acid solution shows that the quaternary salt has the structure assigned to it, and that the migration takes place during the treatment with alkali.

EXPERIMENTAL.

The following tertiary bases were prepared according to the references quoted : β-phenylethyldimethylamine (Decker and Becker,· *Ber.*, 1912, **45**, 2404), dimethylpiperazine (Eschweiler, D.R.-P. 80520, 1893; Knorr, Hörlein, and Roth, *Ber.*, 1905, **38**, 3136), benzyldimethylamine (Eschweiler, *loc. cit.*; Sommelet and Guioth, *Compt. rend.*, 1922, **174**, 687). The quaternary salts were obtained by refluxing the base (1 mol.) with bromoacetophenone (1 mol.) in benzene solution for ½—1 hour, except in the case of that derived from diethylaniline, the reaction here being carried out in hot alcohol or cold acetone. The bromide was either recrystallised from alcohol–ether, or converted by potassium iodide solution into the iodide, and the latter purified in like manner. Reduction of the salts was carried out in hot aqueous solution by an excess of sodium amalgam.

Phenacylphenyldiethylammonium iodide forms a microcrystalline powder, m. p. 133° (Found : I, 32·5. $C_{18}H_{22}ONI$ requires I, 32·2%). The preparation of this and other quaternary salts containing the nitrogen atom directly attached to an aromatic nucleus did not proceed smoothly (compare Wedekind, *Ber.*, 1908, **41**, 2802), and their degradation appeared to take an abnormal course, which is under investigation.

Phenacyl-β-phenylethyldimethylammonium bromide forms clusters of minute prisms, m. p. 191° (Found : Br, 23·2. $C_{18}H_{12}ONBr$ requires Br, 23·0%). After degradation, the β-phenylethyldimethylamine was identified as picrate and as methiodide (Decker and Becker, *loc. cit.*).

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Diphenacyldimethylpiperazinium dibromide is rather sparingly soluble in water or alcohol, and crystallises from these solvents in small laminæ, m. p. 222—225° (decomp.) (Found : Br, 30·8. $C_{22}H_{28}O_2N_2Br_2$ requires Br, 31·2%). The salt appeared to be homogeneous, but no very thorough search was made for the second theoretically possible stereoisomeride. After reduction, the regenerated dimethylpiperazine was distilled in steam and isolated as the very sparingly soluble picrate (decomp. 280°) (Knorr, Hörlein, and Roth, *loc. cit.*). It was further characterised by the red precipitate produced with potassium bismuth iodide, and by reconversion, through the hydrochloride, into the original phenacylobromide.

Hydrohydrastinine phenacyloiodide separates from water or alcohol, in both of which it is sparingly soluble, in spherical aggregates of minute prisms, m. p. 190° (Found : I, 28·9. $C_{19}H_{20}O_3NI$ requires I, 29·1%). From the liquors after reduction, benzene extracted hydrohydrastinine, m. p. and mixed m. p. 64°.

Phenacylbenzyldimethylammonium bromide forms small prisms, m. p. 167—168° (Found : Br, 24·2. $C_{17}H_{20}ONBr$ requires Br, 24·0%). Reduction with zinc dust and sulphuric acid gave a steam-volatile base whose methiodide underwent partial fusion at 170° (m. p. of benzyltrimethylammonium iodide, 177—178°), but was not completely melted below 250°. With picric acid, however, the iodide yielded benzyltrimethylammonium picrate, m. p. and mixed m. p. 173—174° (Goss, Hanhart, and Ingold, J., 1927, 259, give 168—169°); the crude iodide probably contained phenacyltrimethylammonium iodide, or the tetramethylammonium salt produced from the latter by the action of excess of methyl iodide.

ω-*Dimethylamino-ω-benzylacetophenone* (V).—(*a*) Phenacylbenzyldimethylammonium bromide is heated on the water-bath with excess of 10%₀ sodium hydroxide solution for 1 hour. The oily product solidifies on cooling and is recrystallised from aqueous methyl alcohol. Yield, 90%. (*b*) ω-Bromo-ω-benzylacetophenone (*vide infra*) (1 mol.), dimethylamine hydrochloride (2 mols.), and sodium methoxide (2 mols.) are mixed in methyl-alcoholic solution, kept over-night, and warmed for 2 hours on the water-bath. The diluted mixture is extracted with benzene and the product is extracted from the benzene by hydrochloric acid and precipitated by ammonia.

ω-*Dimethylamino-ω-benzylacetophenone* forms colourless leaflets, m. p. 77—79°, which are moderately easily soluble in methyl alcohol and readily soluble in benzene or light petroleum (Found : C, 80·7, 80·8; H, 7·4, 7·4; *M*, cryoscopic in benzene, 252. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·5%; *M*, 253). The substance is slightly volatile in steam and slowly resinifies on keeping. It does not

appear to react with hydroxylamine, semicarbazide, or p-nitrophenylhydrazine, and is comparatively stable towards acid permanganate. The *picrate* crystallises from alcohol in bright yellow sword-blades, m. p. 147—149° (Found : N, 11·8. $C_{17}H_{19}ON,C_6H_3O_7N_3$ requires N, 11·6%). The identity of the products yielded by methods (a) and (b) was shown by direct comparison and mixed melting points of the base and of the picrate.

The methosulphate, prepared in benzene solution, yields the *methobromide* on addition of potassium bromide to its solution in water. This salt separates from alcohol–ether in faintly pink prisms, m. p. 195—197° (Found : Br, 21·9, 21·4; loss at 130°, 6·2. $C_{18}H_{22}ONBr,\frac{1}{2}C_2H_6O$ requires Br, 21·6; loss, 6·2%). On heating on the water-bath with dilute sodium hydroxide solution it yields phenyl styryl ketone, identified as the α-dibromide (Pond, York, and Moore, *J. Amer. Chem. Soc.*, 1901, **23**, 790), m. p. and mixed m. p. 157°. By reduction with zinc dust and sulphuric acid, the methobromide yields benzylacetophenone, which was characterised by conversion into the semicarbazone (most readily purified from ether–light petroleum), m. p. and mixed m. p. 143° (Jacobson and Ghosh, J., 1915, **107**, 962).

ω-*Bromo-ω-benzylacetophenone* (VII) is obtained by the action of the theoretical quantity of bromine on benzylacetophenone in carbon tetrachloride. The reaction proceeds rapidly, and after the hydrogen bromide has been removed by a current of dry air the solvent is evaporated and the residue recrystallised from methyl alcohol. It forms minute prisms, m. p. 57—59° (Found : Br, 27·8. $C_{15}H_{13}OBr$ requires Br, 27·7%); the m. p. is depressed by admixture with β-bromobenzylacetophenone, prepared by the method of Vorländer and Tubandt (*loc. cit.*). The substance (IV) appears to show the acidic properties associated with α-halogeno-ketones in that it yields a golden-yellow solution with aqueous-alcoholic alkali.

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