69. *Degradation of Quaternary Ammonium Salts. Part VIII. Necessary Structural Conditions for Migration in Radicals.*

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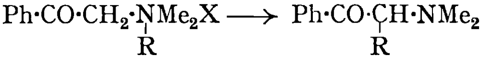
Previous studies have suggested that the migratory aptitude of a radical R in the rearrangement (I) ⟶ (II) can be correlated with its (not necessarily very pronounced) anionic stability (J., 1932, 55, 1932, and earlier papers).

(I.)

$$\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}\underset{R}{N}Me_2X \longrightarrow Ph{\cdot}CO{\cdot}\underset{R}{C}H{\cdot}NMe_2}$$
(II.)

Most of the substances studied in this investigation were chosen to test the necessity, rather than to illustrate the sufficiency, of this condition; the results, collected in Table I, are in accordance with anticipation.

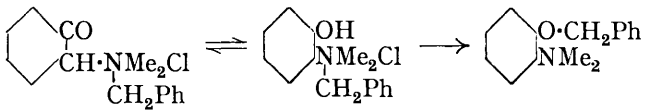
The choice of radical in case (F) was influenced by the known instability of primary and secondary nitro-compounds towards alkali, and (G) was chosen as another example in which R contained no α-hydrogen atom. In salts (H) and (J), the mobile benzyl radical in (I; R = $\mathrm{CH_2Ph}$) is modified by interpolation of further methylene groups between the aromatic nucleus and the quaternary nitrogen atom; (J) was selected in order to disclose any possible " alternation " in the relation between the effect of a phenyl group and its position, and (K) to test the possibility that increase in the number of phenyl groups might compensate for their remoteness. The decomposition of (L), although facile, is less so than the rearrangement of (I; R = $\mathrm{CH_2Ph}$). (N) was chosen as containing the nearest possible saturated analogue of benzyl, and (O) was thought to be a favourable case for migration of a saturated radical, because the secondary radical α-phenylethyl migrates with enormously greater speed than the primary radical benzyl.

In cases (H), (J), (M), and (N), the decomposition required long boiling with concentrated alkali, in contrast with the facility of the successful rearrangements; but it is emphasised that the negative results are not absolute, and merely show that migration of the radical concerned is less facile than the observed decomposition. Hughes and Ingold (J., 1933, 71) record a case in which a more robustly constituted salt appears to exhibit migration of methyl ($\mathrm{CHPh_2{\cdot}NMe_3{\cdot}OH \longrightarrow CMePh_2{\cdot}NMe_2}$).

As the migrating radicals (A), (B), (C), and (E), with the possible exception of phenacyl, could be regarded as possessing *both* cationic and anionic stability in virtue of the βγ multiple linkage, the extreme case (P) was considered important, in which R is a radical of unambiguous electrochemical character. No mechanism is suggested meantime for the surprising reaction which prevented the realisation of this case.

Two modifications of the " recipient " radical were also 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 group of the phenacyl radical and the ammonium nitrogen atom, but interaction of ω-dimethylaminopropiophenone and benzyl chloride yielded only dibenzyldimethylammonium chloride.

o-*Hydroxyphenylbenzyldimethylammonium chloride* (III) is of peculiar interest from the analogy between its ketonic form (IV) and (I). When the salt was fused with sodamide, however, the benzyl group migrated, not to carbon, but to oxygen, yielding (V). Comment on this result is deferred pending further investigation.

(IV.)


(V.)

(III.)

Constitutions of the Rearrangement Products.—The products from (C) and (E) were converted into the methosulphates 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, $\mathrm{Ph{\cdot}CO{\cdot}[CH_2]_3{\cdot}COPh}$. Attempts to prepare product (E) from ω-piperidinoacetophenone, formaldehyde, and phenylacetylene were unsuccessful. The methiodide of (V) was identical with a specimen prepared by successive reduction and methylation of *o*-nitrophenyl benzyl ether.

TABLE I.

Case.	R.	Result.	Case.	R.	Result.
A	CH_2Ph	Rearrangement [1]	J	$CH_2\cdot CH_2\cdot CH_2Ph$	Loss of phenacyl or of γ-phenylpropyl
B	$CH_2\cdot COPh$	Rearrangement [1]	K	$CH_2\cdot CPh_3$	*$R\cdot NMe_2$ did not combine with $Ph\cdot CO\cdot CH_2Br$
C	$CH_2\cdot CH{:}CH_2$	Rearrangement	†L	Ph	Loss of ethyl
D	$CH_2\cdot C\vdots CH$	*(See experimental part)	M	Me	Loss of phenacyl
E	$CH_2\cdot C\vdots CPh$	Rearrangement	N	Hexahydrobenzyl	Total decomposition
F	$CMe_2\cdot NO_2$	*[2]	O	CMe_3	*[2]
G	CMe_2Ph	*$R\cdot NMe_2$ did not combine with $Ph\cdot CO\cdot CH_2Br$	P	OMe	*$R\cdot NMe_2$ and $Ph\cdot CO\cdot CH_2Br$ gave $Ph\cdot CO\cdot CH_2\cdot NMe_2,HBr$
H	$CH_2\cdot CH_2Ph$	Loss of phenacyl			

* Quaternary salt could not be obtained. † Salt contained NEt_2 instead of NMe_2. [1] Previously reported. [2] RBr gave only $NHMe_2,HBr$ with $NHMe_2$, and did not combine with $Ph\cdot CO\cdot CH_2\cdot NMe_2$.

EXPERIMENTAL.

(C) Allyldimethylamine (Knorr and Roth, *Ber.*, 1906, **39**, 1427) was added to phenacyl bromide (1 mol.) in ether, and an oil separated, from an aqueous solution of which sodium picrate and acetic acid precipitated *phenacylallyldimethylammonium picrate*, m. p. 78—79° after crystallisation from methyl alcohol (Found : $C_6H_2O_7N_3'$, 52·7. $C_{13}H_{18}ON{\cdot}C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 52·8%). The picrate was treated with dilute sulphuric acid, picric acid removed, and sufficient sodium hydroxide added to give a final alkalinity of 2·5*N*. After 2 hours' refluxing, the basic material was isolated in dry ethereal solution; ethereal picric acid precipitated *ω-dimethylamino-ω-allylacetophenone 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 C, 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, *Ber.*, 1921, **54**, 930, give 156—157°) (Found : C, 66·5; H, 7·0. Calc. for $C_{12}H_{13}ON_3$: C, 66·4; H, 6·9%).

(D) αβγ-Tribromopropane, on distillation over solid potash, yielded β-bromoallyl bromide, but none of the propargyl bromide reported by Henry (*Annalen*, 1870, **154**, 371). 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; a heavy oil then 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%). Treatment with alkali either left the base unchanged or led to total decomposition.

(E) *Phenacylphenylpropargyldimethylammonium bromide* separated from a benzene solution of phenylpropargylpiperidine (Mannich and Chang, *Ber.*, 1933, **66**, 418) and phenacyl bromide in 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%). An aqueous solution of the salt (which is completely decomposed by caustic alkali) was heated for a few minutes on the water-bath with excess of 8% sodium carbonate solution, and the basic material isolated as an uncrystallisable gummy solid. 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° (decomp.) (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 methyl sulphate, 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-dibenzoylpropane prepared by the method of Japp and Michie (J., 1901, **79**, 1017).

ω-Piperidinoacetophenone hydrobromide was prepared by adding piperidine (1 mol.) to phenacyl bromide (1 mol.) in three times its weight of alcohol and warming the mixture for ½ hour on the water-bath. On cooling, the product crystallised in 65% yield, m. p. after crystallisation 227—228° (Van Ark, *Arch. Pharm.*, 1900, **228**, 330, gives 220°) (Found: HBr, 28·4. Calc. for $C_{13}H_{17}ON,HBr$: HBr, 28·2%).

(G) α-Dimethylamino*iso*butyronitrile (Henry and Dewael, *Bull. Acad. roy. Belg.*, 1904, 741) 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 solely of phenyl*iso*propyldimethylamine, isolated as *picrate*, yellow laminæ 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%).

(H) Phenacyl-β-phenylethyldimethylammonium bromide (Stevens, Creighton, Gordon, and MacNichol, J., 1928, 3193) was heated to 150—160° with powdered sodamide (2 mols.). The only basic product obtained was 40% of β-phenylethyldimethylamine as picrate (m. p. and mixed m. p.), and an odour like that of styrene was noticed. The salt was similarly decomposed on long boiling with concentrated sodium hydroxide solution.

(J) β-Phenylpropionitrile (Baker and Lapworth, J., 1924, **125**, 2334) was reduced with sodium (20 atoms) and boiling alcohol. The mixture was acidified with concentrated hydrochloric acid, filtered, concentrated, and basified, and the γ-phenylpropylamine extracted with ether. It was isolated in 30—40% yield as the hydrochloride, m. p. 218° (compare Tafel, *Ber.*, 1889, **22**, 1857), which on Eschweiler methylation gave γ-phenylpropyldimethylamine, isolated in good yield as the picrate, m. p. 99°, as found by Senfter and Tafel (*Ber.*, 1894, **27**, 2311). *Phenacyl-γ-phenylpropyldimethylammonium bromide*, rapidly produced from its generators in benzene, 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* (X), 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 = $\cdot(CH_2)_3Ph$], *i.e.*, $C_{19}H_{23}ON,C_6H_3O_7N_3$, requires $C_6H_3O_7N_3$, 45·3%). Each experiment gave traces of a neutral substance insoluble in ether, which crystallised from much alcohol in colourless needles, m. p. 210°. The quaternary salt and sodamide at 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 tetrachloride, evaporation of the solvent, and crystallisation from methyl alcohol, yielded fine needles, m. p. 63—65°, not depressed by admixture with authentic propenylbenzene dibromide prepared by distillation of phenylethylcarbinol over potassium bisulphate, followed by bromination (compare Hell and Bauer, *Ber.*, 1903, **36**, 206). Allylbenzene, the normal product of Hofmann degradation of the quaternary salt, is known to yield propenylbenzene on heating with alkali. One experiment gave, not phenacyldimethylamine picrate, but the picrate (X), which is not identical with the β-hydroxy-β-phenylethyldimethylamine picrate described by Tiffeneau and Fourneau (*Bull. Soc. chim.*, 1913, **13**, 971), nor with the picrate of either of the possible products of addition of dimethylamine to propenylbenzene. β-Dimethylamino-α-phenylpropane (Thomson and Stevens, J., 1932, 1940) yielded a picrate, yellow prisms from methyl alcohol, m. p. 135—139°. The isomeric α-dimethylamino-α-phenylpropane was prepared from dimethylaminophenylacetonitrile (Stevens, Cowan, and MacKinnon, J., 1931, 2568) 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%).

(K) βββ-Triphenylethylamine (Hellerman, *J. Amer. Chem. Soc.*, 1927, **49**, 1737) 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%).

(L) *Phenacylphenyldiethylammonium 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.

(M) Phenacyltrimethylammonium bromide (Rumpel, *loc. cit.*) was heated for an hour with 25—30% sodium hydroxide solution in a slow current of steam, and the distillate collected in hydrochloric acid. The residue contained some benzoic acid (m. p. and mixed m. p.), but no basic material. 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 base. The salt reacted explosively with sodamide at 170°; no high-boiling basic material could be detected.

(N) Hexahydrobenzyl bromide, prepared after Noller and Adams (" Organic Syntheses," **6**, 22), distilled at 79—81°/30 mm. The bromide (1 mol.) was heated with dimethylamine (2 mols.) in 70% alcohol on the water-bath for 24 hours. An ethereal solution of the basic material, dried over potassium carbonate and concentrated (column), gave with ethereal picric acid 30% of *hexahydrobenzyldimethylamine picrate*, which separated from methyl alcohol first in yellow needles, and then, more slowly, in 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 over-night 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. $C_{17}H_{26}ON{\cdot}C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 46·8%). The bromide, refluxed for 1 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 salt could be isolated. Heating the salt to 160° with sodamide gave similar results.

(P) *ONN*-Trimethylhydroxylamine (Major and Fleck, *J. Amer. Chem. Soc.*, 1928, **50**, 1480; Jones and Major, *ibid.*, p. 2744), 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 $C_{10}H_{13}ON,HBr$: HBr, 33·2%).

β-Dimethylaminopropiophenone (Mannich and Heilner, *Ber.*, 1922, **55**, 356) 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 (Pinnow, *Ber.*, 1899, **32**, 1405), 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, mixed with finely divided sodamide, reacted violently at 110°. The basic products, isolated in dry ether, 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. $C_{16}H_{20}ON{\cdot}C_6H_2O_7N_3$ requires 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, *Annalen*, 1884, **224**, 121), prepared by boiling equimolecular quantities of *o*-nitrophenol, benzyl chloride, and sodium ethoxide in alcohol for 8 hours, distilled at 210°/12 mm. It was reduced by West's method; after filtration, the residue, and the concentrated 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° (Höchster 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 ½ 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; H_2O, 4·65%).

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