

THE DEGRADATION OF QUATERNARY AMMONIUM SALTS

With an additional paper - -

THE ACTION OF THE GRIGNARD REAGENT UPON
AMINO-NITRILES.

BY

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APRIL 1933.

P A P E R S .

S E C T I O N I

THE DEGRADATION OF QUATERNARY AMMONIUM SALTS

(A) NEW CASES OF RADICAL MIGRATION

(B) MOLECULAR REARRANGEMENT IN RELATED
SULPHUR COMPOUNDS

(C) THE RELATIVE MIGRATORY VELOCITIES OF
SUBSTITUTED BENZYL RADICALS

S E C T I O N II

THE ACTION OF THE GRIGNARD REAGENT UPON AMINO-NITRILES

I N D E X

Page

I - THE DEGRADATION OF QUATERNARY AMMONIUM
SALTS.

Introductory	1
General Outline of Results	4
A - New Cases of Radical Migration.	
Discussion	8
Experimental	17
B - Molecular Rearrangement in Related Sulphur Compounds.	
Discussion	32
Experimental	36
C - The Relative Migratory Velocities of Substituted Benzyl Radicals.	
Discussion	41
Experimental	52

II - THE ACTION OF THE GRIGNARD REAGENT UPON
AMINO-NITRILES.

Introductory	77
General Outline of Results	79
Discussion	80
Experimental	85

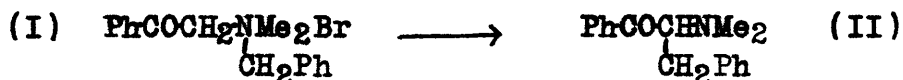
SUMMARY	94
---------------	----

ACKNOWLEDGEMENTS	102
------------------------	-----

THE DEGRADATION OF QUATERNARY AMMONIUM SALTS.

INTRODUCTORY

The results of an investigation of the degradation of quaternary ammonium salts of the type $\text{PhCOCH}_2\text{N}^+\equiv\text{R}_3\text{Br}^-$ showed that, in most cases, on treatment with sodium amalgam and water the products of degradation were $\text{Ph}\cdot\text{CO}\cdot\text{CH}_2\text{Br}$ and $\text{N}^+\equiv\text{R}_3$. In the case of phenacylbenzyl-dimethylammonium bromide, however, it was shown that the reaction did not proceed normally, but took the following course, in an alkaline medium, irrespective of the reducing agent -

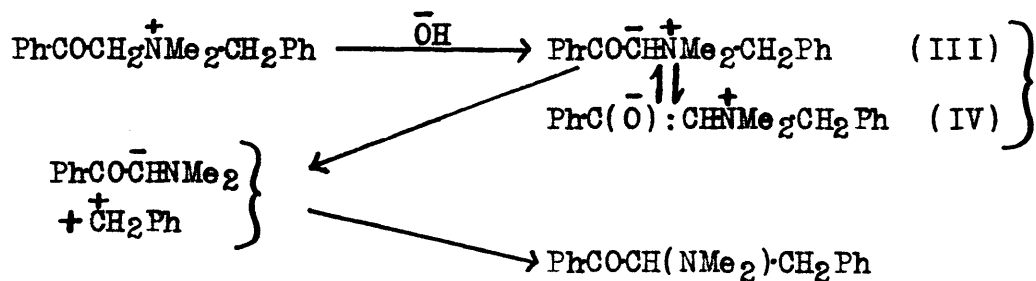


(Stevens, Creighton, Gordon and MacNicol^{*,*}) The reaction thus involved the migration of the benzyl radical from the nitrogen atom to the carbon atom of the adjacent methylene group. A further study of this reaction showed that the migration/

* NOTE - The references are collected on folding leaves at the end of the Thesis, and are referred to in the text by small index numerals.

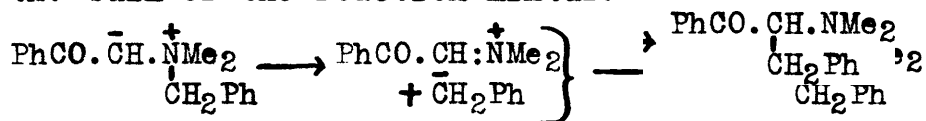
migration also occurred when the benzyl radical was replaced by *m*-bromobenzyl, *p*-bromobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, Δ -phenylethyl, benzhydryl, or 9-fluorenyl. Further, replacement of the phenacyl group by *p*-bromophenacyl or acetyl, and of the dimethylammonium system by piperidinium, did not prevent the migration. (Stevens²; Stevens, Snedden, Stiller, and Thomson³.)

It was suggested by Stevens², in the first instance, that the most feasible mechanism of the migration appeared to be the conversion of the salt, by alkali, into the keto-enolic betaine (III \rightleftharpoons IV), followed by the detachment of the benzyl radical as a kation, and its reattachment at the original methylene carbon atom.



With a view to confirmation or refutation of this hypothesis, measurements of the relative migratory tendencies of several, substituted benzyl radicals were carried out. Velocity measurements showed that the reaction was unimolecular in absolute alcoholic sodium ethoxide solution, and the values obtained, which are to be regarded as of a preliminary character, were quite irreconcilable with the suggested mechanism of the rearrangement. Indeed, the results obtained suggested that the benzyl radicals were detached as anions, which consideration gave rise to the following suggested mechanism, in/

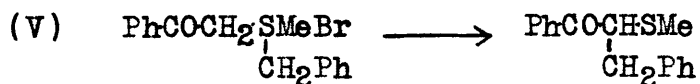
in which the ω -carbon atom of the phenacylidene group is considered to "capture" the benzyl anion before it can escape into the bulk of the reaction mixture -



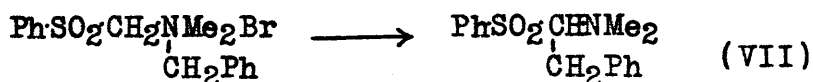
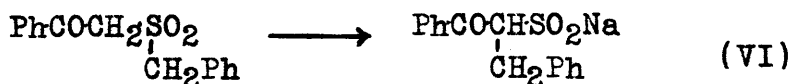
(compare Stevens²).

It was hoped to provide more complete substantiation of the suggested reaction mechanism and to obtain more accurate and more rigorously valid data for the relative ease of migration of substituted benzyl radicals in the reaction, by preparing salts of the type $\text{PhCOCH}_2\text{NMeX}(\text{CH}_2\text{Ar})\text{CH}_2\text{Ar}'$, and determining the proportions in which the two possible products of their rearrangement are formed. Unfortunately, the preparation of such salts was found to be impracticable (Stevens, Snedden, Stiller, and Thomson³).

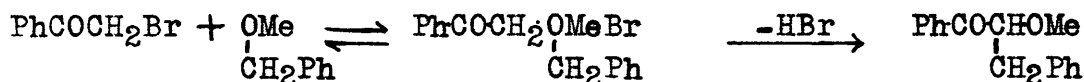
The work to be described hereafter is essentially a continuation of the two main lines of study outlined above; firstly, further extensions of the generality of the reaction ($\text{I} \rightarrow \text{II}$) (Sections A and B) and, secondly, a more accurate and comprehensive series of velocity determinations with a view to the confirmation of the proposed reaction mechanism and the evaluation of accurate values for the relative migratory velocities of substituted benzyl radicals (Section C).



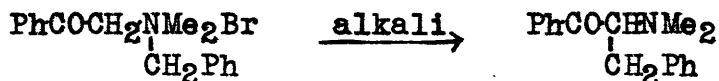
Further extensions to the reactions (VI) and (VII) were unsuccessful.



Attempts to realise rearrangement of an oxonium salt, according to the scheme below, also failed.



C - An experimental technique has been elaborated for the measurement of the velocity of the reaction



The reaction has been investigated in a series of alcohols and in water, and the following general results are discussed:-

- (1) Good first order constants are obtained, except in aqueous solution, when they fall off as the reaction proceeds.
- (2) A second equivalent of alkali produces a considerable increase in velocity, but a third equivalent has little further effect.
- (3) The velocity varies with the medium in the order $\text{MeOH} \ll \text{EtOH} < \text{Pr}^\alpha\text{OH} \ll \text{Pr}^\beta\text{OH}$. Replacement of part of the solvent alcohol by toluene causes a marked acceleration in velocity.
- (4) The temperature coefficient of the reaction in methyl alcohol/

alcohol is unusually high, $Q_{10} = 5.70$.

(5) The quaternary iodide rearranges at the same rate as the bromide.

The rearrangement of salts containing o-, m-, and p-chloro-, bromo-, iodo-, nitro-, methoxy-, and methyl-benzyl radicals has been investigated, and the migratory velocities of these radicals relative to unsubstituted benzyl found to be

	Cl	Br	I	NO ₂	OMe	Me
<u>o</u>	35.6	47.7	81	1040	1.91	15.3
<u>m</u>	2.44	2.09	1.92	3.81	0.93	0.97
<u>p</u>	2.77	2.86	3.25	73	0.76	1.06

The ratios of the velocities of migration of benzyl, p-chlorobenzyl, m-bromobenzyl, p-bromobenzyl, and m-nitrobenzyl are approximately the same, whether the radicals are associated with phenacyl or with p-bromophenacyl radicals in the quaternary salts.

The following points are discussed :-

- (1) In each position, the effects of substituents are in the order OMe < Me < Hal. < NO₂ .
- (2) In the o- and p-positions the halogens fall in the "wrong" order among themselves.
- (3) o- Substitution usually causes very marked acceleration.
- (4) The nitro- group accelerates far more strongly from the p-, than from the m-position.

The analogous diammonium salts containing m- and p-xylylene radicals have been incidentally found to undergo twofold rearrangement/

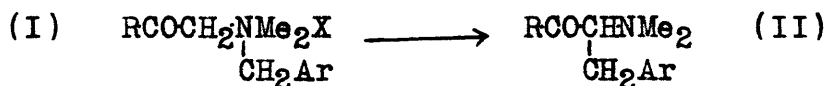
rearrangement under the usual reaction conditions.

A - NEW CASES OF RADICAL MIGRATION

The quaternary salts whose degradations have been the subject of previous study (Stevens, Creighton, Gordon and MacNicol¹; Stevens²; Stevens, Snedden, Stiller and Thomson³;) all conform to the type $\text{RCOCH}_2\text{NMe}_2\text{X}$, and their rearrangement involves the

$$\begin{array}{c} \text{CH}_2\text{Ar} \\ | \\ \text{CH}_2 \end{array}$$

migration of a substituted benzyl radical from the quaternary nitrogen atom to the methylene carbon atom of a phenacyl or acetyl radical, thus -



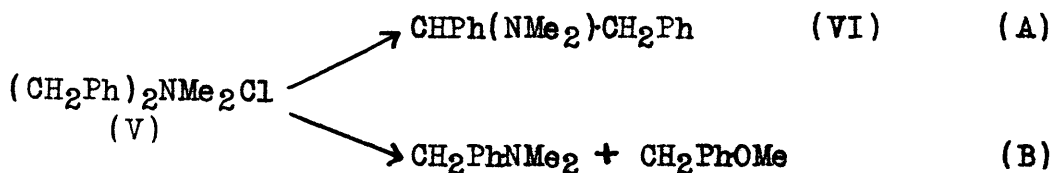
In the present investigation, the rearrangement (I→II) has been extended to compounds which do not conform to the type represented by (I). In the first instance, the rearrangement of diphenacyldimethylammonium bromide (III), in which the migrating radical is phenacyl, has been accomplished. Treatment of (III) with aqueous alkali gives the rearrangement product (IV) readily.



The attempted rearrangement of the analogous compounds, di-p-bromo phenacyldimethylammonium bromide and diacetyl dimethylammonium chloride, /

chloride, was unsuccessful. In the former case, although the quaternary salt was completely destroyed, on treatment with methyl-alcoholic sodium methoxide solution, with production of a black-red solution from which dimethylamine was evolved, the only isolable products of degradation were minute quantities of two, unidentifiable, non-basic products, neither of which was identical di-4-bromobenzoylethylene, $\text{Br} \langle \bigcirc \rangle \text{COCH} = \text{CHCO} \langle \bigcirc \rangle \text{Br}$, which might have arisen from the expected rearrangement product by loss of the elements of dimethylamine. In the second case, though the quaternary salt was again completely destroyed, no isolable products of degradation whatever were obtained.

The rearrangement (I→II) has been further extended to a type of compound in which the methylene carbon atom to which migration takes place is that of a benzyl group, as in the rearrangement (V→VI) below.

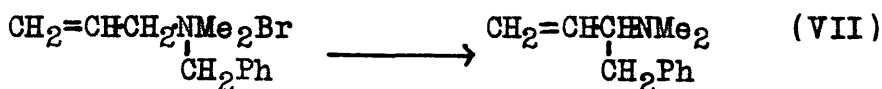


That the functions of the phenacyl and the benzyl radicals in the rearrangement should be thus interchangeable, points to a confirmation of the view that the characteristic of a radical which enables it to lose a hydrogen ion and act as the recipient of the migrating group is the same as that which enables it to function as the migrating radical itself. On the view of the reaction mechanism postulated (vide introductory section) this characteristic is assumed to be some degree of anionic stability.

Attempts to bring about rearrangement in the case of di-p-bromobenzyldimethylammonium bromide met with failure, for, though the quaternary salt was completely destroyed under the conditions used, no isolable products of degradation were obtained. Better results attended the rearrangement of phenyldibenzylmethylammonium iodide (vide infra) and of benzyldimethylallylammonium bromide, both of which may be regarded as potential analogues of (V). The latter case was suggested by the observation of Dunn and Stevens⁴ that the allyl radical can replace CH₂Ar in the reaction (I→II), thus -



Instead, however, of the allyl radical wandering to the benzyl group in the rearrangement of benzyl dimethylallylammonium bromide, the migration takes place wholly in the opposite direction -



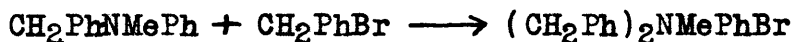
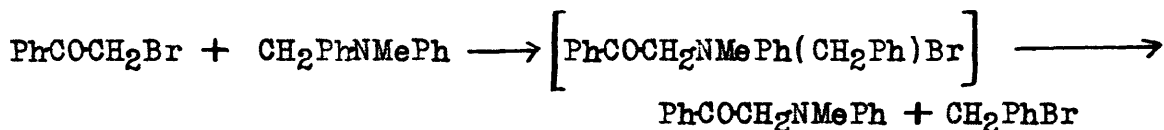
In this connection, it would be of interest to compare the relative velocities of rearrangement of phenacylbenzyl dimethylammonium iodide and of phenacyl dimethylallylammonium iodide, but the author has been advised by Mr. Dunn that the latter salt is not tractable to the velocity technique elaborated in Section IC of this thesis.

The change (V→VI) and its analogues require far more drastic conditions than have hitherto been used in these investigations. Dibenzyl dimethylammonium chloride (V), on refluxing/

refluxing with methyl-alcoholic sodium methoxide solution or with isopropyl-alcoholic sodium isopropoxide solution, is recovered unchanged. Treatment with methyl-alcoholic sodium methoxide solution at 120-140° results in the salt being totally decomposed into benzyldimethylamine and benzyl methyl ether, according to scheme (B) above. The same result is obtained by refluxing the salt with amyl-alcoholic sodium amyloxide solution. These results are in good agreement with those obtained by Achmatowicz, Perkin, and Robinson⁵ on treatment of benzyl-trimethyl-ammonium chloride and phenylbenzyldimethylammonium chloride with methyl-alcoholic potassium hydroxide solution. Treatment with solid sodium methoxide at 140° results in 50% of the salt being rearranged according to scheme (A), while 50% undergoes decomposition according to (B). When dibenzyldimethylammonium chloride is fused with sodamide (140-150°), the quaternary salt is converted completely into rearrangement product (scheme A). From these results it is concluded that, in those salts in which the hydrogen atom which is to be replaced by the migrating radical has little mobility, as in the case of the hydrogen atom of the methylene carbon atom of a benzyl group, the extraction of that hydrogen atom becomes the primary and determining condition of the rearrangement. This conclusion forms a direct contrast to the experience of Dunn and Stevens⁶, whose observations with more acidic quaternary salts (containing negative substituents in the phenacyl group) suggest that, in these cases, the determining factor in the rearrangement is the instability/

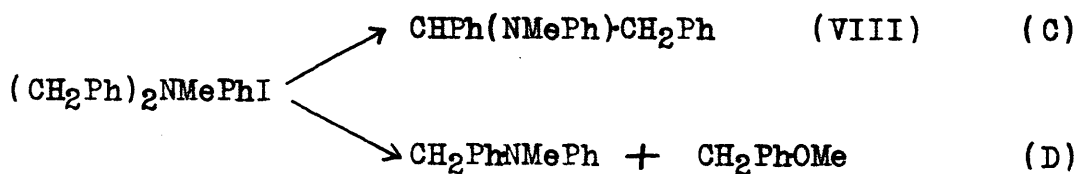
instability of the anionic carbon atom in the neutral ion, $\text{RCOCH}^-\text{N}^+\text{Me}_2\text{CH}_2\text{Ar}$, which is assumed, in the reaction mechanism proposed, to be the initial, intermediate product of the action of the alkali on the original quaternary salt. It has also been observed that the rearrangement product (VI) may be converted into stilbene by further treatment with sodamide. It is suggested that this apparently paradoxical elimination of dimethylamine by a powerfully alkaline reagent which has already effected removal of the elements of hydrogen chloride is to be explained by the fact that the initial and determining stage of the process may be regarded as removal of a hydrogen ion, in the same way as the removal of a hydrogen ion from the original quaternary salt is considered to be the conditioning factor in the rearrangement.

An investigation of the degradation of phenacylphenylbenzylmethylammonium bromide, $\text{PhCOCH}_2\text{NMePh}(\text{CH}_2\text{Ph})\text{Br}$, and of phenyldibenzylmethylammonium iodide, $(\text{CH}_2\text{Ph})_2\text{NMePhI}$, has been attempted with a view to the determination of the possible influence of an aryl radical attached to the nitrogen atom on the course of the rearrangement. Unfortunately, the preparation of the first-mentioned salt proved to be impracticable. According to Wedekind⁷, phenacylphenylbenzylmethylammonium bromide is prepared by the interaction of ω -bromoacetophenone and benzylmethylaniline, but it has now been shown that the product obtained from this reaction is really phenyldibenzylmethylammonium bromide, which is probably produced by a dissociation and combination of the type discovered by Wedekind⁸, according to the following scheme-



Other methods of preparation of the salt were likewise unsuccessful, for ω -methylanilinoacetophenone can not be combined either with benzyl chloride or with benzyl iodide.

Better results attended the investigation of phenyldibenzylmethylammonium iodide. This salt, on refluxing with methyloalcoholic sodium methoxide solution, is wholly decomposed to give benzylmethylaniline and benzyl methyl ether, according to scheme (D) below, a reaction analogous to the decomposition reaction observed with dibenzyl dimethylammonium chloride (vide supra). Fusion with sodamide, however, results in some 70% of the salt being decomposed to give benzylmethylaniline (compare D), while some 20% undergoes rearrangement according to scheme (C).



The use of sodamide as the alkaline reagent in the degradation is thus seen to favour rearrangement of the salt, as it does also in the case of the analogous salt (V), whereas the replacement of one of the methyl groups attached to the nitrogen atom in (V) by phenyl definitely facilitates the decomposition reaction (scheme D).

The possibility of inducing a change in the direction of the rearrangement (I \rightarrow II) by substitution of the two hydrogen atoms/

atoms of the phenacyl methylene group has been considered. It was thought that the substituted phenacyl radical might, possibly, migrate into the benzyl group. The preparation of such substituted quaternary salts was accordingly undertaken. ω-Methyl-phenacylbenzyl dimethylammonium iodide (IX), on treatment with aqueous alkali, gives the rearrangement product (X) smoothly, but it was found impossible to obtain salts in which one of the hydrogen atoms of the phenacyl methylene group is replaced by phenyl, or both by methyl.



The investigations show that the progressive replacement of the hydrogen atoms of the methylene carbon atom of the phenacyl group leads to a progressive decrease in the ease of quaternary salt formation. Thus, although ω-bromoacetophenone and benzyl-dimethylamine combine readily in the cold, bromopropiophenone and benzyl dimethylamine show no tendency whatever to combine under similar conditions, and the combination of dimethylamino-propiofenone and benzyl chloride is slow. Likewise, though chlorodeoxybenzoïn reacts with dimethylamine, it requires a temperature of 100-110° for the reaction to proceed readily, while with benzyl dimethylamine no reaction whatever occurs. Neither does dimethylaminodeoxybenzoïn combine with benzyl chloride or iodide. Further, bromo*isobutyro*phenone gives only traces of tertiary base with dimethylamine, and no quaternary salt with benzyl dimethylamine.

It is of interest that the interaction of bromopropiophenone and/

and benzyldimethylamine, when carried out in hot, benzene solution, produces not α -methylphenacylbenzyldimethylammonium bromide (IX), but dibenzyldimethylammonium bromide, which, in all probability, arises in a similar manner to the formation of phenyldibenzylmethylammonium bromide from ω -bromoacetophenone and benzylmethylaniline (vide supra).

CONSTITUTION OF THE REARRANGEMENT PRODUCTS. To confirm the constitution of the rearrangement product (IV), the latter was converted to the methosulphate, which, on reduction with zinc dust in absolute alcoholic solution, gave diphenacyl, $\text{PhCOCH}_2\text{CH}_2\text{COPh}$, identical with an authentic, synthetic specimen. The methosulphates of the rearrangement products (VI) and (VIII), on treatment with alkali, yielded stilbene, thus confirming the structures assigned to those products. The structure of substance (X) was confirmed by the fact that its methosulphate, on treatment with alkali, yielded α -benzylidenepropiophenone, identical with an authentic, synthetic specimen. The methosulphate of substance (VII), on treatment with alkali, yielded α -phenylbutadiene, showing that the structure to be assigned to the rearrangement product was either



Synthetic experiments were carried out to decide upon the appropriate structure. The interaction of benzylmagnesium chloride and α -dimethylaminovinylacetonitrile, $\text{CH}_2\text{CHCH}(\text{NMe}_2)\text{CN}$ (compare Stevens, Cowan and MacKinnon⁹) was expected to yield substance/

substance (a), but the required nitrile could not be obtained, for the interaction of acrolein, dimethylamine and hydrogen cyanide gives rise, not to the unsaturated compound, but to the diamino-nitrile, $\text{CH}_2(\text{NMe}_2)\text{-CH}_2\text{CH}_2(\text{NMe}_2)\text{-CN}$, (compare Bruylants¹⁰). The attempted synthesis of (b) by the action of allylmagnesium bromide on α -dimethylaminophenylacetonitrile was unsuccessful, as the reaction did not proceed smoothly. Catalytic reduction of the rearrangement product, however, gives β -dimethylamino- α -phenylbutane, $\text{CH}_3\text{CH}_2\text{CH}(\text{NMe}_2)\text{-CH}_2\text{Ph}$, the structure of which was established by its synthesis from ethylmagnesium bromide and α -dimethylamino- β -phenylpropionitrile. This proves the rearrangement product (VII) to have the structure represented by (a).

EXPERIMENTAL

Diphenacyldimethylammonium bromide was prepared from ω -bromoacetophenone (2 mols.) and dimethylamine (1 mol.) in alcohol after Rumpel". After removal of most of the alcohol, the addition of ether precipitated an oil which solidified on standing in the cold. Any phenacyldimethylamine hydrobromide formed was removed by washing with a little cold water. The solid mass was then washed with ether, and crystallised from alcohol-ether in fine needles, m.p. 155 - 156° (Rumpel gives m.p. 156°). On warming the foregoing bromide with aqueous caustic soda solution there resulted ω -dimethylamino- ω -phenacylaceto-phenone which was obtained as a gummy solid which could not be crystallised satisfactorily, but which gave a picrate from methyl alcohol, small, yellow prisms, m.p. 128 - 130° (Found: $C_6H_3O_7N_3$, 44.9. $C_{18}H_{19}O_2N$, $C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 44.9%.)

Constitution of ω -Dimethylamino- ω -phenacylaceto-phenone.- By treatment of ω -bromoacetophenone with alcoholic sodium ethoxide solution Fritz¹² obtained a so-called "bromodiphenacyl", m.p. 161-162°, which on reduction in absolute alcoholic solution with zinc dust gave diphenacyl, m.p. 143-145°, of well established constitution. ω -Dimethylamino- ω -phenacylaceto-phenone, on refluxing in benzene solution with an equivalent quantity of methyl sulphate, yielded an oily methosulphate which on reduction with zinc dust and dilute sulphuric acid yielded diphenacyl, m.p. and mixed m.p. 143-145°. An attempt to synthesise ω -dimethylamino- ω -phenacylaceto-phenone by the interaction of "bromo-diphenacyl" and dimethylamine in alcohol yielded a picrate which/

which was obtained from benzene in small yellow prisms, m.p. 184-186° (Found: $C_6H_3O_7N_3$, 45.5). That this picrate is not identical with ω -dimethylamino- ω -phenacylacetophenone picrate is probably to be accounted for by the fact that several "bromo-diphenaclys" are known, whose structures are a matter of doubt.

Di-p-bromophenacyldimethylammonium bromide. - The interaction of p-bromophenacyl bromide (2 mols.) and dimethylamine (1 mol.) in alcohol resulted in the almost instantaneous separation of colourless crystals which quickly filled the liquid. Unchanged p-bromophenacyl bromide was removed with boiling benzene and the residue, on crystallisation from alcohol, was obtained as colourless prisms, m.p. 215° (decomp.) (Found: ionisable Br, 15.0. $C_{18}H_{18}O_2NBr_2.Br'$ requires Br', 15.4%). On gently warming the foregoing bromide with methyl alcoholic sodium methoxide solution there resulted a black-red solution from which dimethylamine was evolved. The solution was diluted with water and extracted with ether. The ether extract on treatment with dilute hydrochloric acid deposited a small amount of an orange-red solid which was comparatively insoluble in alcohol and acetone, and melted at 170-171° (decomp.). The hydrochloric acid layer on making alkaline with ammonia yielded a small amount of a cream-coloured solid, m.p. 253-255°, which was completely insoluble in absolute alcohol, and did not redissolve in dilute acid. The residual ether layer yielded a black-red tar which could not be crystallised. No unchanged quaternary salt was obtained. The solid products isolated represented only a minute fraction/

fraction of the original quaternary salt used. Neither of these solid products obtained was identical with di-4-bromobenzoyl-ethylene which is yellow in colour and has m.p. 188° (compare Conant and Lutz¹⁴). This might have been formed if the expected rearrangement product had lost the elements of dimethylamine.

Diacetyldimethylammonium chloride was prepared from chloroacetone (2 mols.) and dimethylamine (1 mol.) in alcohol. It was obtained as a brownish, mobile oil which could not be crystallised. The picrate was obtained from methyl alcohol in yellow, prismatic needles, m.p. $198-199^{\circ}$ (decomp.). (Found : $C_6H_2O_7N'_3$, 59.4. $C_8H_{16}O_2N.C_6H_2O_7N_3$ requires $C_6H_2O_7N'_3$, 59.1%.) Treatment of the quaternary chloride with aqueous caustic soda solution or with methyl alcoholic sodium methoxide solution resulted in complete destruction of the quaternary salt, but no isolable products were obtained from the degradation.

Dibenzoyldimethylammonium chloride, prepared from benzyl-dimethylamine and benzyl chloride in cold benzene, separated as an oil which slowly solidified, and crystallised from acetone in stout prisms, m.p. $93-95^{\circ}$ (Found: Cl, 13.7. $C_{16}H_{20}NCl$ requires Cl, 13.6%). The iodide crystallised from alcohol in stout prisms, m.p. 192° (Found: I, 35.9. $C_{16}H_{20}NI$ requires I, 36.0%). The picrate, glistening yellow leaflets from methyl alcohol, melted at $148-150^{\circ}$ (Goss, Ingold, and Wilson¹⁵ give m.p. 146°). (Found: $C_6H_2O_7N'_3$, 50.4. $C_{16}H_{20}N.C_6H_2O_7N_3$ requires $C_6H_2O_7N'_3$, 50.2%). Refluxing the quaternary salt for several hours with methyl alcoholic sodium methoxide solution and with isopropyl alcoholic/

alcoholic sodium isopropoxide solution resulted in its being recovered unchanged practically quantitatively. Refluxing the quaternary salt with amyl alcoholic sodium amyloxide solution for six hours gave a quantitative yield of benzyldimethylamine, isolated as picrate, m.p. and mixed m.p. 93-95°. The quaternary chloride was heated at 120-140° for two hours with methyl alcoholic sodium methoxide solution, and the resultant solution was diluted with water and extracted with ether. The ether extract yielded benzyldimethylamine, isolated as picrate, to dilute hydrochloric acid, and from the residual ether layer there was obtained benzyl methyl ether, b.p. 169-170°. The amounts of these products accounted satisfactorily for the original quaternary salt used. With solid sodium methoxide (not alcohol - free) at 140° there resulted on working up as just described, benzyl methyl ether and a mixture of bases which were separated by crystallisation of the picrates from methyl alcohol. There was deposited first $\alpha\beta$ -diphenylethyldimethylamine picrate, yellow leaflets from methyl alcohol, which even after repeated recrystallisation softened markedly about 130° and finally melted at 156-157° (compare Stevens, Cowan, and MacKinnon⁹). The mother liquors deposited benzyldimethylamine picrate, m.p. and mixed m.p. 93-95°. A very small amount of unchanged quaternary salt was isolated as picrate, m.p. and mixed m.p. 148-150°. The rearrangement product isolated corresponded to about 50% of the quaternary salt destroyed, as did the benzyldimethylamine. On heating the quaternary salt with/

with sodamide until fusion occurred (140-150°) there was isolated only $\alpha\beta$ -diphenylethyldimethylamine as picrate, no benzyldimethylamine being detected. From the residual ether extract a small amount of stilbene, m.p. and mixed m.p. 123-125°, was obtained. The amount of rearrangement product isolated accounted satisfactorily for the quaternary salt used.

Constitution of $\alpha\beta$ -Diphenylethyldimethylamine. - Equimolecular quantities of the base and methyl sulphate were refluxed in benzene solution for an hour. The oily quaternary salt obtained, on boiling for a short time with caustic soda solution, gave stilbene, m.p. and mixed m.p. 123-125°. Treatment of $\alpha\beta$ -diphenylethyldimethylamine with sodamide at 200° also gave stilbene.

Di-p-bromobenzyldimethylammonium bromide, from 2 mols. of p-bromophenacyl bromide, prepared as described by Stevens, Snedden, Stiller, and Thomson³, and 1 mol. of dimethylamine in alcohol. After distillation of most of the alcohol, the addition of ether precipitated an oil which solidified on standing and crystallised from alcohol - ether in long, prismatic needles, softening at about 170° and finally melting at 193-195° (Found: ionisable Br, 17.0. $C_{16}H_{18}NBr_2 \cdot Br'$ requires Br', 17.2%). The foregoing bromide on fusion with sodamide at 160-170° was completely destroyed, but no products of degradation could be isolated. A mere trace of basic material was obtained, which, however, was insufficient to permit of isolation in a state of purity.

The Supposed Phenacylphenylbenzylmethylammonium bromide. - Benzylmethylaniline was prepared as described by Wedekind¹⁶, and/

and was obtained as a colourless oil, b.p. 205-212°/60 mm. When treated with ω -bromoacetophenone as described by Wedekind⁷ there resulted, from alcohol-ether, fine colourless needles, m.p. 144-146°. (Wedekind gives decomposition point, 149-150°). (Found: Br, 21.9. $C_{22}H_{22}ONBr$ requires Br, 20.2%. Phenyldibenzylmethylammonium bromide, $C_{21}H_{22}NBr$, requires Br, 21.7%). Conversion to the iodide gave colourless prisms from alcohol-ether, m.p. 132-134°. Mixed m.p. with phenyldibenzylmethylammonium iodide (vide infra), 132-134°. Thus Wedekind's preparation gives, not phenacylphenylbenzylmethylammonium bromide, but phenyldibenzylmethylammonium bromide.

Methylanilinoacetophenone was prepared by gently warming ω -bromoacetophenone (1 mol.) with monomethylaniline (2 mols.) (compare Staedel and Siepermann¹⁷). The methylaniline hydrobromide formed was removed by hot water and the methylanilinoacetophenone crystallised from alcohol, from which it was obtained in glistening plates, m.p. 120° (decomp.). Methylanilinoacetophenone could not be combined with benzyl chloride or with benzyl iodide.

Phenyldibenzylmethylammonium iodide. - Benzylmethylaniline could not be combined with benzyl chloride, and its interaction with benzyl iodide required a much longer period than was used by Jones¹⁸. Phenyldibenzylmethylammonium iodide crystallised from alcohol in prismatic needles, m.p. 133-135° (Jones gives m.p. 134-135°). On refluxing the quaternary iodide with methylalcoholic/

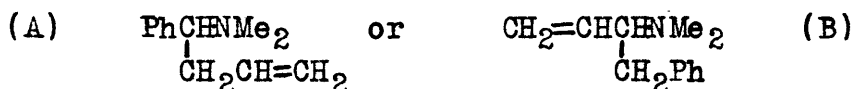
alcoholic sodium methoxide solution for an hour, there was obtained benzylmethylaniline, identified as picrate, m.p. and mixed m.p. 105-107°, and benzyl methyl ether, b.p. 169-170°, the amounts of these products accounting satisfactorily for the quaternary salt used. Benzylmethylaniline picrate, obtained in the first instance from ether, crystallised from methyl alcohol in stout, yellow prisms, m.p. 105-107° (Found: C₆H₃O₇N₃, 54.2. C₁₄H₁₅N, C₆H₃O₇N₃ requires C₆H₃O₇N₃, 53.8%). The quaternary salt was heated to 160-170° with two equivalents of sodamide. The reaction mass was treated with water and extracted with ether. Treatment of the ether extract with dilute hydrochloric acid precipitated αβ-diphenylethylmethylaniline hydrochloride which crystallised from alcohol or from water in fine, glistening, prismatic needles, m.p. 230-232° (Found: HCl, 11.3. C₂₁H₂₁N.HCl requires HCl, 11.3%). Treatment of the hydrochloride with caustic soda solution liberated the free base, αβ-diphenylethylmethylaniline, which crystallised from methyl alcohol in glistening leaflets, m.p. 92-93° (Found: N, 5.1. C₂₁H₂₁N requires N, 4.9%). The hydrochloric acid extract, on making alkaline with ammonia, yielded benzylmethylaniline, identified as picrate, m.p. and mixed m.p. 105-107°. The residual ether layer yielded a very small amount of a viscous oil which had the odour of higher hydrocarbons. No unchanged quaternary salt was isolated. The rearrangement product obtained corresponded to some 20%, and the benzylmethylaniline to some 70%, of the initial quaternary salt used.

Constitution of $\alpha\beta$ -Diphenylethylmethylaniline. - Equimolecular quantities of the base and methyl sulphate were refluxed for some time in benzene solution. The methosulphate separated in colourless crystals which were dissolved in methyl alcohol and boiled with caustic soda solution, the methyl alcohol being used to prevent the methosulphate being precipitated unchanged on the addition of the caustic soda. The reaction mixture was poured into water and extracted with ether. The ether extract yielded stilbene, m.p. and mixed m.p. 123-125°.

Benzyltrimethylammonium bromide, was prepared from allyl bromide and benzyltrimethylamine in cold benzene, and separated as a viscous oil which slowly solidified. The crystals were freed from adhering oil by washing with acetone, and obtained as stout prisms, m.p. 98-100° (Found: Br, 31.2. $C_{12}H_{18}NBr$ requires Br, 31.3%). Attempted crystallisation from alcohol - ether and from acetone resulted in an oil being obtained. The salt is extremely deliquescent. The picrate, clusters of short, yellow prisms from acetone, melted at 108-110° (Found: $C_6H_2O_7N'_3$, 56.6. $C_{12}H_{18}N$. $C_6H_2O_7N_3$ requires $C_6H_2O_7N'_3$, 56.4%). On heating the quaternary bromide with sodamide a violent reaction set in at about 80° and a most pungent odour was apparent. The reaction mixture was treated with water and extracted with ether. The ether extract yielded to dilute hydrochloric acid solution a basic oil which was obtained as an almost colourless liquid, b.p. 121-124°/45mm. The residual ether solution yielded a small amount of a balsam-like compound. The rearrangement product gave a picrate which crystallised/

crystallised from aqueous methyl alcohol in yellow, prismatic needles, m.p. 147-149° (Found: C₆H₃O₇N₃, 57.0. C₁₂H₁₇N, C₆H₃O₇N₃ requires C₆H₃O₇N₃, 56.7%). No unchanged quaternary salt was obtained. The rearrangement product isolated corresponded to some 60% of the original quaternary salt used.

Constitution of the Rearrangement Product. - Analysis of the picrate of the rearrangement product (vide supra) suggested that the structure of the base was either



which fact was confirmed thus. The base was refluxed in benzene solution with an equimolecular quantity of methyl sulphate and the resultant methosulphate boiled for a short time with caustic soda solution. The oil obtained was extracted with chloroform, and the dried extract treated with a solution of bromine in chloroform (1:4) until a brown colouration persisted. The chloroform was removed by aspirating the warm solution, and the residue, on crystallisation from ligroin, yielded pale-yellow prisms of phenylbutadiene dibromide, m.p. 94° (compare the observations of Riiber¹⁹).

Attempted synthesis of (A) by the action of allylmagnesium bromide on α -dimethylaminophenylacetonitrile, prepared as described by Stevens, Cowan and MacKinnon⁹, was unsuccessful, as the reaction did not proceed smoothly. Synthesis of (B) by the action of benzylmagnesium chloride on α -dimethylaminovinylacetonitrile proved to be impracticable, for the interaction of acrolein/

acrolein, dimethylamine, potassium cyanide and acetic acid gave $\alpha\gamma$ -bisdimethylaminobutyronitrile, b.p. $90^{\circ}/11$ mm. (compare Bruylants^{'0}). The interaction of benzylmagnesium chloride and this nitrile gave $\beta\delta$ -bisdimethylamino- α -phenylbutane, $\text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}(\text{NMe}_2)\text{-CH}_2\text{Ph}$, which was obtained as a pale-yellow liquid, b.p. $150\text{-}160^{\circ}/17$ mm. The picrate crystallised from acetone in minute, yellow prisms, m.p. $193\text{-}195^{\circ}$ (decomp.) (Found: $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$, 67.2. $\text{C}_{14}\text{H}_{24}\text{N}_2, 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$, 67.6%).

The rearrangement product was reduced in acetic acid solution by shaking with hydrogen under atmospheric pressure, using activated palladium on charcoal as catalyst. Neither the picrate nor the hydrochloride of the oil so obtained could be crystallised, but the hydrobromide was obtained from alcohol-ether in prismatic needles, m.p. $161\text{-}163^{\circ}$ (Found: HBr, 31.4. $\text{C}_{12}\text{H}_{19}\text{N.HBr}$ requires HBr, 31.4%). Mixed m.p. with α -dimethylamino- α -phenylbutane hydrobromide (vide infra) gave a large depression. Mixed m.p. with β -dimethylamino- α -phenylbutane hydrobromide (vide infra), $161\text{-}163^{\circ}$. The p-bromophenacylobromide was also identical (m.p. and mixed m.p.) with the p-bromophenacylobromide of β -dimethylamino- α -phenylbutane (vide infra). Thus the reduced compound is β -dimethylamino- α -phenylbutane and the original degradation product β -dimethylamino- α -phenyl- Δ^{γ} -butylene (B).

α -Dimethylamino- α -phenylbutane. - The interaction of n-propylmagnesium bromide and α -dimethylaminophenylacetonitrile yielded an almost colourless liquid, b.p. $130\text{-}132^{\circ}/40\text{mm}$. The same compound resulted from the interaction of phenylmagnesium bromide/

bromide and α -dimethylaminovaleronitrile. The latter was obtained from butyraldehyde, dimethylamine, potassium cyanide, and acetic acid in the usual way as a colourless liquid, b.p. 172-175° (Henry²⁰ gives b.p. 175-176°). α -Dimethylamino- α -phenylbutane picrate crystallised from methyl alcohol in glistening, yellow leaflets, m.p. 139-140° (Found: $C_6H_3O_7N_3$, 56.0. $C_{12}H_{19}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 56.4%). The hydrobromide, obtained in the first place from ether, crystallised from alcohol-ether in fine, glistening needles, m.p. 162-163° (Found: HBr, 31.1. $C_{12}H_{19}N.HBr$ requires HBr, 31.4%). The p-bromophenacylobromide, obtained by refluxing the components for a short time in benzene solution, crystallised in minute prisms, m.p. 208-210° (decomp.) (Found: ionisable Br, 17.4. $C_{20}H_{25}ONBr.Br$ requires ionisable Br, 17.6%).

β -Dimethylamino- α -phenylbutane. - α -Dimethylamino- β -phenylpropionitrile, prepared as described by Stevens, Cowan, and MacKinnon⁹, gave with ethylmagnesium iodide an almost colourless liquid, b.p. 133- 138°/36mm. The picrate and the hydrochloride could not be obtained crystalline. β -Dimethylamino- α -phenylbutane hydrobromide, obtained in the first place from ether, crystallised from alcohol-ether in prismatic needles, m.p. 161-163° (Found: HBr, 31.3. $C_{12}H_{19}N.HBr$ requires HBr, 31.4%). The p-bromophenacylobromide, obtained by refluxing the components for a short time in benzene solution, crystallised in minute prisms, m.p. 188-190° (decomp.) (Found: ionisable Br, 17.4. $C_{20}H_{25}ONBr.Br$ requires ionisable Br, 17.6%).

Bromopropiophenone. - The bromination of propiophenone was carried out in glacial acetic acid solution as described by Schmiät²¹. The colourless oil obtained was dried with calcium chloride and used without further treatment owing to its extreme lachrymatory power. Bromopropiophenone did not combine with benzyldimethylamine in cold benzene. Refluxing for several hours produced an oily quaternary salt which was converted to the iodide, and crystallised from alcohol in stout prisms, m.p. 192°. This iodide was identical (m.p. and mixed m.p.) with dibenzyl-dimethylammonium iodide previously described.

α-Dimethylaminopropiophenone. - Bromopropiophenone (1 mol.) and dimethylamine (2-3 mols.) were heated in alcoholic solution for two hours at 100-110°. After distillation of most of the solvent the residue was poured into water and extracted with ether.

α-Dimethylaminopropiophenone picrate was isolated in the first place from ether and crystallised from methyl alcohol in glistening, yellow, prismatic needles, m.p. 128-130° (Found: $C_6H_3O_7N_3$, 56.7. $C_{11}H_{15}ON$, $C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 56.4%).

α-Methylphenacylbenzyldimethylammonium iodide. - The interaction of α-dimethylaminopropiophenone and benzyl chloride in cold benzene over a lengthy period resulted in the formation of an oil which was converted to the iodide, and crystallised from alcohol-ether in minute prisms and from water in clusters of rather irregular, glistening prisms, m.p. 160-161° (decomp.) (Found: I, 32.7. $C_{18}H_{22}ONI$ requires I, 32.2%). Treatment of the foregoing iodide with hot, aqueous caustic soda solution produced/

produced a dark oil. The ether extract yielded an almost colourless oil to dilute hydrochloric acid. α -Dimethylamino- α -benzylpropiophenone picrate crystallised from aqueous methyl alcohol in short, stout, yellow prisms, m.p. 161-162° (Found: $C_6H_3O_7N_3$, 46.0. $C_{18}H_{21}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 46.2%).

Constitution of α -Dimethylamino- α -benzylpropiophenone. -

The base was refluxed in benzene solution for several hours with an equivalent quantity of methyl sulphate. On cooling, the methosulphate separated in fine needles and was heated to boiling with aqueous caustic soda solution. The oil which separated was removed by ether and gave a phenylhydrazone as fine, yellow needles which melted at 127-128° (softening at 115°) alone or mixed with an authentic specimen of benzylidenepropiophenone phenylhydrazone (Abell²² gives m.p. 127-128°, softening at 115°).

Chlorodeoxybenzoin was prepared by treatment of benzoin in chloroform solution with an equimolecular quantity of thionyl chloride (compare the method of Schroeter²³). The product was freed from any unchanged benzoin by repeated crystallisation from alcohol, from which it was obtained in glistening needles, m.p. 66-68°. Chlorodeoxybenzoin did not combine with benzyl-dimethylamine in benzene solution even on prolonged refluxing. Treatment of chlorodeoxybenzoin with 2 - 3 mols. of dimethylamine in alcohol at 100-110° gave α -dimethylaminodeoxybenzoin as a yellow, viscous oil which, after standing for a considerable time in the cold, solidified to stout, prismatic crystals which, after/

after washing with ether to remove traces of oil, melted at 59-61°. Attempted crystallisation from methyl alcohol and from acetone gave only an oil. (Found: N, 5.95. $C_{16}H_{17}ON$ requires N, 5.86%.) The hydrochloride, which was obtained in the first place from ether, crystallised from alcohol-ether in prismatic needles, m.p. 222-225° (decomp.) (Found: HCl, 13.5. $C_{16}H_{17}ON.HCl$ requires HCl, 13.2%). α -Dimethylaminodeoxybenzoin did not combine with benzyl chloride or with benzyl iodide in benzene solution in the cold or on prolonged refluxing, nor did the base combine when dissolved in undiluted benzyl chloride.

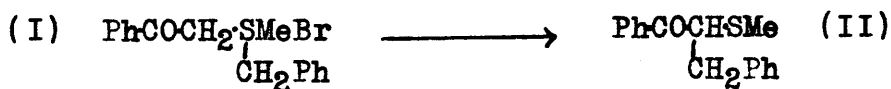
α -Dimethylaminoisobutyrophenone. - Isobutyrophenone was obtained by the action of benzonitrile on isopropylmagnesium chloride in ether solution, or alternatively, by heating propiophenone, methyl iodide, and powdered potassium hydroxide to 120-140° for eight hours as described by Nef²⁴. It formed an almost colourless liquid, b.p. 217-218°. By refluxing with bromine in acetic acid solution there was obtained α -bromo-isobutyrophenone which was isolated as a yellow liquid, b.p. 136-138°/15mm. (Collet²⁵ gives b.p. 146-148°/30mm.). By treatment of α -bromo-isobutyrophenone with dimethylamine in alcohol at 100-110°, only a very small amount of basic material was obtained as a yellow oil, most of the α -bromo-isobutyrophenone being recovered unchanged. α -Dimethylaminoisobutyrophenone picrate crystallised from methyl alcohol in glistening, yellow prisms, m.p. 153-155° (Found: $C_6H_3O_7N_3$, 55.0. $C_{12}H_{17}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 54.5%). The amount of base obtained/

obtained was sufficient only for identification purposes, and was quite useless for further work. With dimethylamine in alcohol at 140-160° for six hours, the bromide gave only the same amount of basic product which, in this case, was very impure. α -Bromoisobutyrophenone, on refluxing with benzyldimethylamine, did not combine.

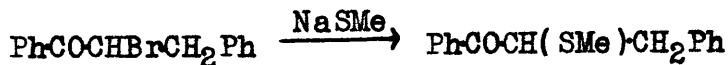
B - MOLECULAR REARRANGEMENT IN RELATED SULPHUR COMPOUNDS

The mechanism of the rearrangement (I → II, introductory section) postulated by Stevens (vide introductory section) involves the fulfilment of the following, necessary conditions before rearrangement can occur : (1) the presence of a reactive methylene group and a group of some anionic stability in the proper relative position and (2) the presence in a suitable position of some grouping which can combine with the liberated anion before it can escape into the bulk of the reaction mixture. On this view, then, the presence of a quaternary nitrogen atom is not considered an essential feature of the rearrangement, and the nitrogen atom should be capable of replacement by other atoms or groups without prevention of the migration.

In order to confirm this view the investigation of certain, related sulphur compounds has been undertaken. In the first instance, phenacylbenzylmethylsulphonium bromide (I), analogous to phenacylbenzyl dimethylammonium bromide, has been prepared from ω-bromoacetophenone and benzyl methyl sulphide. On refluxing this salt with methyl-alcoholic sodium methoxide solution there results the rearrangement product (II) in good yield.



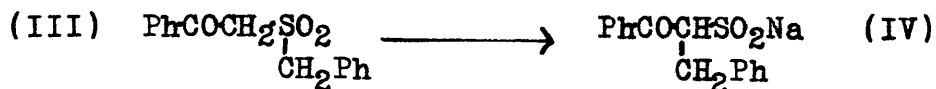
An attempt to synthesise product (II) by the action of sodium methyl mercaptide on ω-bromo-ω-benzylacetophenone, thus -



resulted/

resulted, not in the desired product, but in the replacement of the bromine atom by hydrogen to give benzylacetophenone. This result is rather surprising in view of the fact that Wahl²⁶ readily obtained phenacyl benzyl sulphide from phenacyl bromide and sodium benzyl mercaptide. The structure of product (II) was confirmed, however, by its conversion to the methosulphate, which was then reduced with zinc dust and dilute sulphuric acid to give benzylacetophenone, identical with an authentic, synthetical specimen.

The observations of several investigators point to the fact that the positively charged sulphur atom of a sulphone group behaves in several respects like an "-onium" atom. Particular mention may be made of the investigations of Fenton and Ingold²⁷, from which they conclude that the Hofmann degradation of quaternary ammonium bases finds a parallel in the "olefinic" decomposition of sulphones by alkali. This fact suggested that a sulphone group might replace the quaternary ammonium system in the rearrangement under investigation without prevention of the migration. Accordingly, phenacyl benzyl sulphone (III) was prepared, but, on refluxing with methyl alcoholic sodium methoxide solution, it was recovered unchanged. With methyl alcoholic sodium methoxide solution under more violent conditions (at 120-140^o), phenacyl benzyl sulphone was hydrolysed to give benzyl methyl sulphone and benzoic acid, but no trace of the expected rearrangement product (IV), or of its possible decomposition product, benzylacetophenone, could be detected.



In order to obtain alkaline conditions without the possibility of hydrolysis, the sulphone was heated with a strong tertiary base (benzyl dimethylamine) at 190°, but the only isolable product of the reaction was some unchanged phenacyl benzyl sulphone. Fusion with sodamide likewise failed to bring about any rearrangement, the sulphone being again recovered unchanged.

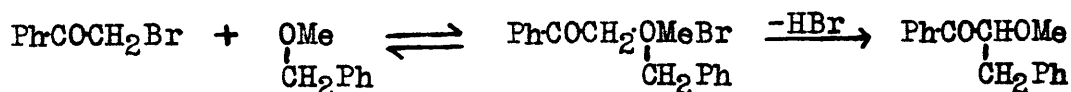
It is a well-known fact that the sulphonyl group, like carbonyl, confers reactivity upon an adjacent methylene group. Since the presence of such a reactive methylene group is considered a necessary condition of the rearrangement, it was hoped to prepare substance (V) with a view to its rearrangement to give (VI).



A comparison of the conditions necessary to effect this migration with those bringing about the rearrangement of phenacylbenzyl dimethylammonium bromide would have been of interest. Unfortunately, however, it was found impossible to obtain the salt (V), for bromomethyl phenyl sulphone could not be induced to combine with benzyl dimethylamine under any conditions. This inertness of the halogen atom in bromomethyl phenyl sulphone was not anticipated, but it was further exemplified when it was found that the bromo-sulphone would not react on refluxing with undiluted piperidine.

The periodic relationship of the elements, sulphur and oxygen, /

oxygen, suggested the possibility of attempting to bring about rearrangement in the case in which the sulphur atom in phenacylbenzylmethylsulphonium bromide (I) is replaced by oxygen. To this end, ω -bromoacetophenone and benzyl methyl ether were heated together, in a non-hydroxylic solvent, in presence of calcium carbonate (to remove the hydrogen bromide liberated), but no evidence of reaction according to the following scheme could be obtained:-



EXPERIMENTAL

Benzyl methyl sulphide. - Benzyl chloride was refluxed with an alcoholic solution of potassium hydrogen sulphide (3-4 mols.) on the water-bath for four hours. To the reaction mixture was added a 20% excess of caustic soda solution, and then, gradually, a slight excess of methyl sulphate. The solution was refluxed for three hours, and the product isolated by dilution with water and extraction with ether. Benzyl methyl sulphide was obtained as a water-clear liquid of powerful, horse-radish odour, b.p. 206-210° / 751mm. Obermeyer²⁸ gives b.p. 195-198°. On account of this discrepancy in boiling point, the identity of the benzyl methyl sulphide was confirmed by conversion to the sulphone by means of hydrogen peroxide in glacial acetic acid (compare Gilman and Beaber²⁹). Benzyl methyl sulphone was obtained in large plates, m.p. 125-127° (Fromm and de Seixas Palma³⁰ give m.p. 127°).

Phenacylbenzylmethylsulphonium bromide, prepared from benzyl methyl sulphide and ω -bromoacetophenone in cold benzene, separated over a long period of time in masses of fine, long needles, m.p. 113-115° (decomp.) (Found: Br, 23.6. $C_{16}H_{17}OSBr$ requires Br, 23.7%). The picrate, masses of fine, yellow, prismatic needles from methyl alcohol, melted at 115-117° (Found: $C_6H_2O_7N_3$, 47.2. $C_{16}H_{17}OS.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3$, 47.0%).

ω -Benzyl- ω -methylthiolacetophenone was obtained by heating the foregoing bromide with an excess of methyl alcoholic sodium methoxide solution for three hours. The product was isolated by dilution/

dilution with water and extraction with ether. Evaporation of the ether extract gave an oil which solidified on standing and crystallised from aqueous methyl alcohol in glistening laminae, m.p. 55-56° (Found: S, 12.2. C₁₆H₁₆OS requires S, 12.5%). An attempt to synthesise this compound from ω-bromo-ω-benzylacetophenone and sodium methyl mercaptide in alcoholic solution led to the formation of benzylacetophenone, m.p. and mixed m.p. 70-72°. To establish the constitution of the rearrangement product, equimolecular quantities of the latter and methyl sulphate were refluxed for six hours in benzene solution. The oily sulphonium salt was reduced with zinc dust and dilute sulphuric acid, and the solution, on extraction with ether, yielded benzylacetophenone, m.p. and mixed m.p. 70-72°; semi-carbazone, m.p. and mixed m.p. 141-143°.

Phenacyl benzyl sulphone. - Phenacyl benzyl sulphide was prepared from sodium benzyl mercaptide and ω-bromoacetophenone in alcoholic solution after Wahl²⁶. The product separated on standing and was washed with water to remove sodium bromide. It was obtained from alcohol in irregular, glistening plates, m.p. 87-89°. Wahl describes needles, m.p. 89°. Phenacyl benzyl sulphone was obtained from the sulphide by heating the latter in glacial acetic acid on the water-bath for three hours with a 50% excess of 30% hydrogen peroxide solution. The sulphone separated on pouring into water and was crystallised from aqueous methyl alcohol in glistening leaflets, m.p. 111-113°, as found by Wahl, who/

who used potassium permanganate as oxidising agent. By treatment of phenacyl benzyl sulphide with hydrogen peroxide in the cold, Wahl obtained the sulphoxide.

Attempted Degradation of Phenacyl benzyl sulphone. - Phenacyl benzyl sulphone was refluxed with an excess of methyl alcoholic sodium methoxide solution for three hours, but the only product isolated was unchanged phenacyl benzyl sulphone which was obtained in almost quantitative yield. It is interesting to compare this result with that of Wahl, who, by refluxing phenacyl benzyl sulphone with a 20% alcoholic potassium hydroxide solution for several hours, obtained benzyl methyl sulphone and benzoic acid. On heating phenacyl benzyl sulphone with methyl alcoholic sodium methoxide solution for five hours at 120-140°, there were obtained from the methyl alcohol solution long, prismatic needles which were shown to be benzyl methyl sulphone, m.p. and mixed m.p. 125-127°. The filtrate, after dilution with water, was extracted with ether. The ether extract yielded benzoic acid, m.p. and mixed m.p. 119-121°, to sodium bicarbonate solution, but no unchanged phenacyl benzyl sulphone to caustic soda solution. No trace of any rearrangement product was obtained, benzylacetophenone, in particular, being looked for. After phenacyl benzyl sulphone had been refluxed with benzyldimethylamine for three hours, the only isolable product was some unchanged starting material. Fusion of the sulphone with sodamide (170°) resulted in its being recovered unchanged practically quantitatively.

Bromomethyl phenyl sulphone. - It was attempted to prepare this compound as described by Otto ³¹ by bromination in the cold of phenylsulphonacetic acid, obtained from sodium benzenesulphinate and chloroacetic acid. It was found, however, that only the di-bromo- compound was obtained and not a mixture of the mono- and di-substituted compounds as stated by Otto. An attempt to convert the dibromomethyl phenyl sulphone into the monobromo- compound by refluxing the former for seven days with alcoholic sodium ethoxide solution (2 mols.), as described for the dichloro- compound by Otto and Engelhardt ³², resulted in a 33% yield of the monobromomethyl phenyl sulphone, m.p. 48-50° (Otto gives m.p. 46-48°). Bromomethyl phenyl sulphone was also obtained by heating methylene bromide and sodium benzenesulphinate in alcoholic solution as described by Otto. The latter gives no experimental details, but it was found that no reaction occurred on refluxing for four hours, whereas on heating for six hours at 120-140°, a moderate yield of bromomethyl phenyl sulphone was obtained.

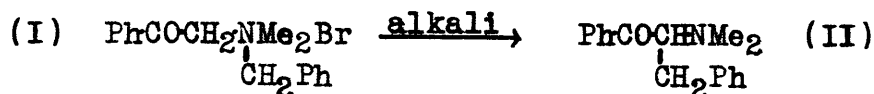
It was found impossible to combine bromomethyl phenyl sulphone with benzyldimethylamine under any conditions whatsoever, nor would it react on refluxing with undiluted piperidine for two hours.

Action of Bromoacetophenone on Benzyl methyl ether. - Equivalent quantities of ω -bromoacetophenone and benzyl methyl ether were refluxed, after the addition of a moderate excess of calcium carbonate, first in dry toluene for five hours and in a later/

later experiment in dry xylene for six hours, but no evidence of rearrangement was obtained, the benzyl methyl ether being recovered unchanged.

C - THE RELATIVE MIGRATORY VELOCITIES OF SUBSTITUTED
BENZYL RADICALS

This investigation is concerned with the effect of substitution in the benzyl group on the velocity of the rearrangement (I → II).



The effect of substitution by Cl, Br, I, NO₂, Me, and OMe in the o-, m-, and p- position has been studied. The ultimate importance of these velocity determinations lies in the fact that, if the mechanism of the reaction postulated by Stevens (vide introductory section) be accepted, they will give an accurate measure of the relative anionic stabilities of radicals for which that stability is relatively low. It is suggested that the good agreement obtained among the results themselves (vide infra) justifies the assumptions made as to the mechanism of the rearrangement, and the values obtained are claimed to represent fairly accurately, at least, a measure of the relative migratory tendencies, in other words, the relative anionic stabilities, of the substituted benzyl radicals investigated. The advantages of the present series of compounds are, firstly, that the reactions proceed smoothly at a moderate temperature and lend themselves to measurement, and, secondly, that the requisite materials are fairly accessible. Further, the reaction products can be fairly completely isolated, and any unexpected complications detected. The fundamental weakness, that the materials are/

are complicated and the true reaction mechanism difficult to establish, applies to every other method; the present series of compounds has the advantage that the results obtained can readily be checked by varying the remaining parts of the molecule, i.e. by using *p*-bromophenacyl instead of phenacyl compounds, for example.

As a necessary preliminary to the investigation of the effect of substitution on the velocity of the rearrangement (I→II), the rearrangement of the unsubstituted compound (I) was investigated in some detail. It was necessary, in particular, to elaborate a suitable technique for the velocity measurements, and to gain experience of the effect of varying conditions upon the course of the reaction. That the rearrangement product (II) is not the only product of the reaction was shown by quantitative isolation of (II) as such and of unaltered quaternary salt (I) as picrate. Under all the conditions employed, some 12-15% of the material was converted into a neutral gum from which no definite compound has been isolated. This by-product is formed much more extensively during the early stages of the reaction than later, but this fact cannot be accounted for by the postulate that the side reaction is bimolecular with respect to the quaternary salt (or the alkali), for the proportion of by-product formed is substantially independent of the concentration of the reactants. In view of this complication, the course of the rearrangement was followed by direct isolation of (II) as such and of (I) as picrate. The quantity k , defined by the equation

$$x = k \int_0^t y \cdot dt \quad ,$$

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 involves the following assumptions: (a) that the main reaction is of the first order with respect to the alkali, and (b) that the side reaction is simultaneous with the rate-determining stage of the main process. This procedure is, however, to be regarded as purely empirical, in view of the lack of evidence as to the nature of the side reaction, but it is claimed to be justified as a method of comparison by the facts that the values of k found during the course of 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 derived from measurements with phenacyl or with *p*-bromophenacyl quaternary salts.

The reaction was investigated in methyl-, ethyl-, *n*-propyl-, and *isopropyl*-alcoholic solutions of the corresponding sodium alkoxides, and the following general observations may be drawn from the results obtained (compare Table I). (1) Good monomolecular constants were obtained for the velocity in each of these solutions. (2) The use of two molecules of alkoxide instead of one produced an appreciable, though not a proportional, increase in velocity, but a third molecule had little further effect. (3) The velocity varied with the medium in the order $\text{MeOH} \ll \text{EtOH} < \text{Pr}^\alpha \text{OH} \ll \text{Pr}^\beta \text{OH}$. The order of these differences would
at/

at first suggest that they were due to a difference in the strength of the alkaline reagent (sodium alkoxide) (compare the observations of Kon and Linstead³³), but this is considered improbable, for, as is noted in observation (2), the reaction velocity was but little dependent on the alkoxide concentration and in no way proportional to it, even in the case of the least effective reagent, sodium methoxide. Further, although salt formation, presumably at the "reactive" methylene group of the phenacyl radical, actually takes place, this process must be rapid and extensive, for the quaternary salt was found to neutralise 0.5-0.75 equivalent of sodium ethoxide on titration with thymolphthalein as indicator. These differences, then, must be attributed to the specific action of the different media, and it has been shown that the reaction is indeed sensitive to change of medium by replacing 60% of the methyl or ethyl alcohol as solvent by toluene, whereupon the velocity was increased 2.7- and 2.3-fold respectively. That the change should be an increase, and greater in the case of the lower alcohol, was to be anticipated. On the other hand, the difference in effectiveness between the two reagents remained more or less unaltered. An effective study of this point was hindered by the difficulty of obtaining media whose inertness towards alkali alkoxides can be relied upon. (4) The by-product was formed principally in the early stages of the reaction, and its quantity which, however, could be determined only roughly, was largely independent of the conditions used, in particular, of the dilution. (5) The quaternary/

quaternary iodide corresponding to (I) is rearranged at the same rate as the bromide, thus indicating that the velocity of the rearrangement is independent of the nature of the anion of the quaternary salt. (6) The temperature coefficient of the reaction has been shown to have the abnormally high value $Q_{10} = 5.70$ for the temperature interval 16.4 - 37.7°.

Table I

Concentration (N)		Coefficients $k \cdot 10^4$ in			
Salt	Alkali	MeOH	EtOH	Pr ⁿ OH	Pr ⁱ OH
0.10	0.10	33.0	99	111	242
0.05	0.05	32.0	106	112	254
0.05	0.10	41.9	107	126	288
0.05	0.15	44.9	-	-	-
0.025	0.05	41.9	-	-	-

Measurements were also carried out in aqueous sodium hydroxide solution. In this case, the reaction proceeded much more slowly than in the alcohols, and the initial velocities were nearly proportional to the alkali concentrations, as well as to those of the quaternary salt. As the reaction proceeded the values of k fell off, but not in such a way as to suggest an essentially "bimolecular" process. It is suggested that the fact that satisfactory first order constants were obtained in the alcohols, but not in water, is to be explained by the neutral ion, $\text{PhCOCH}^+\text{NMe}_2$, which is assumed to be produced by the action of the alkali on the quaternary salt, being little alcoholysed in/

in solution, but largely hydrolysed. Qualitative confirmation of this view was given by titration of the salt with alkali using thymolphthalein as indicator; in ethyl alcohol an indefinite end-point was obtained after addition of 0.50 - 0.75 equivalent of alkali, whereas in water the salt reacted practically neutral.

Effect of Substitution - The measurements, which are summarised in Table II, were carried out in methyl-alcoholic solutions 0.05N with respect to the quaternary salts and 0.1N with respect to sodium methoxide. Two of the salts were studied as iodides instead of bromides, since the latter could not be obtained in a crystalline condition, and in two cases the *p*-bromophenacyl radical was used in place of phenacyl for the same reason. The validity of these expedients has been proved by independent experiments which showed (a) that phenacylbenzyl dimethylammonium bromide and iodide rearrange at the same rate, and (b) that the ratio (but not the absolute values) of the migratory velocities of benzyl, *p*-chlorobenzyl, *m*-bromobenzyl, *p*-bromobenzyl, and *m*-nitrobenzyl is nearly the same, whether they are associated with phenacyl or with *p*-bromophenacyl in the quaternary salts. Owing to the wide range of velocities, it was found necessary to perform several of the measurements at 16.4°, the others were carried out at 37.7°. *p*-Bromophenacylbenzyl dimethylammonium bromide was investigated at both temperatures and gave the temperature coefficient $Q_{10} = 5.61$, compared with 5.70 obtained for the unsubstituted compound (vide supra)/

supra); the two values obtained for the relative migratory velocity of m-nitrobenzyl, which was also studied at both temperatures, (vide Table II) confirm these figures.

TABLE II

Substituent in benzyl group.

	Cl	Br	I	NO ₂	OMe	Me
<u>o</u> -	<u>35.6</u>	<u>47.7</u>	<u>81</u>	<u>1040</u>	† <u>1.91</u>	* <u>15.3</u>
<u>m</u> -	2.44	2.09 †2.10	1.92	+3.80 <u>3.81</u>	0.93	*0.97
<u>p</u> --	2.77 †2.58	2.86 †2.68	3.25	<u>73</u>	0.76	†1.06

* Measured as phenacyldimethylammonium iodide.

† Measured as p-bromophenacyldimethylammonium bromide.

The figure recorded in Table II is in each case the ratio of the speed of migration of the substituted benzyl radical to that of unsubstituted benzyl under the same conditions. The underlined values refer to measurements made at 16.4°, the others to measurements made at 37.7°. The errors of manipulation probably do not exceed ± 2%, but the existence of a side reaction whose nature is obscure introduces an uncertainty which is difficult to compute, and which may be considerably greater than this. The amount of by-product formed is very similar for all the quaternary salts investigated except those containing a nitro-substituted benzyl radical or a p-bromophenacyl radical. The presence of these radicals usually increases the extent of the/

the side reaction, but it has been found that, when the same substituted benzyl radical is investigated in combination both with phenacyl and with p-bromophenacyl in the original quaternary salts, the two values obtained for the relative migratory velocity are in reasonably good agreement.

The following generalities to be noted in Table II are considered worthy of comment.

(1) The order $\text{OMe} < \text{Me} < \text{Hals.} < \text{NO}_2$ holds for all three positions, though the inequality $\underline{m}\text{-OMe} < \underline{m}\text{-Me}$ is not considered as definitely established. This series is of very common occurrence and could be accommodated on most theories dealing with the reactivities of organic molecules in general and on several hypotheses as to the mechanism of the rearrangement at present under investigation. It constitutes an exception, however, to the generalisation of von Braun, Kühn, and Weismantel³⁴ that, although the behaviour of radicals attached to carbon is less simple, those attached to nitrogen show a specific tenacity nearly independent of the nature of the molecule in which they are contained. In the present investigation, this normal "tenacity series" is approximately reversed.

(2) In the o-series the halogens fall in the order $\text{Cl} < \text{Br} < \text{I}$. This order at least as regards Cl and I, appears to be retained in the p-, but reversed in the m- position. The order $\text{OMe} < \text{Me} < \text{Hals.} < \text{NO}_2$, ascending or descending, holds for many, but not all, reactions involving rupture of a linkage of the type $\text{Ar} - \underset{\cdot}{\underset{\cdot}{\text{C}}} - \text{X}$ (compare Williams³⁵) and it could be anticipated that/

that in these cases the order $I > Br > Cl > F$ for halogen substituents would be associated with the order $OMe > Me > Hals. > NO_2$ and $I < Br < Cl < F$ with $OMe < Me < Hals. < NO_2$. The results of several representative investigations are summarised in Table III and show that the anticipation is seldom realised, the word "normal" or "abnormal" indicates respectively conformity or otherwise with the "rule" (compare Ingold³⁶). For reactions I and II, the series $OMe < Me < Hals. < NO_2$ represents a descending order of facilitation, for III, IV, and V an ascending.

TABLE III

	I	II	III	IV	V
<u>o</u> -	Abnormal	-	Normal	-	Abnormal
<u>m</u> -	Abnormal	-	Abnormal	Abnormal	Normal
<u>p</u> -	Abnormal	Abnormal	Abnormal	-	Abnormal

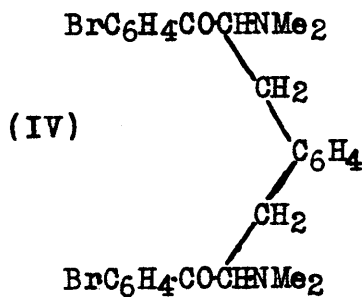
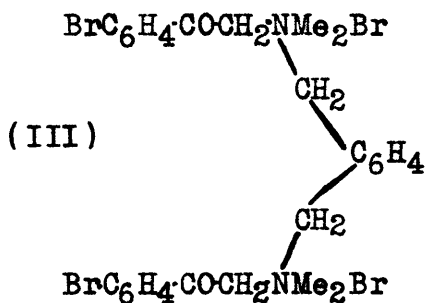
I - Hydrolysis of benzyl halides (Olivier³⁷; Shoesmith and Slater³⁸)
 II - $NMeR_1R_2 \xrightarrow{CNBr} R_1Br \text{ or } R_2Br$; $PhCONR_1R_2 \xrightarrow{PCl_5} R_1Cl \text{ or } R_2Cl$
 (von Braun, Kühn, and Weismantel³⁴; von Braun and Friedsam³⁹).
 III - Hydrolysis of benzoic esters (Kindler⁴⁰).
 IV - Hydrolysis of 5-substituted phthalides (Tasman⁴¹).
 V - Present investigation.

(3) The compounds of the o-series show the same arrangement among themselves, qualitatively, and in some degree quantitatively, as the p-compounds, but with greatly increased velocity of rearrangement, except in the case of OMe.

(4) For each substituent the m- and the p-values are of the same order/

<u>m</u> -Cl	132-134 °	141-143 °	52-53 °
<u>p</u> -Cl	186-187 °	125-126 °	59-61 °
<u>o</u> -Br	153-154 °	151-153 °	79-81 °
<u>m</u> -Br	140-143 °	132-134 °	72-73 °
<u>p</u> -Br	193 °	130-131 °	61 °
<u>o</u> -I	174-176 °	149-151 °	97-98 °
<u>m</u> -I	176-177 °	123-125 °	82-83 °
<u>p</u> -I	183-185 °	139-141 °	67-68 °
<u>o</u> -NO ₂	142-144 °	155-158 °	75-77 °
<u>m</u> -NO ₂	174-175 °	154-156 °	70-72 °
<u>p</u> -NO ₂	169-171 °	110-113 °	79-82 °
<u>m</u> -OMe	150-152 °	111-112 °	61-63 °
<u>p</u> -OMe	133-136 °	112-113 °	52-54 °

A sample of s.-p-xylylenebis-p-bromophenacyltetramethyl-
diammonium dibromide (III) was incidentally obtained during the
course of the preparative work, and it was found that treatment
with alkali caused a double migration, resulting in (IV). The
m-xylylene analogue was also prepared and behaved in a similar
manner.



EXPERIMENTAL

TECHNIQUE OF MEASUREMENTS - The volumetric process used by Stevens in his preliminary velocity measurements depends on the assumption that the reaction proceeds substantially, quantitatively, without the formation of by-products, and a fresh method had therefore to be devised, allowing the estimation both of rearrangement product and of unaltered quaternary salt. After numerous unsuccessful attempts to achieve this object by titration, the following gravimetric procedure was adopted.

The reaction was carried out in a flask (frequently 15c.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 (40c.c.) containing ammonium chloride equivalent to the alkali originally used. The product (II) was extracted with ether (3 x 20c.c.), 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 0.2N-sodium picrate solution (2c.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 10c.c. of 0.1N); and the acid solution heated/

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 5mg. for the tertiary base, and for the picrate, 1mg. + (1mg. per 5c.c. of alcohol used). These corrections raise the reaction coefficients by some 4%.

The tertiary base is little affected by caustic alkali in the absence of air, or by air in the absence of caustic alkali. The quaternary compound is not extracted from its aqueous solutions by ether, nor is it affected by 0.1N-ammonia in several days at room temperature.

The alcohols used were lime-dried and distilled over sodium. With ethyl and iso-propyl alcohols, results some 15% lower were obtained in different specimens; the recorded figures all relate to the same sample. No such behaviour was observed with methyl alcohol.

The measurements on the substituted salts were carried out in the same manner, and it was considered sufficiently accurate to use the same corrections for manipulatory losses. In one or two cases in which the quaternary picrate showed a tendency to separate out in an oily condition, the sodium picrate solution was added dropwise to the hot solution of the quaternary salt.

RESULTS. - Unless otherwise stated, the measurements were carried out at 37.7°, with phenacylbensyldimethylammonium bromide. The definite integral in the expression for k (p.43) is evaluated by Simpson's rules.

I- Medium.

IIa- Normality of quaternary salt.

IIb- Percentage of by-product formed (estimated by difference) when 60% of the initial material has disappeared; very little is produced subsequently.

IIc- Time interval in minutes between successive measurements.

IIIa-VIIIa- Percentage of base (II) formed.

IIIb-VIIIb- Percentage of quaternary salt unchanged.

IIIc-VIIIc- Velocity constants, $k \cdot 10^4$.

IX- Average velocity constant.

I		II	III	IV	V	VI	VII	VIII	IX
0.10N-NaOMe	a	0.10	17.3	29.6	41.2	51.4	-	-	33.0
	b	9	75.5	58.8	50.0	41.1	-	-	
	c	60	32.9	32.0	33.6	33.6	-	-	
0.05N-NaOMe	a	0.05	16.9	29.2	39.7	46.7	-	-	32.0
	b	12	74.6	57.1	49.7	41.4	-	-	
	c	60	32.5	32.1	32.4	31.0	-	-	
0.10N-NaOMe	a	0.05	20.8	36.4	47.8	55.6	62.8	-	41.9
	b	13	70.0	51.5	38.6	30.5	20.5	-	
	c	60	41.3	42.2	42.2	41.6	42.2	-	
0.15N-NaOMe	a	0.05	22.2	36.1	50.6	59.2	-	-	44.9
	b	12	67.6	50.0	37.6	24.9	-	-	
	c	60	44.9	42.9	45.8	45.9	-	-	

0.05N-NaOMe	a	0.025	24.0	42.1	55.2	62.6	-	-	41.9
	b	14	64.2	44.0	30.5	19.8	-	-	
	c	75	39.6	42.0	43.1	42.7	-	-	
*0.10N-NaOMe	a	0.05	20.9	35.9	47.0	55.9	61.7	-	41.5
	b	14	70.0	51.2	39.4	30.4	20.6	-	
	c	60	41.4	41.6	41.5	41.7	41.3	-	
0.10N-NaOEt	a	0.10	25.8	40.7	55.7	65.4	72.6	-	99
	b	8	70.0	51.3	37.0	26.7	19.2	-	
	c	30	102	95	99	99	100	-	
0.05N-NaOEt	a	0.05	26.4	44.6	57.6	64.8	69.4	-	106
	b	9	66.2	47.4	38.6	24.2	19.1	-	
	c	30	108	108	108	105	102	-	
0.10N-NaOEt	a	0.05	25.4	45.6	58.6	65.1	72.6	-	107
	b	9	67.8	46.3	32.2	22.9	16.3	-	
	c	30	102	109	110	106	108	-	
0.10N-NaOPr ^α	a	0.10	27.8	46.0	57.5	-	-	-	111
	b	9	65.7	46.3	33.4	-	-	-	
	c	30	112	112	109	-	-	-	
0.05N-NaOPr ^α	a	0.05	27.2	43.8	56.2	-	-	-	112
	b	13	62.7	43.4	27.7	-	-	-	
	c	30	113	111	112	-	-	-	
0.10N-NaOPr ^α	a	0.05	29.7	47.8	61.0	-	-	-	126
	b	12	60.4	39.4	25.7	-	-	-	
	c	30	126	125	128	-	-	-	
0.10N-NaOPr ^β	a	0.10	-	36.9	47.1	58.9	-	72.6	242
	b	7	-	56.5	46.5	34.5	-	18.5	
	c	10	-	246	234	243	-	246	

0.05N-NaOPr ^β	a	0.05	-	38.6	50.7	57.7	-	69.0	254			
	b	8	-	53.5	41.9	33.5	-	20.2				
	c	10	-	263	261	249	-	244				
0.10N-NaOPr ^β	a	0.05	-	41.9	53.8	63.1	-	74.9	288			
	b	8	-	49.6	38.2	28.2	-	15.0				
	c	10	-	292	288	287	-	284				
†0.05N-NaOMe	a	0.05	28.5	45.0	57.4	-	-	-	87			
	b	12	61.9	43.6	28.1	-	-	-				
	c	40	90	86	86	-	-	-				
†0.05N-NaOEt	a	0.05	35.6	57.5	68.7	-	-	-	240			
	b	11	55.5	31.0	18.6	-	-	-				
	c	20	234	244	242	-	-	-				
0.10N-NaOH	a	0.10	17.5	31.2	39.9	48.3	54.7	-	2.53-2.33			
	b	11	78.5	62.5	51.3	41.0	33.6	-				
	c	780	2.53	2.51	2.38	2.36	2.33	-				
0.05N-NaOH	a	0.05	17.9	31.3	40.5	48.4	53.6	57.3	62.0	65.1	67.6	-1.40-1.18
	b	12	77.8	60.4	50.4	39.1	33.1	29.2	26.1	22.9	19.1	
	c	1440	1.40	1.38	1.33	1.30	1.27	1.23	1.22	1.20	1.18	
0.10N-NaOH	a	0.05	20.2	35.2	45.2	54.2	60.8	-	2.77-2.60			
	b	9	77.2	58.9	46.5	36.2	29.2	-				
	c	828	2.77	2.73	2.62	2.62	2.60	-				
(at 16.4°)	0.10N-NaOMe	a	0.05	24.5	41.8	54.0	63.6	69.4	-	1.03		
b		10	68.1	48.8	35.4	26.7	19.6	-				
c		2880	1.02	1.03	1.03	1.04	1.02	-				

* Phenacylbenzyltrimethylammonium iodide

† Medium : alcohol-toluene, 2:3 by weight

(For the measurements in the propyl alcohols and in the alcohol-toluene media, the author is indebted to Dr. Thomas S. Stevens.)

The measurements in aqueous sodium hydroxide solution were carried out with greater quantities of material, and the manipulatory errors were smaller. In each case the coefficients fell off steadily as the reaction proceeded.

SUBSTITUTED QUATERNARY SALTS AT 37.7°. - The measurements were carried out in 0.10N-sodium methoxide solution, the salt concentration being 0.05N.

Ib- Percentage of by-product formed (estimated by difference) when 60% of the initial material has disappeared.

Ic- Time interval in minutes between successive measurements.

IIa-VIIIa- Percentage of tertiary base produced.

IIb-VIIIb- Percentage of quaternary salt unchanged.

IIc-VIIIc- Velocity constants, $k' \times 10^4$.

IX- Average velocity constant.

	I	II	III	IV	V	VI	VII	VIII	IX
<u>Phenacyl-m-chlorobenzyltrimethylammonium bromide.</u>									
a		24.8	40.5	52.5	60.8	67.5	-	-	
b	13	61.5	47.7	33.4	26.3	16.9	-	-	<u>102.3</u>
c	30	105.1	102.9	101.2	101.1	101.2	-	-	
<u>Phenacyl-p-chlorobenzyltrimethylammonium bromide.</u>									
a		19.7	35.9	46.7	54.9	62.4	69.5	-	
b	9	73.3	55.4	44.2	36.0	28.5	21.3	-	<u>116.5</u>
c	20	115	120	117	115	115	117	-	
<u>p-Bromophenacyl-p-chlorobenzyltrimethylammonium bromide.</u>									
a		20.1	33.7	43.9	51.3	56.7	-	-	

b	22	60.2	44.7	33.3	25.6	19.5	-	-	<u>86.8</u>
c	30	85.8	87.4	87.1	87.1	86.4	-	-	

Phenacyl-m-bromobenzyldimethylammonium bromide.

a		22.2	38.0	48.7	58.5	63.3	-	-	
b	12	69.1	50.8	38.8	29.0	21.2	-	-	<u>87.7</u>
c	30	88.6	88.9	86.8	88.3	85.9	-	-	

p-Bromophenacyl-m-bromobenzyldimethylammonium bromide.

a		25.6	41.9	53.5	59.4	65.3	-	-	
b	17	63.9	42.9	25.4	20.7	16.1	-	-	<u>70.5</u>
c	45	70.5	70.1	71.1	70.3	70.3	-	-	

Phenacyl-p-bromobenzyldimethylammonium bromide.

a		21.8	35.8	46.7	56.2	62.9	67.4	-	
b	10	73.0	54.7	43.0	32.8	26.3	20.5	-	<u>120</u>
c	20	127	120	118	119	119	117	-	

p-Bromophenacyl-p-bromobenzyldimethylammonium bromide.

a		20.7	34.9	45.2	51.2	56.3	-	-	
b	22	59.8	43.5	29.7	23.8	18.0	-	-	<u>90.1</u>
c	30	88.6	91.2	91.4	90.0	89.2	-	-	

Phenacyl-m-iodobenzyldimethylammonium bromide.

a		20.4	35.1	46.1	54.1	60.5	-	-	
b	14	70.8	51.7	40.0	31.0	24.5	-	-	<u>80.3</u>
c	30	80.4	80.9	80.7	79.8	79.6	-	-	

Phenacyl-p-iodobenzyldimethylammonium bromide.

a		23.4	39.0	50.2	58.6	65.5	-	-	
b	12	68.9	50.1	37.0	30.9	21.8	-	-	<u>136</u>
c	20	140	137	135	134	134	-	-	

p-Bromophenacyl-m-nitrobenzyl dimethylammonium bromide.

a		15.5	26.2	35.0	41.1	46.7	-	-	
b	24	64.1	49.0	40.5	34.6	29.0	-	-	<u>128</u>
c	15	129	129	130	126	125	-	-	

Phenacyl-m-methoxybenzyl dimethylammonium bromide.

a		20.3	34.0	44.6	53.1	59.4	65.4	-	
b	15	71.6	53.0	39.7	31.9	24.9	20.3	-	<u>38.9</u>
c	60	39.8	38.7	38.6	38.9	38.7	38.6	-	

Phenacyl-p-methoxybenzyl dimethylammonium bromide.

a		15.8	27.4	40.0	47.3	53.9	60.0	-	
b	13	72.5	58.0	47.6	39.6	31.2	24.7	-	<u>31.8</u>
c	60	30.9	30.6	33.0	32.1	32.0	32.4	-	

Phenacyl-m-methylbenzyl dimethylammonium iodide.

a		20.7	34.7	44.1	52.3	58.8	-	-	
b	15	67.5	50.9	40.1	32.3	26.0	-	-	<u>40.2</u>
c	60	41.9	41.2	39.6	39.4	39.1	-	-	

p-Bromophenacyl-p-methylbenzyl dimethylammonium bromide.

a		24.7	39.2	52.9	58.3	62.5	-	-	
b	21	59.4	38.8	26.0	21.2	16.1	-	-	<u>35.6</u>
c	90	35.2	34.7	37.3	36.0	34.9	-	-	

p-Bromophenacyl benzyl dimethylammonium bromide.

a		17.4	30.6	40.2	49.0	56.1	62.7	-	
b	14	74.2	57.9	46.6	37.4	29.1	22.9	-	<u>33.6</u>
c	60	33.6	33.6	32.9	33.3	33.6	34.3	-	

SUBSTITUTED QUATERNARY SALTS AT 16.4°.

Phenacyl-o-chlorobenzyl dimethylammonium bromide.

a		19.5	34.3	45.1	51.7	59.8	-	-	
b	10	75.3	58.9	49.7	38.2	29.8	-	-	<u>36.7</u>
c	60	37.4	37.3	36.3	36.1	36.6	-	-	

Phenacyl-o-bromobenzyl dimethylammonium bromide.

a		13.3	23.3	32.9	39.1	46.3	51.8	56.1	
b	12	77.5	64.3	56.5	47.4	42.2	35.5	30.0	<u>49.1</u>
c	30	50.4	49.1	50.3	48.2	49.0	48.7	48.3	

Phenacyl-o-iodobenzyl dimethylammonium bromide.

a		30.2	48.6	59.3	66.7	72.9	-	-	
b	13	61.2	38.2	26.8	18.5	13.2	-	-	<u>83.0</u>
c	45	84.6	84.6	82.7	81.3	81.9	-	-	

Phenacyl-o-nitrobenzyl dimethylammonium bromide.

a		38.1	58.0	64.7	-	-	-	-	
b	16	49.0	20.9	14.0	-	-	-	-	<u>1070</u>
c	5	1050	1098	1066	-	-	-	-	

Phenacyl-m-nitrobenzyl dimethylammonium bromide.

a		15.7	28.1	39.2	43.9	48.7	-	-	
b	20	72.5	57.1	41.1	34.7	28.7	-	-	<u>3.92</u>
c	480	3.84	3.93	4.11	3.90	3.81	-	-	

Phenacyl-p-nitrobenzyl dimethylammonium bromide.

a		18.5	30.6	39.2	46.4	51.0	-	-	
b	25	64.9	47.1	34.3	23.7	18.2	-	-	<u>75.3</u>
c	30	76.1	75.2	74.1	75.5	75.4	-	-	

p-bromophenacyl-o-methoxybenzyltrimethylammonium bromide.

a		20.0	34.7	46.1	54.3	60.3	-	-	
b	14	73.2	54.5	40.0	28.9	20.0	-	-	<u>1.63</u>
c	1440	1.62	1.62	1.63	1.64	1.65	-	-	

Phenacyl-o-methylbenzyltrimethylammonium iodide.

a		24.3	38.1	49.1	58.3	65.2	-	-	
b	13	63.8	49.4	37.6	28.2	20.4	-	-	<u>15.8</u>
c	180	16.9	15.7	15.5	15.4	15.4	-	-	

p-Bromophenacylbenzyltrimethylammonium bromide.

a		19.8	35.6	47.0	55.5	62.0	-	-	
b	14	69.4	53.3	39.0	29.5	22.9	-	-	<u>0.854</u>
c	2880	0.823	0.861	0.858	0.863	0.863	-	-	

PREPARATION AND CHARACTERISATION OF MATERIALS.

In methylations by the Eschweiler method, the hydrochloride of the initial base was heated at 130° for 3 hours with a moderate excess of 40% "formalin". The product, separated from non-basic material, was then isolated as described for the individual cases.

The picric acid in the picrates of tertiary bases was estimated by titration with potassium hydroxide in absolute alcohol, phenolphthalein being used as indicator.

Phenacylbenzyltrimethylammonium picrate formed deep yellow needles or stout laminae from methyl alcohol, m.p. 132-134° (Found: $C_6H_2O_7N_3'$, 47.3. $C_{17}H_{20}ON.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 47.3%). The iodide crystallised from water in colourless, sparingly/

sparingly soluble prisms, m.p. 174-176° (Found: I, 33.4.

C₁₇H₂₀ONI requires I, 33.3%). The crystalline ferrocyanide and the amorphous mercuri-iodide and the bismuthi-iodide are highly insoluble, but of inconstant composition.

o-Chlorobenzyl-dimethylamine - o-Chlorobenzyl bromide was conveniently prepared by brominating o-chlorotoluene with undiluted bromine; the reaction, which set in spontaneously, was completed by heating under reflux, and the product isolated by distillation in vacuo. Conversion into the tertiary base by the hexamine method of Sommelet and Guioth⁴³ gave a moderate yield, together with a considerable quantity of o-chlorobenzaldehyde (oxime, m.p. 76°). o-Chlorobenzyl-dimethylamine picrate was isolated in the first place from ether and recrystallised from aqueous methyl alcohol, m.p. 145-146° (von Braun, Kühn, and Weismantel³⁴ give m.p. 146°). Phenacyl-o-chlorobenzyl-dimethylammonium bromide, formed fairly rapidly from chlorobenzyl-dimethylamine and bromoacetophenone in cold benzene solution, separated as an oil which gradually solidified. It crystallised from alcohol-ether in minute prismatic needles, m.p. 149-150° (Found: Br, 20.4, 20.3. C₁₇H₁₉ONClBr, H₂O requires Br, 20.7%). An attempt to dehydrate the salt at 105-110° led to decomposition. The picrate, fine, glistening, yellow needles from methyl alcohol, melted at 154-156° (Found: C₆H₂O₇N₃, 44.6. C₁₇H₁₉ONCl.C₆H₂O₇N₃ requires C₆H₂O₇N₃, 44.1%). ω-Dimethylamino-ω-o-chlorobenzylacetophenone, obtained by the degradation of the quaternary salt, formed long, prismatic needles from methyl alcohol, m.p. 69-71° (Found: Cl, 12.5. C₁₇H₁₈ONCl requires Cl, 12.3%).

m-Chlorobenzyldimethylamine. - m-Chlorobenzyl bromide was prepared by brominating m-chlorotoluene with undiluted bromine at 130° , the bromine being added dropwise under the surface of the liquid. The resultant liquid was allowed to stand in an evacuated desiccator over potassium hydroxide until free from hydrobromic acid, dried over anhydrous sodium sulphate, and distilled in vacuo, the m-chlorobenzyl bromide being isolated as an oil, b.p. $108-111^{\circ}/10\text{mm}$. Conversion to the tertiary base by the hexamine method gave a fair yield. m-Chlorobenzyldimethylamine picrate was isolated in the first instance from aqueous methyl alcohol, and crystallised from benzene in aggregates of minute yellow prisms, m.p. $128-130^{\circ}$ (Found: $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$, 58.0. $\text{C}_9\text{H}_{12}\text{NCl}$, $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires $\text{C}_6\text{H}_3\text{O}_7\text{N}_3$, 57.5%). Phenacyl-m-chlorobenzyldimethylammonium bromide, prepared from the components in cold benzene, separated as an oil which slowly solidified, and crystallised from alcohol-ether in warty masses of minute prisms, m.p. $132-134^{\circ}$ (Found: Br, 21.9%). The picrate, fine, yellow needles from methyl alcohol, melted at $141-143^{\circ}$ (decomp.) (Found: $\text{C}_6\text{H}_2\text{O}_7\text{N}_3$, 43.7%). ω -Dimethylamino- ω -m-chlorobenzylacetophenone formed minute short prisms from methyl alcohol, m.p. $52-53^{\circ}$ (Found: Cl, 12.4%).

p-Chlorobenzyldimethylamine. - p-Chlorobenzyl bromide was prepared as for the ortho- compound, except that the solid reaction product was not distilled, but was recrystallised from methyl alcohol, and obtained in colourless needles, m.p. $62-63^{\circ}$. Conversion to the tertiary base by the hexamine method gave a very/

very good yield. p-Chlorobenzyl dimethylamine picrate was isolated in the first place from ether; it crystallised from acetone-ether in stout yellow prisms, m.p. 125-126° (Found: $C_6H_3O_7N_3$, 57.7%). Phenacyl-p-chlorobenzyl dimethylammonium bromide, prepared from the components in cold benzene, separated as a colourless crystalline solid, and crystallised from alcohol-ether in short prisms, m.p. 186-187° (decomp.) (Found: Br, 21.7%). The picrate, yellow prismatic needles from methyl alcohol, melted at 125-126° (Found: $C_6H_2O_7N_3'$, 44.0%). ω -Dimethylamino- ω -p-chlorobenzylacetophenone formed fine needles from methyl alcohol, m.p. 59-61° (Found: Cl, 12.0%).

o-Bromobenzyl dimethylamine. - o-Bromobenzyl bromide was prepared as for the o-chloro- compound, and gave the tertiary base in good yield by the hexamine method. o-Bromobenzyl dimethylamine picrate, obtained in the first instance from ether, crystallised from aqueous methyl alcohol in small, bright - yellow prisms, m.p. 149-150° (Found: $C_6H_3O_7N_3$, 51.5. $C_9H_{12}N.Br, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 51.7%). Phenacyl-o-bromobenzyl dimethylammonium bromide, prepared from the components in cold benzene, separated as a crystalline solid and crystallised from alcohol-ether in minute prismatic needles, m.p. 153-154° (Found: ionisable Br, 18.2, 18.6; loss at 100°, 4.3. $C_{17}H_{19}ONBr.Br', H_2O$ requires Br', 18.6; loss, 4.2%). The picrate, fine, glistening, yellow needles from methyl alcohol, melted at 151-153° (Found: $C_6H_2O_7N_3'$, 41.0. $C_{17}H_{19}ONBr.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 40.6%). ω -Dimethylamino- ω -o-bromobenzylacetophenone formed fine needles from methyl alcohol, m.p. 79-81°.

(Found: Br, 23.8. $C_{17}H_{18}ONBr$ requires Br, 24.1%).

Phenacyl-m-bromobenzyl²dimethylammonium bromide, prepared as described by Stevens², was obtained in stout needles, m.p. 140-143°. The picrate, yellow prismatic needles from methyl alcohol, melted at 132-134° (Found: $C_6H_2O_7N_3'$, 41.0%).

Phenacyl-p-bromobenzyl³dimethylammonium bromide, prepared as described by Stevens, Snedden, Stiller, and Thomson³, was obtained in minute laminae, m.p. 193°. The picrate formed fine, yellow, prismatic needles from methyl alcohol, m.p. 130-131° (Found: $C_6H_2O_7N_3'$, 40.8%).

The Isomeric Iodobenzyl⁴dimethylamines. - Preliminary experiments with a view to the preparation of these compounds were unsuccessful. For example, p-aminobenzyl⁴dimethylamine was prepared by reduction of p-nitrobenzyl⁴dimethylamine (vide infra) with tin and hydrochloric acid, but the attempted preparation of p-iodobenzyl⁴dimethylamine from the former by the Sandmeyer reaction failed. The reduction of m-nitrobenzaldehyde with stannous chloride and hydrochloric acid, followed by an application of the Sandmeyer reaction (compare Patterson⁴⁴) gave only a very unsatisfactory yield of m-iodobenzaldehyde. The attempted preparation of p-iodobenzyl chloride from iodotoluene and *s.*-dichloromethyl ether in the presence of anhydrous zinc chloride (compare Stephen, Short, and Gladding⁴⁵) was unsuccessful. Attempts to prepare p-iodobenzaldehyde from iodotoluene and chromyl chloride in carbon disulphide solution likewise met with failure.

The preparation of the isomeric iodobenzyl bromides was then attempted as described by Olivier³⁷ by the bromination of the corresponding iodotoluenes, the ortho- compound at 200-205°, the meta- at 200°, and the para- at 150-155°, but the yields were unsatisfactory. It was found that good yields of the bromides could be obtained by carrying out the bromination in the light of a carbon arc lamp (silica flask), in carbon tetrachloride solution at the boiling point. For example, o-iodotoluene (20g.), carbon tetrachloride (80c.c.), and water (40c.c.) were refluxed during the dropwise addition of bromine (5.5c.c. in 20c.c. carbon tetrachloride) and until decolorisation took place. The carbon tetrachloride layer was dried, the solvent distilled off, and the residue crystallised from methyl alcohol. The yields of bromides were 74% for the ortho- compound, 78% for the meta-, and 74% for the para-. The bromides were converted into the tertiary bases by the hexamine method. o-Iodobenzyldimethylamine picrate was obtained in the first instance from ether, and crystallised from aqueous methyl alcohol in aggregates of minute yellow prisms, m.p. 134-136° (Found: C₆H₃O₇N₃, 46.2. C₉H₁₂NI, C₆H₃O₇N₃ requires C₆H₃O₇N₃, 46.7%). m-Iodobenzyldimethylamine picrate was obtained in the first place from ether, and crystallised from benzene in spherical aggregates of minute yellow prisms, m.p. 128-130° (Found: C₆H₃O₇N₃, 46.6%). p-Iodobenzyl dimethylamine was identified as the picrate, m.p. 146-148° (von Braun, Kühn, and Weismantel³⁴ give m.p. 148°).

Phenacyl-o-iodobenzyldimethylammonium bromide, prepared from the components/

components in cold benzene, separated as an oil which solidified quite rapidly, and crystallised from alcohol-ether in minute prismatic needles, m.p. 174-176° (Found: Br, 17.2. $C_{17}H_{19}ONIBr$ requires Br, 17.4%). The picrate, fine yellow needles from methyl alcohol, melted at 149-151° (Found: $C_6H_2O_7N_3'$, 37.3. $C_{17}H_{19}ONI.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 37.5%). ω -Dimethylamino- ω -o-iodobenzylacetophenone formed rectangular prisms from methyl alcohol, m.p. 97-98° (Found: I, 33.8. $C_{17}H_{18}ONI$ requires I, 33.5%).

Phenacyl-m-iodobenzyltrimethylammonium bromide, prepared from the components in cold benzene, separated as an oil which gradually solidified, and crystallised from alcohol-ether in rosettes of stout prismatic needles, m.p. 176-177° (slight decomp.) (Found: Br, 17.6%). The picrate, rosettes of stout yellow prisms from acetone, melted at 123-125° (Found: $C_6H_2O_7N_3'$, 38.0%).

ω -Dimethylamino- ω -m-iodobenzylacetophenone formed rosettes of fine, very faintly yellow needles, m.p. 82-83° (Found: I, 33.4%).

Phenacyl-p-iodobenzyltrimethylammonium bromide, prepared from the components in cold benzene, separated as an oil which solidified quite rapidly, and crystallised from alcohol-ether in minute cubical crystals, m.p. 183-185° (Found: ionisable Br, 16.4, 16.8; loss at 105°, 3.7. $C_{17}H_{19}ONIBr.H_2O$ requires Br, 16.7; loss, 3.8%). The picrate, minute yellow prisms from methyl alcohol, melted at 139-141° (Found: $C_6H_2O_7N_3'$, 37.2%). ω -Dimethylamino- ω -p-iodobenzylacetophenone formed stout prismatic needles from methyl alcohol/

alcohol, m.p. 67-68° (Found: I, 33.3%).

o-Nitrobenzyldimethylamine. - o-Nitrobenzyl bromide was conveniently prepared by brominating o-nitrotoluene in carbon tetrachloride solution in the light from an arc lamp, as described for the preparation of the iodobenzyl bromides, supra. Conversion to the tertiary base was accomplished by treating the bromide with dimethylamine (2-3 mols.) in alcoholic solution. After remaining for 12 hours, the mixture was heated for 2 hours on the water-bath, concentrated, diluted with water, and extracted with benzene. On treatment with picric acid, the benzene layer yielded o-nitrobenzyldimethylamine picrate, which crystallised from acetone-ligroin in clusters of short, yellow prisms, m.p. 138-141° (Found: $C_6H_3O_7N_3$, 55.7. $C_9H_{12}O_2N_2 \cdot C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 56.0%). Phenacyl-o-nitrobenzyldimethylammonium bromide prepared from the components in cold benzene, separated as an oil which gradually solidified, and crystallised from alcohol-ether in minute prisms, m.p. 142-144° (Found: Br, 20.8. $C_{17}H_{19}O_3N_2Br$ requires Br, 21.1%). The picrate, minute, yellow, prismatic needles, from methyl alcohol, melted at 155-158° (Found: $C_6H_2O_7N_3'$, 43.0. $C_{17}H_{19}O_3N_2 \cdot C_6H_2O_7N_3'$ requires $C_6H_2O_7N_3'$, 43.3%). ω -Dimethylamino- ω -o-nitrobenzylacetophenone formed clusters of light-yellow, stout prisms from methyl alcohol, m.p. 75-77° (Found: N, 9.7. $C_{17}H_{18}O_3N_2$ requires N, 9.4%).

m-Nitrobenzyldimethylamine. - m-Nitrobenzyl bromide was prepared from m-nitrobenzaldehyde by conversion of the latter into/

into the alcohol as described by Becker⁴⁶, and treatment of the alcohol in benzene solution with hydrogen bromide. The bromide was converted into the tertiary base by the hexamine method. The picrate formed yellow, rectangular prisms from acetone, m.p. 209-211° (decomp.) (Found: $C_6H_3O_7N_3$, 56.5%). Phenacyl-m-nitrobenzyl-dimethylammonium bromide, prepared from m-nitrobenzyl-dimethylamine and ω -bromoacetophenone in cold benzene, crystallised from alcohol-ether in minute prismatic needles, m.p. 174-175° (Found: Br, 20.7%). The picrate formed minute, yellow, prismatic needles, from methyl alcohol, m.p. 154-156° (Found: $C_6H_2O_7N_3'$, 43.6%). ω -Dimethylamino- ω -m-nitrobenzylacetophenone formed long, fine, straw-coloured needles from methyl alcohol, m.p. 70-72° (Found: N, 9.3%).

Phenacyl-p-nitrobenzyl-dimethylammonium bromide, prepared as described by Stevens, Snedden, Stiller, and Thomson³, was obtained in cubical crystals, m.p. 169-171°. The picrate, fine yellow needles from methyl alcohol, melted at 110-113° (Found: $C_6H_2O_7N_3'$, 43.7%).

o-Methoxybenzyl-dimethylamine. - Salicylaldehyde was methylated as described by Sidgwick and Bayliss⁴⁷. o-Methoxybenzaloxime was reduced substantially as described by Goldschmidt and Ernst⁴⁸. The substitution of methyl for ethyl alcohol in this and similar preparations is advantageous, as it prevents the separation of sodium acetate. The o-methoxybenzylamine hydrochloride formed fine glistening plates, m.p. 149-150° (Goldschmidt and Ernst give m.p. 150°). o-Methoxybenzyl-dimethylamine was obtained by the Eschweiler methylation of the primary base, and identified as hydrochloride/

hydrochloride, m.p. 149° , as found by Stedman⁴⁹. With ω -bromoacetophenone in benzene, the tertiary base gave a yellow, viscous oil which could not, under any conditions, be induced to crystallise. Better results attended the combination of the tertiary base with ω p-dibromoacetophenone. p-Bromophenacyl-o-methoxybenzyl-dimethylammonium bromide, prepared from o-methoxybenzyldimethylamine and ω p-dibromoacetophenone¹³ in cold benzene, separated as an oily solid, and crystallised from alcohol-ether in minute prismatic needles, m.p. $173-176^{\circ}$ (Found: ionisable Br, 17.9. $C_{18}H_{21}O_2NBr.Br'$ requires Br', 18.1%). The picrate formed minute yellow prisms from acetone-ligroin, m.p. $116-119^{\circ}$ (Found: $C_6H_2O_7N_3'$, 38.9. $C_{18}H_{21}O_2NBr.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 38.6%). p-Bromo- ω -dimethylamino- ω -o-methoxybenzylacetophenone formed minute prisms from methyl alcohol, m.p. $82-83^{\circ}$ (Found: Br, 21.8. $C_{18}H_{20}O_2NBr$ requires Br, 22.1%).

m-Methoxybenzyl-dimethylamine was prepared, starting from m-hydroxybenzaldehyde, in a manner analogous to the preparation of the ortho- compound described above. The tertiary base was identified as hydrochloride (compare Stedman⁴⁹). Phenacyl-m-methoxybenzyl-dimethylammonium bromide, prepared from the components in cold benzene, separated as an oil which slowly solidified, and crystallised from alcohol-ether in short stout prisms, m.p. $150-152^{\circ}$ (Found: Br, 21.6. $C_{18}H_{22}O_2NBr$ requires Br, 22.0%). The picrate, stout yellow prisms from methyl alcohol, melted at $111-112^{\circ}$ (Found: $C_6H_2O_7N_3'$, 44.2. $C_{18}H_{22}O_2N.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 44.5%). ω -Dimethylamino- ω -m-methoxybenzylacetophenone,
glistening/

glistening plates from methyl alcohol, melted at 61-63° (Found: N, 5.04. $C_{18}H_{21}O_2N$ requires N, 4.95%).

Phenacyl-p-methoxybenzyl-dimethylammonium bromide, prepared as described by Stevens², was obtained in rosettes of stout needles, m.p. 133-136°.

o-Methylbenzyl-dimethylamine. - Attempts to obtain this compound by the interaction of tetramethylmethylenediamine (from dimethylamine and formaldehyde in aqueous solution after Henry⁵⁰) and the Grignard reagent formed from o-iodotoluene were unsuccessful. o-Xylyl bromide was conveniently prepared by bromination of o-xylene as described by Atkinson and Thorpe⁵¹. Conversion to the tertiary base was accomplished by the hexamine method. o-Methylbenzyl-dimethylamine picrate formed aggregates of minute yellow prisms from benzene, m.p. 148-150°. (Found: $C_6H_3O_7N_3$, 60.2. $C_{10}H_{15}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 60.6%.) Phenacyl-o-methylbenzyl-dimethylammonium bromide, prepared from the components in cold benzene, separated as a dark oil which could not, under any conditions, be induced to crystallise. Conversion to the iodide resulted in a gummy product which, after many attempts, was obtained crystalline from aqueous acetone in the form of minute prisms, m.p. 160-162° (decomp.) (Found: I, 32.3. $C_{18}H_{22}ONI$ requires I, 32.2%). The picrate formed deep-yellow short prisms from methyl alcohol, m.p. 131-133° (Found: $C_6H_2O_7N_3'$, 46.5. $C_{18}H_{22}ON.C_6H_2O_7N_3'$ requires $C_6H_2O_7N_3'$, 46.0%). ω -Dimethylamino- ω -o-methylbenzylacetophenone formed minute prisms from methyl alcohol/

alcohol, m.p. 62-63° (Found: N, 5.45. $C_{18}H_{22}ON$ requires N, 5.24%).

m-Methylbenzyl-dimethylamine. - m-Xylyl bromide was prepared as for the ortho- isomeride. Conversion to the tertiary base was accomplished by the hexamine method. m-Methylbenzyl-dimethylamine picrate formed aggregates of minute yellow prisms from benzene, m.p. 136-138° (Found: $C_6H_3O_7N_3$, 60.3%). Phenacyl-m-methylbenzyl-dimethylammonium bromide, prepared from the components in cold benzene, separated as a dark oil which could not, under any conditions, be induced to crystallise. Conversion to the iodide resulted in a gummy product which, after many attempts in a variety of solvents, was crystallised from aqueous methyl alcohol in clusters of minute prisms, m.p. 134-135° (decomp.) (Found: I, 32.0%). ω -Dimethylamino- ω -m-methylbenzylacetophenone formed rosettes of faintly yellow, short prisms from methyl alcohol, m.p. 74-76° (Found: N, 5.32%).

Tetramethyl-m-xylylenediamine. - m-Xylylene dibromide, obtained along with m-xylyl bromide in the bromination of m-xylene, was treated with dimethylamine (4 - 6 mols.) in alcoholic solution. After remaining for 12 hours, the mixture was heated on the water-bath for 2 hours, concentrated, diluted with water, and extracted with benzene. On treatment with picric acid the benzene extract yielded tetramethyl-m-xylylenediamine picrate which crystallised from acetone-ligroin in masses of minute yellow prisms, m.p. 190-193° (decomp.) (Found: $C_6H_3O_7N_3$, 71.0. $C_{12}H_{20}N_2$, $2C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 70.5%). s.-m-Xylylenebis-p-bromophenacyltetramethyldiammonium dibromide, prepared from tetramethyl-m-xylylenediamine/

tetramethyl-m-xylylenediamine and p-bromophenacyl bromide in cold benzene, formed minute prisms from alcohol-ether, m.p. 205-206° (Found: ionisable Br, 21.2. $C_{28}H_{32}O_2N_2Br_4$ requires 2Br, 21.4%). 4:4'-Dibromo- ω : ω' -bisdimethylamino- ω : ω' -m-xylylene-bisacetophenone was obtained by heating the foregoing bromide on the water-bath for 15 minutes with excess sodium hydroxide solution. The product was recrystallised from methyl alcohol, giving fine, pale yellow needles, m.p. 143-144° (Found: Br, 27.1. $C_{28}H_{30}O_2N_2Br_2$ requires Br, 27.3%).

p-Methylbenzyldimethylamine. - Attempts to obtain this compound by the interaction of tetramethylmethylenediamine and the Grignard reagent formed from p-iodotoluene resulted in failure. The preparation of p-methylbenzyl chloride from toluene and s.-dichloromethyl ether in the presence of anhydrous zinc chloride (compare Stephen, Short, and Gladding⁴⁵) gave only very unsatisfactory yields. The preparation of p-tolualdehyde by the interaction of ethyl orthoformate and the Grignard reagent formed from p-iodotoluene resulted in only a minute yield of the required product. Bromination of p-xylene by the method of Atkinson and Thorpe⁵¹ led to a mixture of p-xylyl bromide and p-xylylene dibromide, which could be separated from each other only with difficulty on the small scale. Crude p-xylyl bromide was treated with dimethylamine (2-3 mols.) in alcoholic solution, and the reaction mixture worked up in the usual way. On treatment with picric acid the benzene layer yielded the picrate of tetramethyl-p-xylylenediamine, while the aqueous/

aqueous layer gave glistening yellow plates of di-p-methylbenzyl-dimethylammonium picrate. The latter was converted into the quaternary chloride, and heated with dimethyl-amine (3 mols.) at 200° for 3 hours. The reaction mixture was basified, extracted with ether, and the p-methylbenzyldimethylamine isolated by distillation, b.p. 196-199°. Neither the phenacylbromide nor the corresponding iodide could be obtained in crystalline condition. p-Bromophenacyl-p-methylbenzyldimethylammonium bromide, prepared from the components in cold benzene, formed rosettes of minute prismatic needles, m.p. 174-176° (decomp.) (Found: ionisable Br, 18.7. C₁₈H₂₁ONBr.Br' requires Br', 18.7%). The picrate formed clusters of fine yellow needles from methyl alcohol, m.p. 128-130° (decomp.) (Found: C₆H₂O₇N₃', 40.1. C₁₈H₂₁ONBr. C₆H₂O₇N₃ requires C₆H₂O₇N₃', 39.7%). p-Bromo-ω-dimethylamino-ω-p-methylbenzylacetophenone formed fine needles from methyl alcohol, m.p. 91-93° (Found: Br, 23.4. C₁₈H₂₀ONBr requires Br, 23.1%).

s.-p-Xylylenebis-p-bromophenacyltetramethyldiammonium dibromide, prepared from tetramethyl-p-xylylenediamine and p-bromophenacyl bromide in cold benzene, formed minute prismatic needles from alcohol-ether, m.p. 220-222° (decomp.) (Found: ionisable Br, 21.7%). 4:4'-Dibromo-ω:ω'-bisdimethylamino-ω:ω'-p-xylylene-bisacetophenone was obtained by heating the foregoing bromide on the water-bath with excess sodium hydroxide solution for 10 minutes. The product was recrystallised from methyl alcohol, giving minute, faintly yellow prisms, m.p. 138-140° (Found: Br, 27.0%).

p-Bromophenacylbenzyldimethylammonium bromide, prepared as described by Stevens², was obtained in stout prisms, m.p. 188-191°. The picrate formed glistening yellow prisms from methyl alcohol, m.p. 159-160° (Found: $C_6H_2O_7N_3'$, 40.4. $C_{17}H_{19}ONBr.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 40.6%).

p-Bromophenacyl-p-chlorobenzyldimethylammonium bromide, prepared from p-bromophenacyl bromide and p-chlorobenzyl dimethylamine in cold benzene, formed rosettes of minute needle-shaped prisms, m.p. 174-175° (Found: ionisable Br, 18.2. $C_{17}H_{18}ONClBr.Br'$ requires Br', 17.9%). The picrate formed yellow, lustrous, prismatic needles from methyl alcohol, m.p. 146-147° (decomp.) (Found: $C_6H_2O_7N_3'$, 38.4. $C_{17}H_{18}ONClBr.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 38.3%). p-Bromo- ω -dimethylamino- ω -p-chlorobenzylacetophenone formed fine, very faintly yellow, prismatic needles from methyl alcohol, m.p. 75-76° (0.1210 gave 0.1086 AgCl + AgBr. $C_{17}H_{17}ONClBr$ requires 0.1094).

p-Bromophenacyl-p-bromobenzyldimethylammonium bromide, prepared from p-bromophenacyl bromide and p-bromobenzyl dimethylamine in cold benzene, formed minute prismatic needles from alcohol-ether, m.p. 187-188° (decomp.) (Found: ionisable Br, 16.6. $C_{17}H_{18}ONBr_2$ requires 1Br, 16.3%). The picrate formed short, stout, yellow prisms from acetone, m.p. 157-158° (decomp. gradually above 128°) (Found: $C_6H_2O_7N_3'$, 35.2. $C_{17}H_{18}ONBr_2.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 35.6%). p-Bromo- ω -dimethylamino- ω -p-bromobenzylacetophenone formed rosettes of fine, pale yellow needles from methyl alcohol, m.p. 77-78° (Found: Br, 38.6. $C_{17}H_{17}ONBr_2$ requires Br, 38.9%).

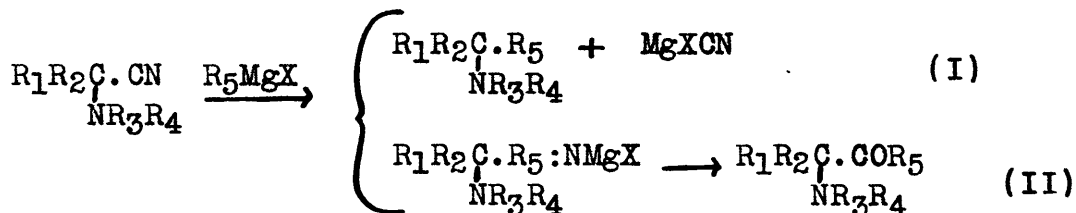
p-Bromophenacyl-m-bromobenzyldimethylammonium bromide, prepared from p-bromophenacyl bromide and m-bromobenzyl dimethylamine in cold benzene, formed stout prisms from alcohol, m.p. 193° (decomp.) (Found: ionisable Br, 16.4%). The picrate formed short yellow prisms from methyl alcohol, m.p. 136-137° (Found: C₆H₂O₇N₃', 35.3%). p-Bromo-ω-dimethylamino-ω-m-bromobenzylacetophenone formed rosettes of stout, straw-coloured prisms from methyl alcohol, m.p. 68-70° (Found: Br, 38.7%).

p-Bromophenacyl-m-nitrobenzyldimethylammonium bromide, prepared from p-bromophenacyl bromide and m-nitrobenzyl dimethylamine in cold benzene, formed minute prismatic needles from alcohol, m.p. 200-201° (decomp.) (Found: ionisable Br, 17.7. C₁₇H₁₈O₃N₂Br.Br' requires Br', 17.5%). The picrate formed small, thick, yellow prisms from methyl alcohol, m.p. 158-159° (Found: C₆H₂O₇N₃', 37.9. C₁₇H₁₈O₃N₂Br.C₆H₂O₇N₃ requires C₆H₂O₇N₃', 37.6%). p-Bromo-ω-dimethylamino-ω-m-nitrobenzylacetophenone formed small, faintly straw-coloured prisms from methyl alcohol, m.p. 72-73° (Found: Br, 21.0. C₁₇H₁₇O₃N₂Br requires Br, 21.2%).

THE ACTION OF THE GRIGNARD REAGENT UPON AMINO-NITRILES.

INTRODUCTORY

In the course of another investigation Stevens² had occasion to study the action of phenylmagnesium bromide on α -dimethylamino- β -phenylpropionitrile, $\text{CH}_2\text{PhCH}(\text{NMe}_2)\text{CN}$, and, instead of the expected ketone being obtained, it was found that the cyano-group was replaced by phenyl, yielding $\text{CH}_2\text{PhCH}(\text{NMe}_2)\text{Ph}$. Further investigation of this process with regard to other amino-nitriles by Stevens, Cowan, and MacKinnon⁹ showed that the reaction might take either the course of double decomposition as above (I), or, less frequently, the normal one of ketone formation (II).

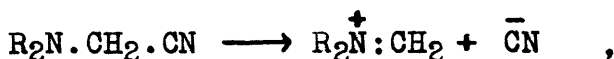


Previous to these investigations, Bruylants¹⁰ and his collaborators found that reaction (I) occurred with a large number of tertiary α -amino-nitriles; their studies were concerned principally with piperidino-nitriles.

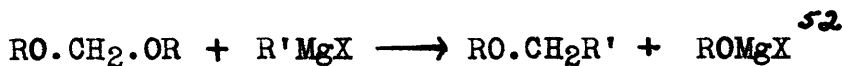
Stevens, Cowan and MacKinnon observed the "normal" Grignard-nitrile reaction (II) only for those cases in which $\text{R}_1=\text{R}_2=\text{H}$, while it was not met with at all by the Belgian investigators, who, however, studied only one compound of the type indicated. On the other hand, the latter frequently observed the reaction



especially when both R_1 and R_2 were hydrocarbon radicals. This reaction was not observed in the studies of Stevens, Cowan, and MacKinnon. These latter investigators suggested that reaction (I) could be correlated with the formal structural possibility of ionisation of the type



in which case mobility of the cyano- group would be expected to be associated with that structural environment which confers "pseudo-basic" properties on a hydroxyl radical. They further suggested that the association of the reaction course (II), in place of (I), with the group $\text{>NCH}_2\text{CN}$ could be classified along with the fact that in the reaction



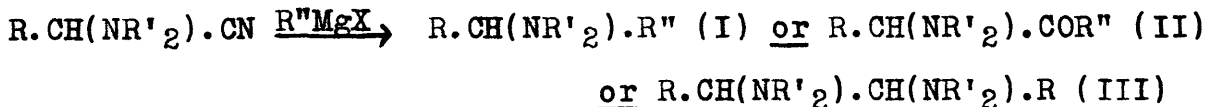
formals are attacked much less readily than the higher acetals. In each case the presence of hydrocarbon substituents in the methylene group favours the process of double decomposition.

A number of applications of reaction (I) occur in the synthetical work recorded in Section IA of this thesis, and it was considered of interest and importance to investigate the process in some further detail.



GENERAL OUTLINE OF RESULTS.

An amino-nitrile and a Grignard reagent may interact in either of three ways :-



Cases in which R and R'' are altered while R' = Me have been investigated, and the following generalities are discussed -

- (1) Reaction (III) is not observed.
- (2) When R = H, product (II) predominates, irrespective of the nature of R''.
- (3) When R is a lower alkyl, (II) predominates if R'' is alkyl, and (I) if R'' is Ph or CH₂Ph.
- (4) When R = Ph, the main product is always (I).

The results obtained are compared with those of various other investigators.

The results of previous investigations on this subject (vide introductory section) show that an α -amino-nitrile and a Grignard reagent may interact in either of three ways, thus :-
 $R.CH(NR'_2).CN \xrightarrow{R''MgX}$, $R.CH(NR'_2).R''$ (I) or $R.CH(NR'_2).COR''$ (II)
or $R.CH(NR'_2).CH(NR'_2).R$ (III)

In the present study the principal object has been the examination of the effect upon the course of the reaction of altering R and R'' while R' = Me. Most of those cases studied by Stevens, Cowan, and MacKinnon⁹ which belong to this category have been re-examined. It is worthy of note that reaction (III) has not been encountered with dimethylamino-nitriles.

From the results which are collected in Table I the following rules may be formulated :-

- (a) When R = H, product (II) predominates irrespective of the nature of R''.
- (b) When R is a lower alkyl, (II) predominates if R'' is alkyl, and (I) if R'' is Ph or CH₂Ph.
- (c) When R = Ph, the main product is always (I).

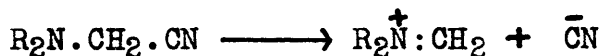
Rule (a) was implicitly stated by Stevens, Cowan, and MacKinnon as a result of their earlier investigations and is commented upon in the introductory section to this work. The further cases examined in the present investigation confirm the observations of these investigators.

From rule (b) it might be concluded that the controlling factor in these cases is the weight of R'', but this conclusion is negated by the observed fact that cyclohexyl behaves like the/

the simple alkyls (case B₄ in Table I).

The fact that the insertion of a phenyl radical in the α -position to the replaceable (CN) group strongly favours the reaction of double decomposition (I) (rule c) is in agreement with the results previously obtained in these investigations and in others of a related character (vide introductory section). That a similar effect should result from insertion of a phenyl group in the β -position to the replaceable (CN) group was not, however, anticipated.

The sensitiveness of the reaction to small constitutional changes is well exemplified by the effect of replacing the dimethylamino- group in the nitrile by piperidino-. The results, which are collected in Table I and are due mainly to Bruylants¹⁰ and to Christiaen⁵³, show that reaction (II) is completely suppressed. In case H₁ (piperidinoacetonitrile and methylmagnesium iodide) this result was especially surprising, for here all other conditions at least favour reaction (II), but the experiment has been repeated and confirmed. In these cases the exclusive formation of product (I) cannot be attributed to some specific property of the heterocyclic piperidino- radical, for Bruylants obtained 83% of product (I) from α -diethylamino-n-valeronitrile and ethylmagnesium bromide. If reaction (I) is to be correlated with the formal structural possibility of ionisation of the type



as suggested by Stevens, Cowan, and MacKinnon (vide introductory section), then these differences due to the nature of the radicals attached/

attached to the amino-nitrogen atom of the nitrile may be associated with the basic strength of the amino-nitrogen atom, amino-nitriles derived from piperidine or diethylamine undergoing reaction (I) more readily than those derived from the weaker bases dimethylamine and ethylaniline (Stevens, Cowan, and MacKinnon found that ethylanilinoacetonitrile and methylmagnesium iodide gave product (II)). The matter, however, requires further investigation before any definite conclusion can be arrived at.

TABLE I

(The numbers recorded are percentage yields of products of types (I) and (II); m signifies main product.)

Dimethylamino-nitriles ($\text{NR}'_2 \neq \text{NMe}_2$).

R in R.CH(NR' ₂).CN	Grignard Reagent.							
	(1)		(2)		(3)		(4)	
	MeMgI.		EtMgBr.		Pr ^α MgBr.		C ₆ H ₁₁ MgCl.	
	(I)	(II)	(I)	(II)	(I)	(II)	(I)	(II)
(A) H	4	50 ^b	0	60	0	58	-	-
(B) Me	14	50	13	50	0	67	0	64
(C) Pr ^α	0	53	-	-	-	-	-	-
(D) CH ₂ (NMe ₂).CH ₂	-	-	-	-	-	-	-	-
(E) CHMe:CH	-	-	-	-	-	-	-	-
(F) CH ₂ Ph	-	-	89	0 ^c	-	-	-	-
(G) Ph	71	0 ^b	-	-	89	0 ^c	-	-

Grignard Reagent.

		Grignard Reagent.					
		(5)		(6)		(7)	
		CH ₂ CMgBr.		CH ₂ Ph.MgCl.		PhMgBr.	
		(I)	(II)	(I)	(II)	(I)	(II)
(A)	H	no reactn.		0	>50	0	78 ^b
(B)	Me	-	-	76	0	78	0
(C)	Pr ^α	-	-	-	-	71	0 ^c
(D)	CH ₂ (NMe ₂).CH ₂	-	-	67	0 ^c	<u>m</u>	0 ^d
(E)	CHMe:CH	-	-	-	-	60	0 ^d
(F)	CH ₂ Ph	-	-	-	-	<u>m</u>	- ^a
(G)	Ph	-	-	<u>m</u>	- ^a	63	0 ^b

Piperidino-nitriles (NR'₂ = C₅H₁₀N).

Grignard Reagent.

		Grignard Reagent.							
		(1)		(2)		(6)		(7)	
		MeMgI.		EtMgBr.		CH ₂ Ph.MgCl.		PhMgCl.	
		(I)	(II)	(I)	(II)	(I)	(II)	(I)	(II)
(H)	H	50	0 ^d *	-	-	-	-	-	-
(J)	Me	<u>m</u>	0 ^d *	-	-	63	0 ^f	63	0 ^b
(K)	Et	<u>m</u> †	0 ^d *	-	-	90	0 ^d	<u>m</u>	0 ^d
(L)	CH ₂ :CH	-	-	-	-	-	-	40	0 ^d
(M)	Ph	-	-	80	0 ^e	60	0 ^e *	83	0 ^e

^aStevens, Cowan, and MacKinnon⁹. ^bRe-examination of case studied by Stevens, Cowan, and MacKinnon⁹. ^cCompare this thesis, pp.26-27; EtMgI was used in case F₂. ^dBruylants¹⁰. ^eChristiaen⁵³.

^fDerived from "competitive" experiment (compare experimental part). *Grignard reagent of type RMgBr. †Almost quantitative.

The interpretation of the results of this investigation is exceedingly difficult, because the effect of a given structural change upon the nature of the final product may be regarded as compounded of its separate effects upon the velocities of the individual reactions (I) and (II). In an endeavour to establish something of the nature of these effects in cases B₁, B₆, and B₇ (dimethylaminopropionitrile and different Grignard reagents), the Grignard reagents were allowed to compete in pairs (1 mol. of each) for 1 mol. of (a) propionitrile, with which reaction is exclusively according to (II), and (b) piperidinopropionitrile, with which reaction is exclusively according to (I). The results obtained (vide infra) are expressed as percentage yields of product, calculated on the nitrile used. They show, if the method of attack be assumed valid, that, unfortunately, both reaction (I) and reaction (II) can be strongly affected, and affected in the same sense, by the same constitutional change; and, in particular, that the exclusive formation of product (I) in case B₆ (dimethylaminopropionitrile and benzylmagnesium chloride) and in case B₇ (dimethylaminopropionitrile and phenylmagnesium bromide) is not to be attributed to inhibition of reaction (II).

	MeMgI	:	CH ₂ Ph.MgCl.		MeMgI	:	PhMgBr.
Me.CH ₂ .CN	23		38		0		67
Me.CH(NC ₅ H ₁₀).CN	0		63		0		60

EXPERIMENTAL

The amino-nitriles were prepared in each case according to the authority cited, the known substances having the properties ascribed to them in the literature. In reactions of the Strecker type it was found convenient to employ the combination : aldehyde - potassium cyanide - amine hydrochloride or amine + acetic acid, the use of hydrogen cyanide or the conversion of the aldehyde into bisulphite compound being avoided. The amino-nitrile (1mol.), in ether, was added gradually to the cooled Grignard reagent (2mols.), and, after 15 hours, the products obtained in ether, either after decomposition of the reaction mixture with ice and ammonium chloride, or after treatment with ice and dilute sulphuric acid and steam-distillation of the basified acid layer into dilute hydrochloric acid solution, followed by evaporation of the hydrochloric acid and basification of the residue with concentrated caustic soda solution in presence of ether. The method used in each individual case is specified by " H_2SO_4 " or " NH_4Cl ", and the word "negative" refers to the result of the qualitative test (vide infra) for product (I).

Preliminary experiments on the quantitative separation of products of types (I) and (II) were carried out with mixtures of benzyldimethylamine, CH_2PhNMe_2 , and phenacyldimethylamine, $PhCOCH_2NMe_2$. Methods depending on the use of reagents for the carbonyl group, or on the difference in basic strength between the two products, were not satisfactory. After reduction of the mixed/

mixed methosulphates with zinc and acetic acid, (I) was recovered quantitatively as methopicate, and (II) in part as acetophenone, Ph.CO.CH₃. This process was used to identify many of the ketonic bases as nitrogen-free ketones, which latter are included below, without further comment, among the derivatives of the amino-ketones. It was further used as a qualitative test for product (I); the test being regarded as reliable and sensitive, except possibly for the bases of lowest molecular weight.

As these methods were not quantitative, the products were separated as far as possible by distillation (in cases A₁, B₁, and B₂, some or all of product (I) distilled with the ether) and the fractions converted into crystalline derivatives, usually picrates, whose homogeneity was carefully examined. The materials were so tractable that the zero values in Table I are considered to represent at most very small quantities of the corresponding substances, especially of the products (I). The same applies to the figures quoted from Bruylants¹⁰ and from Christiaen⁵³, who used relatively large quantities of materials, and state expressly that formation of (II) was never observed.

(A) Dimethylaminoacetonitrile (von Braun⁵⁴); the picrate was obtained in fine yellow needles, m.p. 168-169°, from alcohol. (Found: C₆H₃O₇N₃, 73.4. C₄H₈N₂.C₆H₃O₇N₃ requires C₆H₃O₇N₃, 73.2%).

(1) With methylmagnesium iodide (H₂SO₄) there resulted 4% of ethyldimethylamine which passed over with the ether and was identified as picrate, m.p. and mixed m.p. 200-201° (compare Hanhart/

Hanhart and Ingold⁵⁵), and 50% of acetyl dimethylamine which distilled at 123° and gave a methiodide, m.p. 166-167°, alone or mixed with authentic acetyltrimethylammonium iodide prepared according to the method of Stoermer and Dzinski⁵⁶.

(2) Ethylmagnesium bromide (H₂SO₄; negative) gave dimethylaminomethyl ethyl ketone in 60% yield. Neither the hydrochloride nor the hydrobromide could be obtained crystalline, and it was difficult to free the picrate from occluded picric acid, but the p-bromophenacylobromide crystallised from alcohol-ether in small prisms, m.p. 180-181° (decomp.) (Found: ionisable Br, 20.1. C₁₄H₁₉O₂NBr.Br' requires Br', 20.4%). Methyl ethyl ketone 2:4-dinitrophenylhydrazone was obtained as fine orange-red needles from alcohol, m.p. and mixed m.p. 111-112° (Found: N, 22.3. C₁₀H₁₂O₄N₄ requires N, 22.2%).

(3) n-Propylmagnesium bromide (H₂SO₄; negative) gave 58% of dimethylaminomethyl n-propyl ketone which gave a p-bromophenacylobromide in minute prismatic needles, m.p. 178-181° (decomp.; softening at 175°), from alcohol-ether (Found: ionisable Br, 19.4. C₁₅H₂₁O₂NBr.Br' requires Br', 19.7%). Methyl n-propyl ketone 2:4-dinitrophenylhydrazone was obtained as glistening orange-red leaflets, m.p. and mixed m.p. 142-143°, from alcohol (Found: N, 21.0. C₁₁H₁₄O₄N₄ requires N, 21.1%).

(5) The amino-nitrile, after treatment with acetylenemagnesium bromide, CH₂:C.MgBr, prepared as described by Salkind and Rosenfeld⁵⁷, was recovered quantitatively as picrate. No attempt was made to "force" reaction by heating.

(6) With benzylmagnesium chloride there was obtained a 75% yield of crude product (H_2SO_4 ; negative) which decomposed partially on steam-distillation. Dimethylaminomethyl benzyl ketone hydrobromide formed fine needles or minute short prisms, m.p. $151-153^\circ$, from alcohol-ether (Found: HBr, 31.9. $C_{11}H_{15}ON \cdot HBr$ requires HBr, 31.4%). Phenylacetone semicarbazone melted at $187-189^\circ$ (Wolff⁵⁸ gives m.p. $188-189^\circ$) and the phenylhydrazone at $83-85^\circ$ (Miller and Rohde⁵⁹ give m.p. 85°).

(7) Phenylmagnesium bromide (NH_4Cl ; negative) gave 78% of phenacyldimethylamine, identified as picrate, m.p. and mixed m.p. 143° (decomp.); acetophenone phenylhydrazone, m.p. and mixed m.p. $105-106^\circ$.

(B) α -Dimethylaminopropionitrile (Henry⁶⁰).

(1) With methylmagnesium iodide (H_2SO_4) there was obtained 14% of isopropyldimethylamine which passed over with the ether and gave a picrate, fine yellow needles from alcohol, m.p. $240-241^\circ$ (decomp.) (Found: $C_6H_3O_7N_3$, 72.6. $C_5H_{13}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 72.5%). There also resulted 50% of methyl α -dimethylaminoethyl ketone, isolated as picrate, minute yellow prisms from alcohol, m.p. $166-168^\circ$ (after frequent recrystallisation to remove traces of isopropyldimethylamine picrate) (Found: $C_6H_3O_7N_3$, 66.9. $C_6H_{13}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 66.6%); methyl ethyl ketone 2:4-dinitrophenylhydrazone, m.p. and mixed m.p. $111-112^\circ$. For comparison, isopropyldimethylamine was prepared by Eschweiler methylation of isopropylamine which was obtained as described by Goldschmidt⁶¹. The reaction product was diluted with water, evaporated/

evaporated to dryness, and the hydrochloride decomposed with strong aqueous alkali in presence of ether. The ethereal solution gave isopropyldimethylamine picrate, identical with that described above.

(2) Ethylmagnesium bromide (H_2SO_4) gave 13% of sec.-butyldimethylamine which passed over with the ether and gave a picrate, fine yellow needles, m.p. $192-193^\circ$, from alcohol (Found: $C_6H_3O_7N_3$, 69.6. $C_6H_{15}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 69.4%); and also 50% of ethyl α -dimethylaminoethyl ketone, obtained as picrate, minute yellow prisms, m.p. $161-163^\circ$, from acetone (Found: $C_6H_3O_7N_3$, 64.5. $C_7H_{15}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 64.0%). Diethyl ketone semicarbazone melted at $138-139^\circ$ (Dilthey⁶² gives m.p. 139°). For comparison, sec.-butyldimethylamine was prepared by Eschweiler methylation of sec.-butylamine, obtained as described by Freylon⁶³, and the picrate was identical with that described above.

(3) n-Propylmagnesium bromide (H_2SO_4 ; negative) gave 67% of α -dimethylaminoethyl n-propyl ketone, obtained as picrate, small yellow prisms, m.p. $200-201^\circ$, from acetone (Found: $C_6H_3O_7N_3$, 62.0. $C_8H_{17}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 61.6%). Ethyl propyl ketone semicarbazone melted at 110° (compare Blaise⁶⁴).

β -Dimethylaminopentane picrate, synthesised for comparison in the same way as isopropyldimethylamine picrate, formed small yellow prisms from acetone, m.p. $208-210^\circ$, strongly depressed on admixture with dimethylaminoethyl n-propyl ketone picrate (Found: $C_6H_3O_7N_3$, 66.4. $C_7H_{17}N, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 66.6%).

(4) The amino-nitrile, with cyclohexylmagnesium chloride (NH_4Cl), gave/

gave 64% of α -dimethylaminoethyl cyclohexyl ketone, b.p. 220-240°; the picrate, which was somewhat difficult to crystallise, gave yellow prisms, m.p. 165-167°, from methyl alcohol (Found: $C_6H_3O_7N_3$, 55.9. $C_{11}H_{21}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 55.6%). The p-bromophenacylobromide, minute prismatic needles from alcohol-ether, melted at 213-214° (decomp.) (Found: ionisable Br, 17.2. $C_{19}H_{27}O_2NBr.Br'$ requires Br', 17.4%). Ethyl cyclohexyl ketone semicarbazone melted at 149-150° (compare Hell and Schaal⁶⁵).

(6) With benzylmagnesium chloride (NH_4Cl) there was obtained β -dimethylamino- α -phenylpropane as a pale - yellow liquid, b.p. 148-150°/100 mm., in 76% yield. The methiodide crystallised from alcohol in rectangular prisms, m.p. 227-228° (von Braun, Heider, and Neumann⁶⁶ give m.p. 228°) (Found: I, 41.4. $C_{12}H_{20}NI$ requires I, 41.6%). The methopicrate, glistening yellow prisms from aqueous alcohol, melted at 103-105° (Found: $C_6H_2O_7N_3'$, 56.4. $C_{12}H_{20}N.C_6H_2O_7N_3$ requires $C_6H_2O_7N_3'$, 56.2%).

(7) Phenylmagnesium bromide (NH_4Cl) gave 78% of α -phenylethyl-dimethylamine, b.p. 194-195°, identified as picrate, glistening yellow leaflets from aqueous methyl alcohol, m.p. 136-139°, alone or mixed with authentic α -phenylethyldimethylamine picrate prepared as described by Stevens².

(C) α -Dimethylamino-n-valeronitrile boiled at 170-175°. Henry²⁰ gives b.p. 175-176°.

(1) Methylmagnesium iodide (H_2SO_4 ; negative) gave 53% of methyl α -dimethylamino-n-butyl ketone, isolated as picrate, stout, yellow, prismatic needles, m.p. 118-120°, from alcohol (Found: $C_6H_3O_7N_3$, 61.9. $C_8H_{17}ON, C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 61.6%).

Methyl n-butyl ketone semicarbazone melted at 126-127°

(Bouveault and Locquin⁶⁷ give m.p. 127°).

(H) Piperidinoacetonitrile (Knoevenagel⁶⁸).

(1) Methylmagnesium iodide (H_2SO_4) yielded 50% of ethylpiperidine, b.p. 126-129°; the picrate, fern-like aggregates of yellow prisms from alcohol, melted at 167-168° (Found: $C_6H_3O_7N_3$, 67.2. $C_7H_{15}N$, $C_6H_3O_7N_3$ requires $C_6H_3O_7N_3$, 67.0%) (Bruylants¹⁰ gives base, b.p. 128-129°; picrate, m.p. 165°). A small amount of a higher boiling liquid was also obtained, as found by Bruylants, which gave an apparently homogeneous methiodide crystallising from alcohol-ether in prismatic needles, m.p. 296-297° (decomp.), which was thus not identical with the methiodide of acetonylpiperidine, a possible product of the reaction, which has m.p. 126° (compare Störmer and Buckert⁶⁹).

(J) α -Piperidinopropionitrile (Knoevenagel⁶⁸).

(7) Phenylmagnesium bromide (H_2SO_4) gave 63% of 1- α -phenylethylpiperidine, identified as picrate, m.p. 145-147° (softening at 142°), alone or mixed with authentic 1- α -phenylethylpiperidine picrate prepared as described by Stevens, Cowan, and MacKinnon⁹.

(G) α -Dimethylaminophenylacetonitrile (Stevens, Cowan, and MacKinnon⁹).

(1) Methylmagnesium iodide (H_2SO_4) yielded 71% of α -phenylethyldimethylamine, isolated as picrate, m.p. and mixed m.p. 134-137°.

(7) With phenylmagnesium bromide (H_2SO_4) there resulted 63% of benzhydryldimethylamine, /

benzhydryldimethylamine, m.p. 68-69°, alone or mixed with authentic benzhydryldimethylamine prepared as described by Stevens².

Competitive Experiments. - The nitrile (1 mol.) was added to Grignard reagents (1 mol. of each, estimated by acid titration; compare Gilman and Meyer⁷⁰) in ether, and the reaction products worked up, mutatis mutandis, as in the previous experiments.

Propionitrile (Walden⁷¹) gave with methylmagnesium iodide + benzylmagnesium chloride (H₂SO₄) 23% of methyl ethyl ketone, isolated as 2:4-dinitrophenylhydrazone, m.p. and mixed m.p. 111-112°; and also 38% of ethyl benzyl ketone, b.p. 222-227°, identified as semicarbazone, m.p. 150-153° (Tiffeneau and Fourneau⁷² give m.p. 153°). Ethyl benzyl ketone 2:4-dinitrophenylhydrazone crystallised from alcohol in fine, deep-yellow needles, m.p. 140-141° (Found: N, 17.2 C₁₆H₁₆O₄N₄ requires N, 17.1%). With methylmagnesium iodide + phenylmagnesium bromide (H₂SO₄) there resulted only propiophenone (yield 67%), b.p. 217-220°, identified as 2:4-dinitrophenylhydrazone, glistening red leaflets from alcohol, m.p. and mixed m.p. 187-189° (Found: N, 17.8 C₁₅H₁₄O₄N₄ requires N, 17.8%).

α-Piperidinopropionitrile with methylmagnesium iodide + benzylmagnesium chloride (H₂SO₄) gave only α-phenyl-β-piperidino-propane (yield 63%). The picrate proved difficult to obtain crystalline, but the p-bromophenacylobromide gave minute prisms, m.p. 197-199°, from alcohol-ether (Found: ionisable Br, 16.8. C₂₂H₂₇ONBr.Br' requires Br', 16.6%). For comparison, the same substance/

substance was prepared according to the reaction of Leuckart and Wallach⁷³ by heating ethyl benzyl ketone (1 mol.), piperidine (1 mol.), and formic acid (80%; 2-3 mols) at 170-200° for 3 hours (sealed tube). The benzene extract of the basified product was thoroughly washed with water, evaporated, and the residue converted to p-bromophenacylobromide, which proved identical with that described above. With the same nitrile, methylmagnesium iodide + phenylmagnesium bromide (H₂SO₄) gave only 1-α-phenylethylpiperidine (yield 60%), identified as picrate, m.p. and mixed m.p. 145-147° (softening at 142°).

S U M M A R Y.

SECTION I - THE DEGRADATION OF QUATERNARY AMMONIUM SALTS

A - In the previous work on this subject, the salts investigated have been of the type $R.CO.CH_2.NMe_2X$. The rearrangement has now been extended to salts not strictly adhering to this type. For example, the rearrangement of salts in which the migrating radical is phenacyl (I→II), or in which the methylene carbon atom to which migration occurs is that of a benzyl group (III→IV) has now been effected.



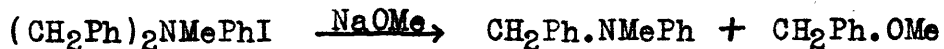
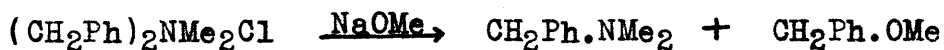
Analogous attempts to effect the rearrangement of di-p-bromophenacyldimethylammonium bromide and of diacetyldimethylammonium chloride (compare I), and also of di-p-bromobenzyl-dimethylammonium bromide (compare III) resulted in total decomposition of the salts.

The rearrangement of phenyldibenzylmethylammonium iodide and of benzyldimethylallylammonium bromide, both of which may be regarded as potential analogous of (III), has been accomplished. In the latter case, however, the benzyl group was found to migrate to the methylene carbon atom of the allyl radical, thus -



The conditions necessary to effect the rearrangement of (III) and its analogues are much more violent than those hitherto employed in these investigations.

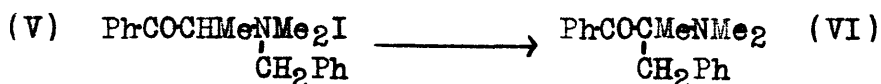
The preparation of phenacylphenylbenzylmethylammonium bromide has been undertaken in order to study the effect of replacement of one of the methyl groups attached to the quaternary nitrogen atom by phenyl on the rearrangement. It has been shown, however, that the interaction of ω -bromoacetophenone and benzylmethylaniline gives rise, not to the required salt, but to phenyldibenzylmethylammonium bromide. Other methods of preparation being likewise unsuccessful, the afore-mentioned effect has therefore been investigated by a comparison of the conditions of degradation of dibenzyltrimethylammonium chloride (III) and of phenyldibenzylmethylammonium iodide. It has been shown that, in addition to the rearrangement mentioned above, both of these salts, on treatment with alkali, undergo decomposition in the direction -



The presence of the phenyl group is shown to facilitate decomposition in this manner at the expense of the rearrangement proper.

The preparation of quaternary salts of the type $\text{PhCOC}(\text{R}_1)(\text{R}_2)\underset{\text{CH}_2\text{Ph}}{\text{NMe}_2}\text{X}$, in which the hydrogen atoms of the phenacyl methylene group are replaced, has been undertaken with a view to the/

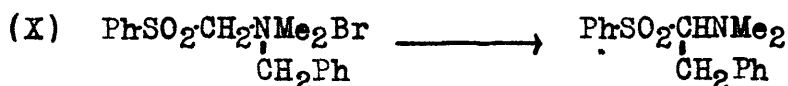
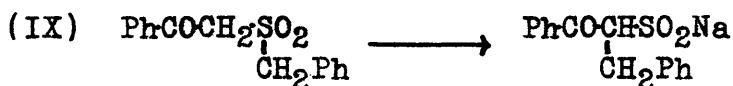
the investigation of their rearrangement. The monomethylated substance (V) gives (VI) readily, but salts in which one of the hydrogen atoms in question is replaced by phenyl, or both by methyl, could not be prepared. It has been shown that the progressive replacement of the hydrogen atoms of the methylene carbon atom of the phenacyl group leads to a progressive decrease in the ease of quaternary salt formation.



B - The generality of the rearrangement under investigation has been further extended by the fact that the sulphonium salt (VII), analogous to phenacylbenzyltrimethylammonium bromide, has been shown to rearrange to give (VIII) readily, on treatment with alkali.

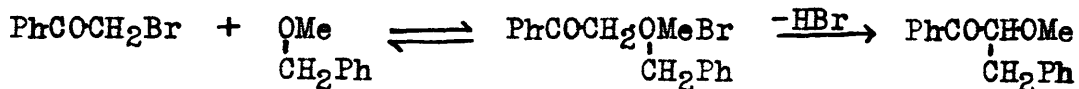


Further extensions to the reactions (IX) and (X) were unsuccessful, because the sulphone (IX) was hydrolysed by alkali to benzyl methyl sulphone and benzoic acid, while the initial salt (X) could not be obtained from bromomethyl phenyl sulphone and benzyltrimethylamine, owing to the unexpected inertness exhibited by the halogen atom of the bromo-sulphone.

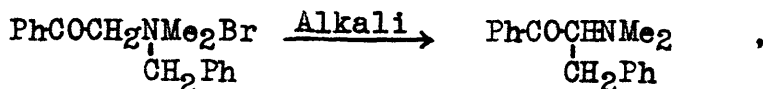


Attempts to bring about the rearrangement of an oxonium salt/

salt, according to the scheme outlined below, were also unsuccessful.



C - An experimental technique has been devised for the measurement of the velocity of the reaction



and, as a necessary preliminary to the measurement of the relative migratory velocities of substituted benzyl radicals, the unsubstituted salt has been studied in some detail. The rearrangement has been found not to proceed quantitatively, but to give rise to a quantity of by-product which is largely independent of the conditions, but whose nature is uncertain. Good, monomolecular constants have been obtained for the velocity of migration in methyl-, ethyl-, n-propyl-, and iso-propyl-alcoholic solutions of the corresponding sodium alkoxides. In aqueous sodium hydroxide solution the reaction velocities are smaller, and the values of *k* (the velocity "constants") fall off as the reaction proceeds. Increase in the alkoxide concentration produces an appreciable, but not a proportional, increase in velocity. The velocity has been found to vary with the medium in the order MeOH ≪ EtOH < Pr^αOH ≪ Pr^βOH. The attribution of these differences to specific medium effects rather than to a difference in reagent (sodium alkoxide), which is another possibility, has been confirmed by experiment. The velocity of the/

the rearrangement has been shown to be independent of the nature of the anion of the quaternary salt, while the temperature coefficient of the reaction has been found to have the unusually high value, $Q_{10} = 5.70$.

The velocities of rearrangement of salts containing o-, m-, and p-chloro-, bromo-, iodo-, nitro-, methoxy-, and methylbenzyl radicals have been studied, and the migratory velocities of these radicals, relative to unsubstituted benzyl, found to be

	Cl	Br	I	NO ₂	OMe	Me
<u>o</u> -	35.6	47.7	81	1040	1.91	15.3
<u>m</u> -	2.44	2.09	1.92	3.81	0.93	0.97
<u>p</u> -	2.77	2.86	3.25	73	0.76	1.06

It has been shown for a sufficient number of cases to justify the assumption of the generality of the statement that the ratios of the velocities of migration of these radicals are the same whether the radicals are associated with phenacyl or with p-bromophenacyl in the quaternary salts.

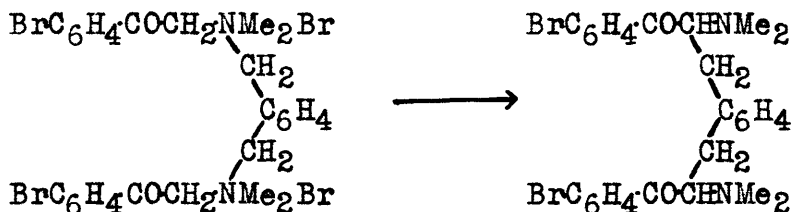
The following generalities are noted and discussed. In all three positions the effects of substituents are in the order OMe < Me < Hal. < NO₂ (the inequality m-OMe < m-Me is not held to be established). The halogens fall in the same order in the o- and in the p-series, but in the reverse order in the m-series. There is a distinct parallelism between the compounds of the o- and of the p-series, qualitatively, and to some extent, quantitatively, except that all the compounds of the o-series, with the exception of o-methoxybenzyl-, have a greatly increased velocity/

velocity of rearrangement. Except in the case of the nitro-benzyl radicals, the m- and the p-values for each substituent are of the same order of magnitude.

It is suggested that the values obtained represent fairly accurately a measure of the relative migratory tendencies, in other words, the relative anionic stabilities, of the substituted benzyl radicals investigated, and that the good agreement obtaining among the results themselves justifies the postulates made as to the mechanism of the rearrangement.

Unusual behaviour in the melting points of the various sets of isomerides is noted, though no generalities have been recognised.

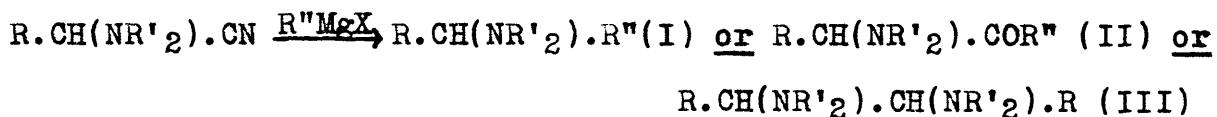
Incidentally, the analogous diammonium salts containing m- and p-xylylene radicals have been found to undergo twofold rearrangement under the usual reaction conditions. Thus -



SECTION II - THE ACTION OF THE GRIGNARD REAGENT UPON
AMINO-NITRILES

The work of previous investigators has shown that an α -aminonitrile and a Grignard reagent may interact in either of/

three ways, thus -



A detailed investigation has now been made of the effect of varying R and R'' upon the course taken by the reaction, while R' = Me. The results obtained give rise to the following general observations. Reaction (III) is not observed with dimethylamino-nitriles. When R = H, product (II) predominates irrespective of the nature of R''. This association of the group >N.CH₂CN with reaction course (II) has previously been noted by Stevens, Cowan, and MacKinnon⁹. When R is a lower alkyl, (II) predominates if R'' is alkyl, and (I) if R'' is Ph or CH₂Ph. That the controlling factor in these cases is not simply the weight of R'' is shown by the fact that cyclohexyl behaves like the simple alkyls. When R = Ph, the main product is always (I), which is in agreement with previous work on the subject.

The sensitiveness of the reaction to small constitutional changes is shown by a comparison of the results obtained with dimethylamino-nitriles and with piperidino-nitriles. With the latter reaction (II) is completely suppressed. In this respect it is suggested that the basic strength of the amino-nitrogen atom is a controlling factor of importance.

It is suggested that the effect due to a given substituent upon the nature of the final product is to be regarded as compounded of its separate effects upon the velocities of reactions (I) and (II), and an attempt has been made in several cases/

cases to obtain some idea of these separate effects by a series of "competitive experiments".

Further investigation is necessary, however, before any rigid conclusions can be formulated.

A C K N O W L E D G E M E N T S

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