CCV.—*The Replacement of Alkyl Radicles by Methyl in Substituted Ammonium Compounds.*

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It was shown by one of us (Proc., 1901, **17**, 205) that dibenzyl-aniline and quaternary ammonium compounds containing the methyl and benzyl groups, when heated with methyl iodide, yielded benzyl iodide and phenyltrimethylammonium iodide. No other alkyl iodide among those tried, namely, ethyl, propyl, *isobutyl*, and allyl iodides, was found to effect this displacement of the methyl group, and it could not be shown that other groups were displaced by methyl (at this time allyl compounds were not examined). Later (Trans., 1905, **87**,

1726), it was found that the allyl group is displaced from benzylallyl-aniline by methyl iodide in the cold, and the benzyl group on heating.

At this time, it seemed that the allyl and benzyl groups were the only ones that could be replaced by the methyl group, since optically active compounds containing these radicles racemised readily in chloroform solution, and also their iodides have the greatest capacity for uniting with aromatic tertiary amines, the conclusion that the displacement was dependent on their common properties was apparently justified.

This displacement of benzyl and allyl groups by methyl was found to be general, as proved by the following transformations, in addition to those already mentioned, which were found to take place rapidly when the first-mentioned compound was heated to 100° with methyl iodide alone or with methyl iodide and alcohol or chloroform.

Phenylbenzylmethyl*iso*amylammonium iodide $\rightarrow$ phenyldimethyl-*iso*amylammonium iodide, phenylbenzylmethyl*iso*propylammonium iodide $\rightarrow$ phenyldimethyl*iso*propylammonium iodide, phenyldimethylallylammonium iodide $\rightarrow$ phenyltrimethylammonium iodide, phenylmethyl*iso*amylallylammonium iodide $\rightarrow$ phenyltrimethylammonium iodide, phenylmethyl*iso*amylallylammonium iodide $\rightarrow$ phenyldimethyl*iso*-amylammonium iodide.

Ethyl, propyl, *isobutyl*, and *isoamyl* iodides, when heated with benzyl and allyl compounds, did not effect any displacement, although the odour of allyl or benzyl iodide was always noticeable.

In 1906, some anomalous results were obtained while attempting to prepare a series of compounds containing the phenyl, methyl, and ethyl groups together with propyl, *isopropyl*, *isobutyl*, and *isoamyl* groups. Ethyl*iso*amylaniline and methyl iodide were found to combine slowly in the cold, and the resulting product was, as expected, phenylmethylethyl*iso*amylammonium iodide.

Ethyl*iso*propylaniline and methyl iodide reacted very slowly in the cold, but eventually deposited a crystalline solid which, after repeated crystallisations, melted at 167—168°. It was found to be identical with phenyldimethyl*iso*propylammonium iodide (m. p. 168°), prepared from methyl*iso*propylaniline and methyl iodide. It was evident therefore that the ethyl group was in this case displaced by methyl in the cold.

Ethylpropylaniline and methyl iodide reacted slowly, depositing a gum which became crystalline on standing; after recrystallising, the following numbers were obtained on analysis:

Found, C = 45.12, 45.4; H = 6.39, 6.4.

MeEtPh(C₃H₇)NI requires C = 47.2; H = 6.56 per cent.

Me₂Ph(C₃H₇)NI „ C = 45.12; H = 6.14 „

A similar displacement of the ethyl group has evidently taken place here. This compound and the product from methylpropylaniline and methyl iodide are very soluble, and difficult to recrystallise and purify; hence their absolute identity has not yet been established.

Later, it was found that the series of substituted *p*-bromoanilines already described (Hill, *Proc. Camb. Phil. Soc.*, 1907, **14**, 166) all reacted at 100° with methyl iodide and gave *p*-bromophenyltrimethylammonium iodide. This compound is very easy to isolate and identify, even when formed in quite small quantities, on account of its small solubility in alcohol, its characteristic appearance, and melting point of 200°, a melting point which is higher than that of any of the other ammonium iodides derived from this series of amines.

p-Bromomethylethylaniline or *p*-bromophenyldimethylethylammonium iodide and the corresponding propyl, *isopropyl*, *n*-butyl, and *isobutyl* compounds were found to give some *p*-bromophenyltrimethylammonium iodide after heating at 100° for two hours in a sealed tube with excess of methyl iodide; the *isobutyl* compound appeared to be completely transformed, whilst the ethyl, propyl, and *isopropyl* compounds yielded a moderate quantity of the trimethyl compound.

The *isoamyl* compound, however, seemed to react much less readily, and at first it was thought that no action had taken place; but after prolonged heating, the trimethyl compound was detected: *p*-bromophenylbenzylmethyl*isoamyl*ammonium iodide yielded the trimethyl compound in somewhat larger quantity.

It was clear therefore that the six saturated hydrocarbon radicles mentioned above behaved in the same way as the benzyl and allyl groups, but that they were not always so readily nor so completely displaced by methyl, as the benzyl and allyl groups.

Attention was now directed to the corresponding series of phenyl compounds to determine whether they behaved in the same way as the bromophenyl derivatives. Phenyldimethylethylammonium iodide and the corresponding propyl, *isopropyl*, *isobutyl*, and *isoamyl* compounds were heated with methyl iodide and examined for phenyltrimethylammonium iodide. This compound is easy to identify on account of its slight solubility, which, however, is much greater than that of the corresponding bromo-compound, and its behaviour on heating, when it volatilises at 220°. All the compounds, except the *isoamyl* derivative, were found to give phenyltrimethylammonium iodide, but even after prolonged heating none could be obtained from this.

It was found, however, that phenylbenzylmethyl*isoamyl*ammonium iodide yielded some phenyltrimethylammonium iodide after heating with a large excess of methyl iodide.

Here, the ease with which a radicle was displaced seemed to diminish with increasing molecular weight, except that the *isobutyl* group appears to be more readily replaced than the propyl; but the ease with which displacement took place in all cases was distinctly less than in the corresponding bromo-compounds. Phenylbenzylmethyl-*l*-amylammonium iodide (Trans., 1905, **87**, 135) was found to give the trimethyl compound with difficulty, like the corresponding *isoamyl* derivative.

It seems probable that the difference between the *isoamyl* and the other groups as regards the ease with which they are replaced is merely one of degree.

The displacement of alkyl radicles by methyl could take place in one of two quite distinct ways: (1) by direct action between methyl iodide and the ammonium iodide, thus:

or (2) partial dissociation into tertiary amine and an alkyl iodide might occur in the methyl iodide solution; then the methyl iodide being present in great excess would react with the tertiary amine to form an ammonium iodide until equilibrium was established in solution, thus:

On consideration, the latter view appears the more probable, since we know that the dissociation postulated does occur in chloroform solution and results in gradual racemisation of active ammonium iodides. That this same dissociation also occurs in solution in alkyl iodides was shown by examining solutions of *l*-phenylbenzylmethyl*isopropyl*ammonium iodide (Thomas and Jones, Trans., 1906, **89**, 289) in methyl iodide and in ethyl iodide. The salt is extremely sparingly soluble in the iodides, but the addition of a few drops of alcohol enabled a solution to be prepared which gave a rotation great enough for the changes to be observed.

In methyl iodide:

Initial rotation, -0.57° ; after six hours, -0.32° ; after twenty-four hours, -0.14° ; after thirty hours, -0.03° ; after forty-eight hours, inactive.

In ethyl iodide:

Initial rotation, -0.62° ; after six hours, -0.40° ; after twenty-three hours, -0.12° ; after thirty hours, -0.07° ; after forty-eight hours, inactive.

Hence this iodide racemises in methyl and in ethyl iodide solution at practically the same rate as in chloroform (compare Trans., 1906,

89, 290). It follows, therefore, that a dissociation into tertiary amine and alkyl iodide must take place in the case of compounds containing other groups besides benzyl and allyl. Unfortunately, up to the present time, no optically active nitrogen compound is known which does not contain either the benzyl or allyl group together with methyl, otherwise this dissociation could be shown by their auto-racemisation.

The ease of replacement would then depend on the extent to which this dissociation into alkyl iodide and tertiary amine occurred. It seems probable that the order of the alkyl radicles as regards extent of dissociation would be the same as that for ease of addition. Taking Wedekind's values for the percentage amount of ammonium salt formed from these alkyl iodides and dimethylaniline in fifty-three hours (*Stereochemie des fünfwertigen Stickstoffs*, 1899, 21), namely, methyl, 89; ethyl, 15; *n*-propyl, 28; *isopropyl*, 5; *n*-butyl, 17; *isobutyl*, 1.6; *isoamyl*, 2.5; allyl, 93; benzyl, 83, we see that the ease of replacement, which is determined presumably by the extent of the dissociation, is roughly in the same order as the ease of formation of quaternary salt by the alkyl iodide in question.

There is, however, an apparent exception in the case of the *isoamyl* group, which we find to be the most difficult to displace, more difficult than the *isobutyl* group, yet its iodide appears to combine with dimethylaniline more readily than the latter.

We therefore examined this point further by allowing mixtures of dimethylaniline and equivalent quantities of ethyl iodide, *isobutyl* iodide, and *isoamyl* iodide to remain for one month at the ordinary temperature. The much longer time was allowed in order to avoid such a large percentage error from the solubility of the salt in the mixture of amine and iodide, which, when very small quantities such as Wedekind obtained (0.15—0.8 gram) are concerned, must exert a disturbing influence on the quantitative results. One-twentieth of a gram-molecule of each mixture was taken, and after standing one month the iodide was separated, dried between filter paper, and weighed (the *isobutyl* compound was crystalline), and found to be 23.6 per cent. for ethyl, 2.0 per cent. for *isobutyl*, and 1.3 per cent. for *isoamyl*. Hence it would appear that the *isoamyl* iodide has not, at any rate, a greater reaction velocity than the *isobutyl*.

Methyl iodide comes third in order of rapidity of reaction with dimethylaniline, and it is therefore surprising to find that it is the one that is capable of replacing all the others; the explanation of this is probably to be found in the very small solubility of the methyl compound as compared with the others, which also accounts for the much greater ease with which replacement takes place in the *p*-bromophenyl than in the phenyl series. The solubilities of the substituted

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ammonium iodides in alcohol at the ordinary temperature, expressed in grams in 100 grams, are as follows:

		Solubility.	Melting point.	<i>p</i> -Bromophenyldimethyl.	
				Solubility.	Melting point.
Phenyldimethyl.	-methyl	1.1	220° (volatilises)	0.12	200°
	-ethyl	45.1	136	1.15	189
	-isopropyl	11.8	168	3.30	167
	-isobutyl	24.1	155—156	5.69	167—168
	-isoamyl	18.4	138	2.38	176
	-benzyl	2.7	165	—	—

It therefore appears that the ease with which a radicle is displaced by methyl is dependent on two factors; first, the amount of dissociation into tertiary amine and alkyl iodide, of which the rate of formation of the salt from alkyl iodide and amine may be regarded as a measure, and secondly, the solubility of the ammonium salt from which the group is to be displaced. The slight solubility of the trimethyl compound enables this to separate from the solution and so to be removed from the sphere of action.

The ready solubility of the *isobutyl* compound of the *p*-bromophenyl series probably accounts for the fact that this group is more readily displaced than all the others.

On the view expressed above, that the extent of the dissociation is determined by the velocity of addition of the alkyl iodide to the tertiary amine, ammonium salts containing the methyl group should dissociate into amine and methyl iodide to quite a considerable extent. That this is actually the case is shown by the following observations: *p*-bromodimethylaniline was allowed to stand with the iodides of the following radicles, ethyl, propyl, *isopropyl*, *isobutyl*, and *isoamyl*. In the cold, the reaction was extremely slow, except in the case of the ethyl compound. The solid deposited in this case was found to consist chiefly of *p*-bromophenyltrimethylammonium iodide. At 100°, the other four alkyl radicles also yielded a considerable quantity of the trimethyl compound.

It would appear that the following scheme is the probable explanation of these results:

The quaternary salt first formed is dissociated in two distinct ways, so that in the solution we have an equilibrium between two alkyl iodides and two tertiary amines. The very small solubility of the trimethyl compound then determines the separation of this salt from the solution. A dissociation of ammonium salts into two amines

and two alkyl iodides on heating has been observed by Wedekind (*Ber.*, 1902, **35**, 766).

The results may be summarised as follows: the groups, allyl, benzyl, ethyl, *isobutyl*, propyl, *isopropyl*, and *isoamyl*, are displaced from ammonium salts by the methyl group on treating with methyl iodide, sometimes in the cold, more usually on heating. The displacement takes place owing to the salt dissociating in methyl iodide solution into tertiary amines and alkyl iodides; an equilibrium is set up between the dissociated amines, iodides, and the methyl iodide, and, since in each case the trimethyl compound is much less soluble than the other, this separates, and so is found in much greater quantity than the other in the solid product.

The order given is roughly that of the ease of displacement of these radicles, which is determined by the extent of the dissociation and the solubility of the ammonium salt in question. The *isoamyl* group is the most difficult to displace.

The expenses of this investigation have been defrayed by grants from the Government Grant Committee of the Royal Society, for which we are glad to take this opportunity of expressing our thanks.

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