[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

# REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XXXVII. THE CLEAVAGE OF QUATERNARY AMMONIUM SALTS WITH GRIGNARD REAGENTS

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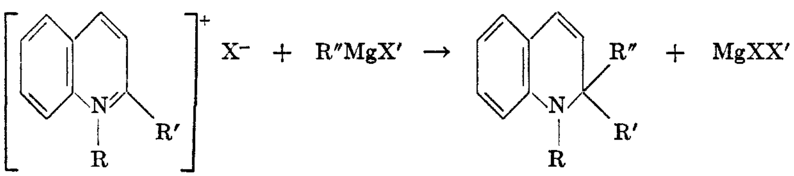
The most widely investigated reaction between quaternary ammonium salts and Grignard reagents is that of the quinolinium and similar salts. Freund (1) found, for example, that 1-methylquinolinium and 9-phenyl-10-methylacridinium iodides react with Grignard reagents to give products in which the organic radical of the Grignard is attached to some atom other than the nitrogen atom. An organic molecule containing only covalent bonds is thus formed according to the following general equation.

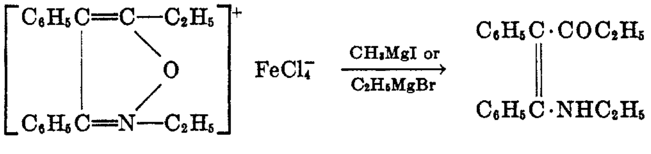


Reactions of the type indicated have also been reported by Freund and Richard (2) and by Craig (3). Similar reactions in the isoquinoline series were found by Freund and Bode (4) and by Bergmann and Rosenthal (5). In the reactions involving acridinium salt, bond formation takes place at the 9-position (see ref. 1, 4, 6). The 2,4-dihydropyrazinium salts (7), quinoxalinium salts (2), and phenazinium salts (8) react similarly with Grignard reagents. The literature contains other examples of reactions of the type under discussion. Among them are those of the salts of the "triphenylmethane dye" type where the radical from the Grignard reagent adds to the methane carbon atom (see ref. 2, 9).

The tetraalkylmethyleneimmonium salts (10) react with Grignard reagents to form tertiary amines, *e.g.*

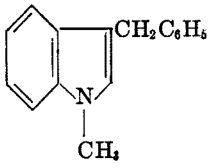
$$[(CH_3)_2C{=}N(C_2H_5)_2]^+I^- \quad + \quad CH_3MgI \quad \longrightarrow \quad tert\text{-}C_4H_9(C_2H_5)_2N \quad + \quad MgI_2$$

Isoxazolinium salts are reduced by Grignard reagents (11) as indicated below:

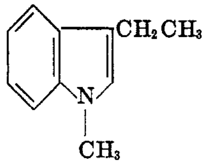


However, the corresponding chloride reacts very slowly with methylmagnesium iodide; with phenylmagnesium bromide it does not react at all.

The first recorded work on the cleavage by Grignard reagents of carbon-nitrogen bonds in quaternary ammonium salts is that of Snyder, Eliel, and Carnahan (12), who studied the reactions of gramine methiodide and 1-methylgramine methiodide with methyl- and phenyl-magnesium bromide. Their work followed that of Snyder and Eliel (13), who alkylated cyanoacetic ester and acetamidomalonic ester with these gramine derivatives. These workers found that 1-methylgramine methiodide and phenylmagnesium bromide (equivalent quantities, heated together in dibutyl ether at 100° for 114 hours) react to give Compound **A** (1-methyl-3-benzylindole, 73% yield); with methylmagnesium iodide, Compound **B** (1-methyl-3-ethylindole, 43% yield) was obtained.

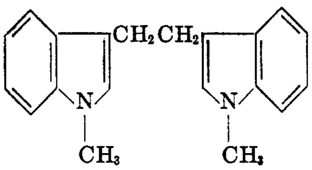


**A**



**B**

Compound **C** was also formed in small quantities during these reactions.



**C**

Similar results were obtained when gramine methiodide was treated with phenyl-, methyl-, and benzyl-magnesium halides. The yields in these latter experiments were somewhat lower.

The authors (12) also claim that benzyltrimethylammonium iodide and benzylpyridinium chloride do not react in the manner indicated above with Grignard reagent, nor is there any similar reaction when compounds containing a pyrrole, in place of the indole, nucleus are used.

In view of the "forcing conditions" used in the work just cited, and the production of a certain amount of the dimeric Compound **C**, we considered it likely that the reactions in question were homolytic in type. The present work was therefore undertaken to determine whether such is really the fact and to determine the scope of the reaction.

The work of Snyder, *et al.* (12) has been criticized by Geissman and Armen (14) who found that "gramine methiodide" prepared by Snyder's method is a mixture of the two compounds $[(CH_3)_4N^+]I^-$ and $[(RCH_3)_2N^+(CH_3)_2]I^-$, where R = 3-indolyl. This criticism does not, however, affect the validity of the argument stated in the preceding paragraph, since in any case some kind of cleavage is necessary if products of the types **A**, **B**, and **C** are to be produced by the reactions with Grignard reagents. If the reactions are indeed homolytic, then they should be catalyzed by metallic (*e.g.* cobaltous, nickelous, ferrous) halides, and by the use of such halides it should be possible to cleave quaternary salts under quite mild conditions. Allyltrimethylammonium bromide was chosen for first investigation since the allyl group insofar as it possesses a $\beta$, $\gamma$-double bond is analogous to the 3-indolyl group.

## RESULTS

In the following Tables (I–IV) are summarized the results of experiments conducted on the cleavage of a number of quaternary salts. Three distinct experimental *procedures* were employed in various experiments. These are designated *I*, *II*, and *III*, respectively, and are described in detail in the experimental section. Briefly, however, in *procedure I* cobaltous bromide (5 mole-%) was added in portions over a period of one hour to a stirred mixture of the salt and the Grignard reagent at room temperature; finally the mixture was heated under reflux for one hour. The excess Grignard reagent then was destroyed by hydrolysis. In *procedures II* and *III* the cobaltous bromide was added over a period of five hours; the mixture then was heated for one hour. In some cases, the excess Grignard reagent was destroyed by hydrolysis (*procedure II*); in others by carbonation (*procedure III*). The longer reaction period was employed because it was found to increase the yields. Divergencies from these general procedures in individual runs are noted in the Tables.

Complete analyses of all the products of the reaction were carried out only in selected cases. In other experiments, the amounts of amine formed were taken as a measure of the extent of the cleavage. Here the appropriate columns are left blank in the Tables. Details of the methods whereby the various products were identified are included in the experimental section.

## DISCUSSION

Examination of the products formed, when quaternary ammonium salts react with Grignard reagents at 20–35°, indicates (in spite of the small number of the salts thus far examined) that four distinct type reactions are possible. These type reactions are mostly associated with the nature of the groups attached to the quaternary nitrogen atom. The part played by the group attached to the Grignard reagent (RMgX) appears to be of minor (if any) importance insofar as the cleavage of the quaternary ammonium salt is concerned.

*Type I.* In this class belong quaternary ammonium salts which do not react with Grignard reagents in the absence or even the presence of metallic salts ($CoBr_2$, $NiBr_2$, $FeBr_3$); *i.e.* tetramethylammonium bromide and other simple tetraalkyl-ammonium salts.

*Type II.* This type includes quaternary salts which are cleaved by Grignard reagents only in the presence of metallic halides (5 mole-%) mentioned above, and in which the ejected group combines with the radical R of the Grignard reagent.

Allyltrimethylammonium halides belong in this group, and presumably all allyl trialkylammonium halides. The end products may be accounted for on the basis of schemes 1 and 2. The schemes as written do not have any mechanistic implications.

1. $$C_6H_5MgBr + CoBr_2 \rightarrow C_6H_5CoBr + MgBr_2$$

2. $$[(CH_3)_3NCH_2CH{=}CH_2]^+Br + C_6H_5CoBr \rightarrow (CH_3)_3N + C_6H_5CH_2CH{=}CH_2 + CoBr_2$$

About all that can be said at this time about these reactions is that they are of a homolytic *chain* type, because of the small amounts (2–5 mole-%) of the

TABLE I

SALTS OF TYPE I (1 MOLE OF SALT)

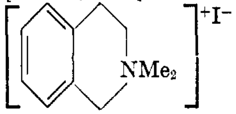
| Expt. No. | Salt (1 mole) | Grignard (moles) | | $CoBr_2$ (moles) | Procedure | Yield of Amine (moles) |
|---|---|---|---|---|---|---|
| 5 | $[PhCH_2NMe_3]^+Br^-$ | MeMgBr | 1 | 0.05 | I | 0 |
| 6 | $[PhCH_2NMe_3]^+Br^-$ | PhMgBr | 1 | 0.05 | I | 0.035 |
| 12 | $[PhCH_2NEt_3]^+Cl^-$ | PhMgBr | 1 | 0.05 | I | 0.05 |
| 15 |  | PhMgBr | 1 | 0.05 | I | 0 |
| 28 | $[PhCH_2NMe_3]^+Br^-$ | *iso*-PrMgBr | 1 | 0.05 | I | 0 |
| 46 | $[PhCH_2NMe_3]^+Br^-$ | PhMgBr | 2 | 0.05 | III | 0 |
| 47 | $[(PhCH_2)_2NMe_2]^+Cl^-$ | PhMgBr | 2 | 0.05 | III | 0.04 |
| 48 | $[Me_4N]^+I^-$ | PhMgBr | 2 | 0.05 | III | 0 |

TABLE II

SALTS OF TYPE II. (All Expts. by Procedure I)

| Expt. No. | Salt (1 mole) | Grignard (moles) | | Metal Halides (moles) | Amine (moles) | Coupled Product (moles) | Other product (moles) |
|---|---|---|---|---|---|---|---|
| 1 | $[C_3H_5NMe_3]^+Br^-$ | PhMgBr | 1 | $CoBr_2$ 0.05 | $Me_3N$ 0.46 | Allylbenzene 0.23 | Biphenyl 0.31 |
| 2 | $[C_3H_5NMe_3]^+Br^-$ | PhMgBr | 1 | 0 | $Me_3N$ 0.07 | — | — |
| 3 | $[C_3H_5NMe_3]^+Br^-$ | PhMgBr | 1 | $CoBr_2$ 0.05 | $Me_3N$ 0.48 | Allylbenzene 0.22 | Biphenyl 0.31 |
| 26 | $[C_3H_5NMe_3]^+Br^-$ | *iso*-PrMgBr[a] | 1 | $CoBr_2$ 0.05 | $Me_3N$ 0.62 | — | — |
| 24 | $[C_3H_5NMe_3]^+Br^-$ | *iso*-PrMgBr[a] | 1 | 1 | 0 | — | — |
| 34 | $[C_3H_5NMe_3]^+Br^-$ | PhMgBr | 1 | $FeCl_3$ 0.05 | $Me_3N$ 0.41 | Allylbenzene 0.38 | Biphenyl 0.49 |

[a] Sublimed magnesium was used in the preparation of this Grignard reagent.

cobalt halide used. It may well be that the reaction of the allyl trimethylammonium salt is initiated by an attack at the carbon atom of the double bond of the allyl group. If such is the case, the reaction must be accompanied by an allylic rearrangement.[1]

*Type III.* Aryltrialkylammonium salts belong in this group. These salts do not react at ordinary temperatures with Grignard reagents in the absence of metallic halides (Co, Ni, Fe). In the presence of small amounts (2–5 mole-%) of the metallic halides, the over-all reaction may be represented as follows:

$$3.\quad [C_6H_5N(CH_3)_3]^+Br^- + 2\ C_6H_5MgBr \xrightarrow[5\text{ mole-}\%]{CoBr_2} C_6H_5N(CH_3)_2 + C_6H_5C_6H_5 + CH_3MgBr + MgBr_2$$

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[1] This explanation may account for the unreactivity of the benzyltrimethylammonium salts.

Note that in these reactions the ejected group is converted into a Grignard reagent. In the reaction cited above, the formation of methylmagnesium bromide was demonstrated by the addition of water to the ethereal solution (after the reaction has ceased) and collection of the methane thus generated. Over 80 per cent of the calculated amount of methane was thus obtained.

When phenylbenzyldimethylammonium bromide was treated with two moles of phenyl magnesium bromide in the presence of two mole-per cent of cobalt bromide, the products of the reaction were: dimethylaniline, biphenyl, and benzylmagnesium bromide. The presence of this Grignard was demonstrated by carbonation of the reaction mixture and isolation of phenylacetic acid.

There is little doubt that the reaction of aryltrialkylammonium salts with phenylmagnesium bromide in the presence of cobalt salts proceeds by a free radical chain mechanism. One such mechanism is indicated below:

4. $$C_6H_5MgBr + CoBr_2 \rightarrow C_6H_5CoBr + MgBr_2$$

5. $$C_6H_5CoBr \xrightarrow[C_6H_5CoBr]{C_6H_5MgBr} C_6H_5C_6H_5 + 2(CoBr\cdot) \text{ or } [(CoBr)\cdot + (MgBr)\cdot]$$

6. $$[C_6H_5N(CH_3)_3]^+ + (CoBr)\cdot \text{ or } (MgBr)\cdot \rightarrow C_6H_5N(CH_3)_3\cdot + Co^+Br \text{ (or } {}^+MgBr)$$

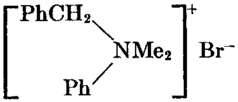
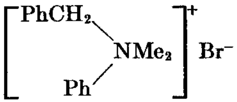
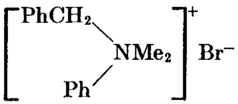
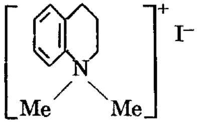
7. $$[C_6H_5N(CH_3)_3]\cdot + (MgBr)\cdot \rightarrow C_6H_5N(CH_3)_2 + CH_3MgBr$$

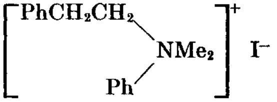
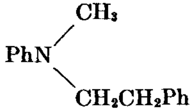
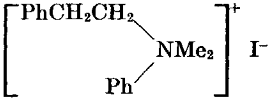
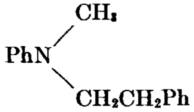
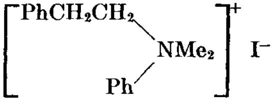
It makes little difference whether the free radical $(MgBr)\cdot$ or $(CoBr)\cdot$ reduces the quaternary salt. The reactions 6 and 7 have no mechanistic implications. They merely represent a stoichiometric relation between oxidant (quaternary salt) and reductant (sub-halides of the metal). The experimental evidence at present available does not permit a fruitful discussion of the reactions in greater detail.

For a mixed quaternary salt, when the four groups R′ are not identical, there arises the question of the relative facilities of removal of the various groups. Such experiments as have already been performed indicate that (with one exception) methyl groups are ejected preferentially, although when the various groups R′ are closely similar [*e.g.*, methyl and ethyl (Expt. 53, Table III)] a mixed product may be obtained. However, with phenylphenethyldimethylammonium iodide, and with kairoline methiodide, methyl groups are removed. The exception to this rule is benzylphenyldimethylammonium bromide from which the benzyl group is preferentially removed (Expt. 11, 43; Table III). This reaction is probably due to the considerable energetic advantage enjoyed by the benzyl, compared with the methyl radical.

The homolytic nature of these reactions is also demonstrated by Expt. 59 (Table III) in which thermal decomposition (at 140°) of the Grignard reagent (in place of the metallic halide) was employed to furnish radicals. The isolation of the dimethylaniline, and diphenyl in the expected equimolar amounts indicates that the course of reaction is probably similar to that followed in the cobalt-catalyzed reactions. This fact also indicates that the thermal reactions investigated by Snyder, *et al.* (12) were homolytic in nature. Thermal cleavage is, however, less satisfactory than the use of metal halides, not only because of increased experimental complexity but also because the salts themselves are not

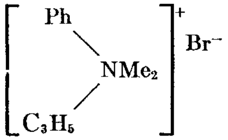
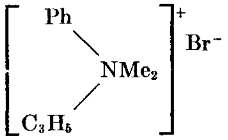
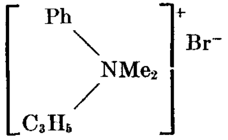
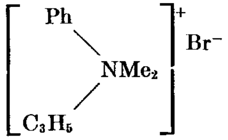
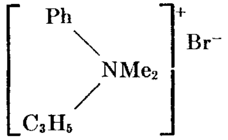
## TABLE III
SALTS OF TYPE III

| Expt. No. | Salt (1 mole) | Grignard (moles) | $CoBr_2$ (moles) | Procedure | Amine (moles) | Benzoic acid (moles) (Pro. III only) | Other Products (moles) |
|---|---|---|---|---|---|---|---|
| 40 | $[PhNMe_3]^+I^-$ | PhMgBr 2 | 0.05 | III | $PhNMe_2$ 0.65 | 0.32 | $(Ph)_2$ 0.7 |
| 41 | $[PhNMe_3]^+I^-$ | PhMgBr 2 | .05 | III | $PhNMe_2$ .67 | .42 | $(Ph)_2$ .6 |
| 44 | $[PhNMe_3]^+I^-$ | PhMgBr 2 | 0 | III | 0 | — | — |
| 45 | $[PhNMe_3]^+I^-$ | PhMgBr 2 | .05 | II | — | — | Methane gas (m.w. 16) |
| 11 |  $[PhCH_2N(Me_2)Ph]^+Br^-$ | PhMgBr 1 | .05 | I | $PhNMe_2$ .39 | — | — |
| 42 |  $[PhCH_2N(Me_2)Ph]^+Br^-$ | PhMgBr 2 | 0 | III | $PhNMe_2$ .04 | — | — |
| 43 |  $[PhCH_2N(Me_2)Ph]^+Br^-$ | PhMgBr 2 | .05 | III | $PhNMe_2$ .62 | — | Biphenyl .8<br>Benzene .32<br>$PhCH_2CO_2H$ .42 |
|  |  | PhMgBr | .05 | I |  | — | — |
| 13 | $[\alpha\text{-}C_{10}H_7NMe_3]^+I^-$ | PhMgBr 1 | .05 | I | $\alpha\text{-}C_{10}H_7NMe_2$ .11 | — | — |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 39 | $[p\text{-MeOC}_6\text{H}_4\text{NMe}_3]^+\text{I}^-$ | PhMgBr | 2 | .04 | III | $p\text{-MeOC}_6\text{H}_4\text{NMe}_2$ | .25 | 1 | — | |
| 50 | | PhMgBr | 2 | .05 | II | | .32 | — | — | |
| 53 | $[\text{PhNMe}_2\text{Et}]^+\text{I}^-$ | PhMgBr | 2 | .05 | II | 77% PhNMeEt<br>23% $\text{PhNMe}_2$ | .23 | — | — | |
| 59[a] | $[\text{PhNMe}_3]^+\text{I}^-$ | PhMgBr | 3 | 0 | III | $\text{PhNMe}_2$ | 0.78 | — | — | |
| 60[a] | $[\text{PhNMe}_3]^+\text{I}^-$ | | 0 | 0 | II | $\text{PhNMe}_2$ | 0.27 | — | — | |
| 61 |  | PhMgBr | 3 | 0.1 | III |  | 0.50 | — | — | |
| 62 |  | PhMgBr | 3 | 0.1 | II |  | 0.51 | — | Methane | 0.5 |
| 63 |  | PhMgBr | 3 | 0 | II | | 0 | — | — | |

[a] Heated at 140° in refluxing di-$n$-butyl ether for 24 hours.

## TABLE IV
### SALTS OF TYPE IV

| Expt. No. | Salt (1 mole) | Grignard | (moles) | $CoBr_2$ (moles) | Proc. | Amine | (moles) | Coupled product | (moles) | Other Products (moles) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 |  | PhMgBr | 1 | 1 | I | $PhNMe_2$ | 0.42 | Allylbenzene | 0.23 | $Ph_2$ | 0.3 |
| 23 |  | PhMgBr | 1 | 0 | I | $PhNMe_2$ | .75 | Allylbenzene | .36 | $Ph_2$ | .05 |
| 27[a] |  | PhMgBr | 1 | 0 | I | $PhNMe_2$ | .42 | Allylbenzene | .27 | $Ph_2$ | .05 |
| 29 |  | PhMgBr | 1 | 0.05 | I | $PhNMe_2$ | .71 | Allylbenzene | .56 | $Ph_2$ | .15 |
| 31 |  | PhMgBr | 1.6 | .05 | I | $PhNMe_2$ | .90 | Allylbenzene | .44 | $Ph_2$ | .65[b] |

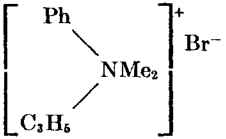
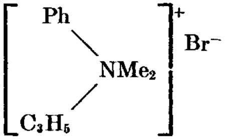
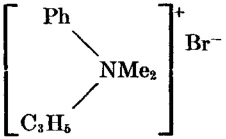
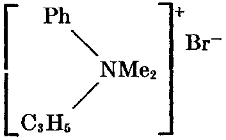
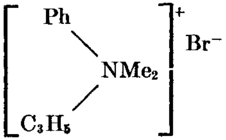
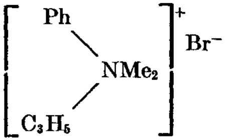
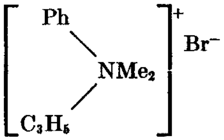
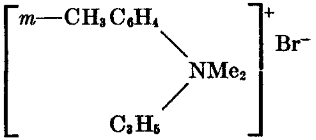
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 32 |  $[\mathrm{Ph(C_3H_5)NMe_2}]^+\mathrm{Br}^-$ | PhMgBr | 2 | .05 | I | $PhNMe_2$ | .83 | Allylbenzene | .67 | $Ph_2$ | .13 |
| 36[a] |  $[\mathrm{Ph(C_3H_5)NMe_2}]^+\mathrm{Br}^-$ | PhMgBr | 1 | 0 | II | $PhNMe_2$ | .81 | — | | — | |
| 18 |  $[\mathrm{Ph(C_3H_5)NMe_2}]^+\mathrm{Br}^-$ | *iso*-PrMgBr | 1 | .05 | I | $PhNMe_2$ | .85 | — | | — | |
| 20 |  $[\mathrm{Ph(C_3H_5)NMe_2}]^+\mathrm{Br}^-$ | *iso*-PrMgBr | 1 | 0 | I | $PhNMe_2$ | .74 | — | | — | |
| 22[a] |  $[\mathrm{Ph(C_3H_5)NMe_2}]^+\mathrm{Br}^-$ | *iso*-PrMgBr | 1 | 0 | I | $PhNMe_2$ | .42 | — | | — | |
| 8 |  $[\mathrm{Ph(C_3H_5)NMe_2}]^+\mathrm{Br}^-$ | MeMgBr | 1 | 1 | I | $PhNMe_2$ | .52 | — | | — | |

TABLE IV. (*Continued*)

| Expt. No. | Salt (1 mole) | Grignard | (moles) | $CoBr_2$ (moles) | Proc. | Amine | (moles) | Coupled product | (moles) | Other Products (moles) |
|---|---|---|---|---|---|---|---|---|---|---|
| 9 |  | MeMgBr | 1 | 1 | I | $PhNMe_2$ | .54 | — | | — |
| 19 |  | PhMgBr | 2 | .05 | I | $m$-$CH_3C_6H_4NMe_2$ | .93 | Allylbenzene | .72 | $Ph_2$ .5[b] |

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[a] Sublimed magnesium used in preparation of Grignard reagent.

[b] Air not rigorously excluded during experiment. The excess phenylmagnesium bromide in the presence of the cobaltous halide therefore became oxidized to diphenyl.

completely stable at the temperature used (*cf* Expt. 60, Table III). The products of the thermal decomposition of the salts thus are not necessarily identical with those of the cleavage reaction, though in the present instance dimethylaniline picrate was obtained from the products of Expt. 59 and 60, albeit with difficulty, and (see Expt. 60) in low yield. The amine resulting from the thermal decomposition of phenyltrimethylammonium bromide is largely dimethylaniline, but the product may be contaminated with other amines, possibly the N,N-dimethyltoluidines.

*Type IV.* The only simple quaternary salt found which is cleaved by Grignard reagents, in the absence of metallic halides (*i.e.*, when sublimed magnesium is used), is phenylallyldimethylammonium bromide. The conditions under which this reaction proceeds demonstrate that, in contrast to the other cleavages investigated, this is a heterolytic reaction. In fact it is probably a simple nucleophilic substitution reaction in which the carbanion of the Grignard reagent functions as the nucleophilic reagent.

## EXPERIMENTAL

### GENERAL PROCEDURES

*Procedure I.* The Grignard reagent, in dry ether, together with sufficient dry ether to render the concentration of the Grignard reagent approximately 1 *N* was added to the quaternary ammonium salt contained in a 3-necked flask equipped with a "Truebore" stirrer, a condenser in the reflux position, and a device whereby cobaltous bromide could be added portionwise without opening the reaction vessel to the atmosphere. The top of the condenser was attached to a mercury U-tube bubbler, and a soda-lime guard-tube. In those experiments in which gases were collected, the guard-tube was attached to a vessel wherein the gas was collected over brine. "Linde" nitrogen dried over $P_2O_5$ was passed through the apparatus before addition of any cobaltous bromide in order to displace the air in the apparatus. The nitrogen supply then was cut off and the cobaltous bromide was added portionwise over 1 hour. The mixture was stirred for 1 hour at room temperature and finally boiled under reflux for 1 hour. The whole was then poured into a mixture of dilute ($\sim 2$ *N*) HCl and ice, and allowed to stand until a clear aqueous solution resulted. The aqueous and ethereal layers were separated. The ethereal layer was shaken twice with 2 *N* HCl, and once with water, and these washings were added to the aqueous layer. The aqueous layer was shaken twice with ether, and these washings added to the ethereal layer.

The aqueous layer was made alkaline with saturated sodium carbonate solution, and steam-distilled. When the amine formed was a simple aliphatic one (trimethylamine in most cases), the receiver was protected with a solid $CO_2$/acetone trap, and at the end of the steam-distillation, the contents of this were washed into the main distillate with water. The volume of the distillate was measured, and the yield of trimethylamine estimated by titration with standard acid (Methyl Red indicator). When the amine formed was aromatic (*e.g.*, dimethylaniline), the cold-trap was omitted, and the steam-distillate was extracted several times with ether. The combined extracts were dried in the usual way and the ether was removed by distillation.

The main neutral ethereal layer was dried, and the ether was removed by distillation through an 8-inch, helix-packed column. The residue finally was distilled, generally at about 20 mm., and the various fractions were collected and identified as indicated below.

*Procedure II.* The procedure used was similar to *procedure I*, except that the addition of cobaltous bromide took place over 5 hours. In some cases, the final heating period was also increased to three hours as indicated in the Tables. Both these measures were found to result in increased yields, and it appears that any salt which is capable of cleavage may be cleaved quantitatively provided sufficient time is allowed for the reaction to proceed to completion, subject to the qualification that in Type III reactions two moles of the Grignard reagent are consumed per mole of salt. Nitrogen was passed through the apparatus for about 10 minutes at two-hourly intervals, in order to ensure that the absence of air was maintained.

*Procedure III.* The reaction was carried out as under *procedure II*, but the excess of the Grignard reagent was destroyed by carboxylation instead of by hydrolysis. When the reaction was complete, an excess of powdered solid $CO_2$ was added and the mixture was stirred and allowed to warm to room temperature. Hydrochloric acid (2 *N*) was added and the mixture was stirred until the metallic cobalt had dissolved. The separation into aqueous and ethereal layers was carried out as in *procedures I* and *II*, and the aqueous layer was treated in the same manner.

The ethereal layer was extracted four or five times with 2 *N* sodium hydroxide, and finally with water. Then it was dried and treated as under *procedures I* and *II*. The combined alkaline extracts were made acid with hydrochloric acid, allowed to cool, and the residue was collected. The filtrate was extracted five times with methylene chloride, and the combined extracts were dried, and the solvent was removed. The residues were combined and worked up as indicated below.

In those experiments which were carried out in the absence of cobaltous bromide, the periods of stirring at room temperature and at the boiling point were not altered, except as indicated in Tables I to IV.

## PREPARATION OF GRIGNARD REAGENTS

*Methylmagnesium bromide.* The magnesium was stirred under dry ether and, after all the air in the flask had been displaced by a stream of dry "Linde" nitrogen, methyl bromide gas was passed in until all the magnesium had dissolved. When necessary, a little iodine was used to start the reaction. At the end of the reaction, dry ether (100 ml.) was added, and this amount of ether was distilled off, in order to remove any excess methyl bromide. The Grignard reagent was filtered (under nitrogen gas) and made up with dry ether to about 2 *N* concentration. It was stored under dry nitrogen.

*Phenylmagnesium bromide and isopropylmagnesium bromide.* A 50%-molar excess of magnesium was employed in the preparation of these reagents. The magnesium was stirred under dry ether and, after all the air in the flask had been displaced by a current of nitrogen, the halide (bromobenzene or *iso*propyl bromide) in dry ether was dropped in at such a rate as to maintain gentle refluxing. When necessary, iodine was used to start the reaction. When the addition was complete, the mixture was stirred at room temperature for 12 hours longer (in a nitrogen atmosphere). At the end of this period the reagent was filtered, made up with dry ether to about 2 *N* concentration and stored under nitrogen.

The Grignard reagents were estimated by addition of a 2-ml. aliquot to a known excess of standard hydrochloric acid and back-titration against sodium hydroxide (Methyl Red indicator).

## PREPARATION OF SALTS

*Allyltrimethylammonium bromide.* Owing to its hygroscopic nature, this salt was never stored, but was prepared separately for each experiment in which it was used. The yield of the cleavage products was calculated on the amount of allyl bromide used in the preparation of the salt, assuming a quantitative conversion. If the quaternization is not quantitative, the yields quoted in Table II are low estimates.

The preparation of the salt (0.1 mole) was carried out as follows. Trimethylamine was distilled from 30 ml. 30% aqueous solution through a drying tube packed with potassium hydroxide pellets into 50 ml. of dry ether contained in a trap at −80°. This solution was added dropwise to a solution of redistilled (b.p. 71°) allyl bromide (12.1 g., 0.1 mole) in 100 ml. of dry ether, at room temperature. A salt precipitated. The ether then was removed and 100 ml. of fresh dry ether was added. This procedure was repeated twice in order to ensure the complete removal of unreacted organic halide and excess amine. The Grignard reagent then was added, and the cleavage reaction was carried out as described below.

*Benzyltrimethylammonium bromide.* The following preparation is typical. Trimethylamine was distilled from 70 ml. of a 30% aqueous solution as described above (0.17 mole). The ethereal solution so obtained was added dropwise to benzyl bromide (29.1 g., 0.17 mole) in dry ether at room temperature. The mixture then was boiled under reflux for 1 hour and left overnight. The salt was collected and crystallized from a mixture of ethanol and ligroin (white plates m.p. 235°, 33 g.).[2]

*Allylphenyldimethylammonium bromide.* Equimolar quantities of allyl bromide and dimethylaniline (redistilled) were mixed and allowed to stand overnight in a tightly stoppered flask. The salt began to separate immediately, and the mixture became solid in a short time. The solid mass was broken up, ground finely, washed well with dry ether, and dried ($P_2O_5$ and paraffin wax) at 80° and 0.05 mm. immediately before use. It was not found possible to purify the salt either by crystallization or by precipitation with ether from ethanolic solution, as all attempts to do so led only to the production of a non-crystalline material. The salt is extremely hygroscopic and also very soluble in water and in ethanol. However, specimens of the salt used for cleavage experiments gave homogeneous aqueous solutions, and gave no amine when an alkaline solution ($Na_2CO_3$) was steam-distilled. Thus the presence of free amine, or amine hydrohalide, and the possibility that cleavage takes place during the working-up of the reaction mixture are excluded.

One remaining possibility, *i.e.*, that of the possible hydrolysis of the salt by magnesium bromide present in the reaction mixture, was excluded in the following manner.

Magnesium bromide was prepared from magnesium (2.64 g.) in a little ether by addition (dropwise) of ethylene dibromide (22 g.). Ethylene was evolved steadily during the addition. After the addition was complete, the mixture was boiled under reflux until all the magnesium had disappeared (about 4 hours). To the resulting mixture, after cooling, a suspension of the salt (9.9 g., 0.041 mole) in dry ether was added. The mixture was stirred at room temperature for 2 hours and boiled under reflux for 1 hour. The mixture was poured into a mixture of 2 *N* hydrochloric acid and ice, and worked up (steam-distilled) as described above. Only a trace of amine (<3%) was obtained.

*Phenyltrimethylammonium iodide.* This was prepared by refluxing methyl iodide with an equimolar amount of dimethylaniline in ethanolic solution. The whole was cooled and the salt was collected. It was crystallized from ethanol until the sublimation point (220°) of the salt did not change on further crystallization.

*Benzylphenyldimethylammonium bromide.* Equimolar quantities of dimethylaniline and benzyl bromide were mixed and allowed to stand at room temperature for 2 hours. The solid product was taken up in ethanol and precipitated with ether. This was repeated until the melting point (96–98°) did not change upon further purification.

*α-Naphthyltrimethylammonium iodide.* Equimolar quantities of N,N-dimethyl-α-naphthylamine and methyl iodide were warmed under reflux for 24 hours on a steam-bath. The solid which separated was collected, washed well with ether, and dried at 80°/0.05 mm. The salt is very hygroscopic.

*Allyl-m-tolyldimethylammonium bromide.* This was prepared by a procedure exactly similar to that adopted for allylphenyldimethylammonium bromide.

*Tetramethylammonium iodide.* Trimethylamine, distilled as previously described from a 30% aqueous solution, in ether, was dropped into an equimolar amount of methyl iodide in dry ether. The salt was collected, washed well with ether, and recrystallized from 50% aqueous ethanol to constant decomposition point (230° with dec.).

*N,N-Dimethyl-1,2,3,4-tetrahydroquinolinium iodide* (*Kairoline methiodide*) (15). Tetrahydroquinoline (50 g.) was dropped slowly into refluxing methyl iodide (53.4 g.). After the addition, the mixture was boiled under reflux for 1 hour. The resulting solid was dissolved

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[2] von Braun, Fussgänger, and Kühn, *Ann.*, **445**, 208, cite a melting point of 230°; Baker and Ingold, *J. Chem. Soc.*, 439 (1929), cite a melting point of 235°.

in water, made alkaline with sodium hydroxide, and the liberated oil was extracted with ether. The extracts were dried and the ether was removed. The residue was distilled (b.p. 120°/13 mm., 33.65 g.). The distillate was dropped slowly into refluxing methyl iodide (100 g., ~3-fold excess), and the mixture was boiled under reflux for 1 hour. The methyl iodide (excess) was removed by distillation and the resulting solid was crystallized to a constant melting point (174°). The yield of product was 29.0 g. Some of the product was dissolved in water, made alkaline with sodium carbonate, and steam-distilled. No amine was found in the distillate.

*Phenyldimethylethylammonium iodide.* Dimethylaniline (36.6 g.) and ethyl iodide (46.8 g.) were heated together under reflux for 3 hours. The solid product was crystallized from ethanol to a constant melting point (133°). The yield of this product was 33 g.[3]

*Phenyl-2-phenylethyldimethylammonium iodide.* The preparation of the corresponding bromide was first attempted by the following procedure. 2-Phenylethyl bromide (55.5 g.) and dimethylaniline (36.6 g.) were heated in a sealed tube (under nitrogen) at 100° for 5 days. At the end of this time some solid had separated. The solid was collected. Then it was dissolved in ethanol and precipitated with ether. This procedure was repeated until the sublimation point (208–209°) remained constant. The yield of this product was 32 g. This salt was shown to be phenyltrimethylammonium bromide.

*Phenyl-2-phenylethyldimethylammonium iodide* therefore was prepared by the following procedure. Methylaniline (b.p. 87–90°/18 mm., 58.8 g., 0.549 mole) was added very slowly at room temperature to *iso*propylmagnesium bromide (343.5 ml. 1.6 *N* solution, 0.549 mole). During the addition about 12 liters of gas were evolved (propane). The ether was removed by distillation and replaced by benzene, in which the residue was completely soluble. 2-Phenylethyl bromide (101.7 g., 0.549 mole) was added, and the mixture was heated under reflux for 36 hours. A considerable quantity of solid material ($MgBr_2$) separated. The mixture was poured onto crushed ice, to which ammonium chloride had been added. The mixture did not separate into two layers, but a large quantity of a dark-colored sludge separated below the aqueous layer. The aqueous layer together with the sludge, which was thought to be the insoluble amine hydrochloride, together with some unreacted 2-phenylethyl bromide, was separated from the benzene and the two-phase system was centrifuged. The sludge then was separated from the aqueous layer. It was stirred with excess 10% sodium hydroxide and the liberated oil was extracted with ether. The extracts were dried and the ether was removed. The residue was distilled and the fraction boiling at 145–155°/1.5 mm. was collected. The distillate then was redistilled through a short Vigreux column and the fraction boiling at 124–128°/0.3 mm. (29.4 g.) was collected. This fraction solidified upon standing and was crystallized from ethanol to a constant melting point (45°).

*Anal.* Calc'd for $C_{15}H_{17}N$: N, 6.63; Mol. wt. 211.
Found: N, 6.62; Mol. wt. 205.

An equimolar mixture of this amine and methyl iodide was warmed for 2 hours under reflux. The resulting solid was taken up in ethanol and precipitated with ether, and this was repeated until a compound of constant melting point (135°) was obtained.

*Anal.* Calc'd for $C_{16}H_{20}NI$: I, 36.2. Found: I, 34.9.

The salts, benzyltriethylammonium chloride, N,N-dimethyltetrahydroisoquinolinium iodide, isoquinoline methiodide, *p*-methoxyphenyltrimethylammonium iodide, and dibenzyldimethylammonium chloride, were prepared by one or more of the procedures outlined above.

### IDENTIFICATION OF PRODUCTS (SEE TABLES I TO IV)

*Trimethylamine.* Expt. 1. The chloroplatinate of this substance melted (with dec.) at 240° and no depression of the melting point was noted by admixture with an authentic sample.

*Dimethylaniline.* Expts. 7, 8, 10, 11, 41, 49,55, 59, 60. The picrate of this substance melted at 162° and the melting point was not depressed by admixture with an authentic sample.

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[3] Gaisnet-Pilaud, *Ann. chim.*, [11], **4**, 365 (1935) reports a melting point of 134°.

Expt. 55. The methiodide of this substance sublimed at 220°. The reported sublimation point of dimethylaniline methiodide is 220°.

Expt. 53. The picrate was crystallized four times from ethanol. The melting points were: (a) 126–128°, (b) 130–134°, (c) 132–142°, (d) 140–146°. The reported melting point of dimethylaniline picrate is 162° and that of the methylethylaniline picrate is 134°.

*Anal.* Calc'd for $C_8H_{11}N$ (dimethylaniline): N, 11.57. Calc'd for $C_9H_{13}N$ (methylethylaniline): N, 10.36. Found: N, 10.64.

The amine isolated, therefore, is a mixture containing about 77% of methylethylaniline and 23% of dimethylaniline.

*Dimethyl-α-naphthylamine.* Expt. 13. The melting point of the picrate of this amine was 145°. The melting point was not depressed by admixture with an authentic sample.

*Dimethyl-m-toluidine.* Expt. 19. The melting point of the picrate of this substance was 128°. The melting point was not depressed by admixture with an authentic sample.

*N-Methyl-1,2,3,4-tetrahydroquinoline (Kairoline).* Expt. 50. The picrate of this substance melted at 145° and the melting point was not depressed by admixture with an authentic sample. The methiodide of this substance melted at 174°; the reported melting point of this methiodide is 174°. The melting point was not depressed by admixture with an authentic sample.

*Methyl-2-phenylethylaniline.* The melting point of methyl-2-phenylethylaniline crystallized from ethanol was 45°. The melting point was not depressed by admixture with an authentic sample.

*Allylbenzene.* Expt. 1, 3, 7, 23, 32, 34. The allylbenzene obtained in these experiments had physical constants similar to those reported for authentic allylbenzene.

*Biphenyl.* Biphenyl melted at 70°. No depression of the melting point was noted by admixture with an authentic sample.

*Benzoic acid.* The crude materials usually melted at 114–120°. Upon crystallization from hot water the material melted at 121° and did not depress the melting point of a known sample of benzoic acid.

*Phenylacetic acid.* Expt. 43. The crude acid melted at 65–70°. The material was taken up in sodium carbonate solution, the small amount of undissolved material was collected, and the filtrate was acidified with dilute hydrochloric acid. The acid which separated was dried. It melted at 77° and did not depress the melting point of an authentic sample of phenylacetic acid. The *p*-bromophenacyl derivatives of the acid obtained as described melted at 89° and did not depress the melting point of an authentic sample of the *p*-bromophenacyl derivatives of phenylacetic acid.

*Methane.* Expts. 45, 56, 62. Methane was identified by its vapor pressure at liquid nitrogen temperature and by molecular weight determination.

## SUMMARY

1. It has been established that four distinct type reactions are possible when quaternary ammonium salts react with Grignard reagents. These differences are due to the nature of the radicals attached to the nitrogen atom.

(a) Type I. Tetraalkylammonium salts. These salts do not react with Grignard reagents in the presence or absence of metallic halides (Co, Ni, Fe).

(b) Type II. Quaternary ammonium salts. These salts are cleaved by Grignard reagents *only in the presence of metallic halides.* Allyltrialkylammonium halides belong in this group. With phenylmagnesium bromide these salts give trialkylamine and allylbenzene.

(c) Type III. Aryltrialkylammonium salts. These salts react with Grignard reagents only in the presence of metallic halides to give a tertiary amine and the Grignard reagent of the ejected group.

(d) Type IV. Aryldialkylallylammonium salts. These salts react with Grignard reagents in the *presence or absence* of metallic halides.

2. It is suggested that the reaction of quaternary salts with Grignard reagents at 140° (in dibutylether) proceeds *via* a free radical chain reaction.

3. Additional work in this field is contemplated.

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## REFERENCES

(1) FREUND, *Ber.*, **37**, 4666 (1904).
(2) FREUND AND RICHARD, *Ber.*, **42**, 1101 (1909).
(3) CRAIG, *J. Am. Chem. Soc.*, **60**, 1458 (1938).
(4) FREUND AND BODE, *Ber.*, **42**, 1746 (1909).
(5) BERGMANN AND ROSENTHAL, *J. prakt. Chem.*, [2], **135**, 267 (1932).
(6) SEMON AND CRAIG, *J. Am. Chem. Soc.*, **58**, 1278 (1936).
(7) ASTON, SILMAN, SCHEUERMAN, AND KOCH, *J. Am. Chem. Soc.*, **56**, 1163 (1934).
(8) HILLEMAN, *Ber.*, **71**, 42 (1938); MCILWAIN, *J. Chem. Soc.*, 1704 (1937).
(9) FREUND AND BECK, *Ber.*, **37**, 4679–80 (1904).
(10) REIBER AND STEWART, *J. Am. Chem. Soc.*, **62**, 3026 (1940).
(11) KOHLER AND RICHTMYER, *J. Am. Chem. Soc.*, **50**, 3092 (1928).
(12) SNYDER, ELIEL, AND CARNAHAN, *J. Am. Chem. Soc.*, **73**, 970 (1951).
(13) SNYDER AND ELIEL, *J. Am. Chem. Soc.*, **71**, 664 (1949).
(14) GEISSMAN AND ARMEN, *J. Am. Chem. Soc.*, **74**, 3916 (1952).
(15) HOFMANN AND KOENIGS, *Ber.*, **16**, 732 (1883).