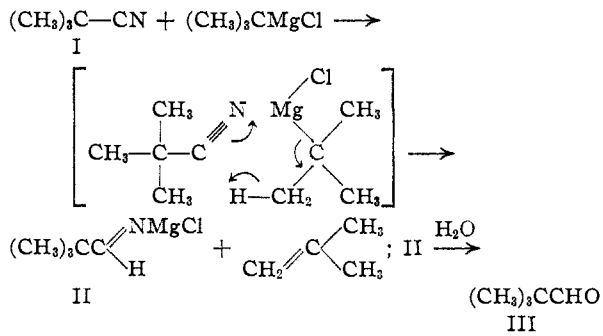
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

The Reduction of Trimethylacetonitrile with Grignard Reagents[1]

BY HARRY S. MOSHER AND WILLIAM T. MOONEY

It has been shown that ethylmagnesium bromide readily adds to trimethylacetonitrile to give a good yield of the normal addition product. However *t*-butylmagnesium chloride does not add normally to this hindered nitrile but instead a small yield of reduction product, trimethylacetaldehyde is formed. This finding is compatible with the six-membered ring transition state mechanism for the "abnormal" Grignard reaction.

From a consideration of the postulated mechanism of the Grignard reduction reaction,[2,3] we have predicted that reduction might occur in the reaction of a hindered Grignard reagent and a hindered nitrile.



Hauser and Humphlett[4] have made this same prediction and have tested it by the reaction of *t*-butylmagnesium chloride on capronitrile. However they were unsuccessful in identifying any reduction product from the reaction.

A search of the literature failed to uncover any other report of the action of a tertiary Grignard reagent on a nitrile.[5] In addition no report was found of the action of a Grignard reagent on a hindered nitrile. A study was therefore undertaken of the action of ethylmagnesium bromide, isopropyl- and *t*-butylmagnesium chlorides on trimethylacetonitrile (I).[6] Trimethylacetaldehyde (III) was found after the hydrolysis of the reaction products from isopropyl- and *t*-butylmagnesium chlorides. The trimethylacetaldehyde must have been formed from the hydrolysis of the predicted magnesium chloride derivative of trimethylacetaldimine (II).

The isolation of this reduction product indicates the value of the six-membered ring transition state theory[2] for predicting the course of the "abnormal" Grignard reactions and these findings are completely compatible with this mechanism for the Grignard reduction reaction.

The reaction of a slight excess of ethylmagnesium bromide with trimethylacetonitrile in refluxing ether for six hours gave an 80% yield of the normal product, ethyl *t*-butyl ketone,[7] with a 5.5% recovery of unreacted nitrile.

Isopropylmagnesium chloride reacted with trimethylacetonitrile incompletely upon six hours refluxing in ether solution; 64.2% of the nitrile was recovered unchanged and 10.8% yield of isopropyl *t*-butyl ketone was formed. There was in addition a certain amount (12.8% based on the weight of nitrile taken) of residue. A small amount of material (1.9%) boiling at 75° was identified as trimethylacetaldehyde by its physical properties and the melting point of its 2,4-dinitrophenylhydrazone which was undepressed when mixed with an authentic sample.[8] Since the yield was unsatisfactory, the reaction was repeated in diisoamyl ether solvent at 100–110° for eight hours. In this reaction a 6.3% yield of trimethylacetaldehyde, 5.5% yield of recovered trimethylacetonitrile, 46.3% yield of isopropyl *t*-butyl ketone, an unidentified solid which might have been trimethylacetaldehyde polymer and an unidentified nitrogen-containing fraction were obtained. The per cent. recovery was not as satisfactory as in the previous experiment because of the diisoamyl ether which made it impossible to isolate the high boiling reaction products.

Trimethylacetonitrile, when treated with *t*-butylmagnesium chloride for eight hours at 100–110° in diisoamyl ether, gave a 39.4% recovery of the nitrile, and a 14.5% yield of trimethylacetaldehyde. No normal addition product, di-*t*-butyl ketone, was detected. Other higher boiling materials may have been present but they could not be separated from the diisoamyl ether. This reaction was also conducted at room temperature for four months but 60% of the trimethylacetonitrile was recovered unchanged and the yield of trimethylacetaldehyde was 7%.

The reduction of a hindered nitrile with a hindered Grignard reagent and the known relationship between the Grignard reduction reaction and the Meerwein–Ponndorf–Verley reduction[3] suggested that aluminum isopropylate might be used in the reduction of nitriles. This has been investigated and it was found that refluxing (186°) benzonitrile with freshly distilled aluminum isopropylate for several days resulted in a 14% yield of acetone. This reaction is obviously very slow and no benzaldehyde was found in the residue.

(1) Abstracted from the thesis submitted by William T. Mooney to Stanford University in partial fulfillment of the requirements for the M.S. degree, June, 1950.

(2) Whitmore and George, "The Common Basis of the Reaction of Grignard Reagents with Carbonyl Compounds; Addition, Reduction, Enolization and Condensation." Paper presented at 102nd Meeting of the American Chemical Society, September 9, 1941. For further details see the Ph.D. Thesis of R. S. George, The Pennsylvania State College, July, 1943; available from University Microfilms, Ann Arbor, Michigan.

(3) Harry S. Mosher and Edward La Combe, THIS JOURNAL, **72**, 3994 (1950).

(4) Hauser and Humphlett, *J. Org. Chem.*, **15**, 359 (1950), footnote.

(5) Since this work was completed, D. E. Pearson, THIS JOURNAL, **72**, 4109 (1950), reported the action of several aromatic Grignard reagents on trimethylacetonitrile.

(6) A generous supply of trimethylacetonitrile was kindly furnished by the Electrochemicals Division of E. I. Pont de Nemours and Co.

(7) F. C. Whitmore, C. I. Noll and V. C. Meunier, THIS JOURNAL, **61**, 683 (1939), mention this reaction in a footnote for the identification of trimethylacetonitrile.

(8) Kindly furnished by Dr. T. S. Oakwood of The Pennsylvania State College.

Experimental

Ethylmagnesium Bromide and Trimethylacetonitrile.—To a titrated ether solution of 0.91 mole of ethylmagnesium bromide was added 55 g. (0.67 mole) of trimethylacetonitrile (b.p. 104–105°).[6] The reaction mixture was refluxed under a nitrogen atmosphere for ten hours, and allowed to stand for 12 hours after which time the Gilman test for Grignard reagent was still positive. Large translucent crystals had separated from the reaction mixture. The crystals and ether solution were hydrolyzed with ammonium chloride solution in the cold. The ether was removed from the resulting dried ether layer and ether extract by distilling through a twenty-plate packed column and the residue fractioned through a thirty-plate column to give the following: cuts 1–6 ether; cuts 7–9, b.p. 70–73°, $n^{20}D$ 1.3747–1.3823, 2.1 g., may be impure trimethylacetaldehyde; cuts 10–13, b.p. 75–80.5°, 4.0 g., ethanol, presumably formed from the Grignard reagent; cuts 15–18, b.p. 100.5–106°, 3.0 g., $n^{20}D$ 1.3780–1.3782, recovered trimethylacetonitrile; cuts 21–30, b.p. 123–125°, $n^{20}D$ 1.4049–1.4052, 60.8 g., ethyl *t*-butyl ketone; residue 6.9 g.

Isopropylmagnesium Chloride and Trimethylacetonitrile.—The isopropylmagnesium chloride from 0.6 mole of the halide was treated with 0.5 mole of trimethylacetonitrile under nitrogen for six hours in refluxing ether. After standing 60 hours, it was worked up as indicated above and fractionated through a thirty-plate column to give a 64.2% yield of recovered nitrile, b.p. 104–105°, $n^{20}D$ 1.3780–1.3783; 10.8% of crude isopropyl *t*-butyl ketone, b.p. 134–137°, $n^{20}D$ 1.4064–1.4168, oxime, m.p. 138–140°, mixed m.p. with authentic sample, m.p. 139–141°, and 1.9% of trimethylacetaldehyde, b.p. 70–80°, $n^{20}D$ 1.3740–1.3802. This latter material gave a positive Schiff test, a semicarbazone, m.p. 187–188.5°, and a 2,4-dinitrophenylhydrazone, m.p. 205–207°; melting point when mixed with authentic sample,[8] 205–207°.

In a second experiment the reaction mixture from 0.5 mole of trimethylacetonitrile was prepared as above. Diisoamyl ether, 600 ml., was added and the diethyl ether removed through a Vigreux column attached to the reaction flask. The reaction mixture was then maintained with stirring at 100–110° for eight hours. After hydrolysis with ammonium chloride solution it was worked up as above; a 5.5% yield of trimethylacetonitrile, a 6.3% yield of trimethylacetaldehyde and a 46.3% yield of crude isopropyl *t*-butyl ketone were isolated. This latter material was not homogeneous; it boiled over a range, 135–144°, and seemed to be composed of two components, one boiling at 135°, $n^{20}D$ 1.4038, and the second boiling at 143°, $n^{20}D$ 1.4180. Both cuts gave good yields of the oxime of *t*-butyl isopropyl ketone (m.p. 139–141° and 140–141°, respectively) but the higher boiling cut contained 0.5% nitrogen which possibly may be due to the presence of isopropyl *t*-butyl ketimine. Immediately before the diisoamyl ether solvent began to distil, a small amount, 1.8 g., of a white solid which is yet unidentified, collected on the condenser. This may be the trimer of trimethylacetaldehyde.

***t*-Butylmagnesium Chloride and Trimethylacetonitrile.**—To 0.45 mole of a titrated *t*-butylmagnesium chloride solution was added 33.3 g. (0.40 mole) of trimethylacetonitrile. The ether solvent was replaced with 500 ml. of diisoamyl ether and the reaction temperature maintained at 100–110° with stirring for eight hours. An olive-colored precipitate was formed in the mixture. After hydrolysis with ammonium chloride solution and working up as above, 11.3 g. (39.4%) of trimethylacetonitrile, 5.0 g. (14.5%) of *t*-butyl alcohol and 4.5 g. (6.1%) of trimethylacetonitrile were isolated.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Curare Substitutes from Stilbazoline Quaternary Ammonium Salts

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In a continuing search for curare-like activity in varied series of synthetic organic compounds active products have again been found in a relatively simple type, stilbazoline quaternary ammonium salts.

While examining the relationship between chemical structure and curare-like activity in a series of simple polymethylene-α,ω-bis quaternary ammonium salts Barlow and Ing[1] and Paton and Zaimis[2] found a maximum activity in the decamethylene-1,10-bis-trimethylammonium iodide.

Exploiting this discovery the corresponding bis-quaternary bromide[3]

$$(CH_3)_3\overset{+}{N}-(CH_2)_{10}-\overset{+}{N}(CH_3)_3$$
$$\qquad\qquad Br^- \qquad\qquad Br^-$$

and bis-quaternary ammonium salts from a series of bis-β-dimethylaminoethyl esters of dicarboxylic acids[4,5] were prepared. In this latter group maximum activity, of the same order of potency as *d*-tubocurarine chloride, was encountered in the succinyl choline derivative

$$(CH_3)_3\overset{+}{N}CH_2CH_2OC(=O)-CH_2CH_2C(=O)-OCH_2CH_2\overset{+}{N}(CH_3)_3$$
$$\qquad\qquad I^- \qquad\qquad I^-$$

in which the quaternary ammonium nitrogens are separated by a chain of ten atoms analogous to the model mentioned above.

There is evidence, however, that, in spite of recent views[6,7,8] the mere existence of such a long chain of atoms, separating two (or more) quaternary ammonium groups by some optimum distance of about 12–14 Å., is in itself neither a *necessary* nor a *sufficient* condition for producing very powerful curariform activity in a molecule. Thus Marsh and Herring[9] report a *mono*-quaternary ammonium chloride from Calabash curarine I to be about six times as active as *d*-tubocurarine chlorine (possessing *two* quaternary nitrogens and the ultimate model from which the decamethylene series was derived) in producing head drop in rabbits. That possession of the optimal long chain bis-quaternary ammonium salt structure was not sufficient to produce invariably strong curare-like effects has been shown by the almost complete lack of such effects in a series of bis-β-tertiaryaminoalkyl amides of dicarboxylic acids and their bis-quaternary ammo-

(1) R. B. Barlow and H. R. Ing, *Nature*, **161**, 718 (1948).
(2) W. D. M. Paton and E. J. Zaimis, *ibid.*, **161**, 718 (1948).
(3) J. C. Castillo, A. P. Phillips and E. J. de Beer, *J. Pharmacol. Exp. Therap.*, **97**, 150 (1949).
(4) A. P. Phillips, THIS JOURNAL, **71**, 3264 (1949).
(5) J. C. Castillo and E. J. de Beer, *J. Pharmacol. Exp. Therap.*, **99**, 458 (1950).
(6) R. B. Barlow and H. R. Ing, *Brit. J. Pharmacol.*, **3**, 298 (1948).
(7) K. K. Kimura, K. Unna and C. C. Pfeiffer, *J. Pharmacol. Exp. Therap.*, **95**, 149 (1949).
(8) W. D. M. Paton, *J. Pharm. Pharmacol.*, **1**, 273 (1949).
(9) D. F. Marsh and D. A. Herring, *J. Pharmacol. Exp. Therap.*, **101**, 26 (1951); (abstracts of papers).