[Contribution from the Department of Chemistry, Reed College]

SOME DERIVATIVES OF *p*-(α-DIMETHYLAMINOETHYL)-BENZOIC ACID

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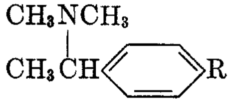
This paper reports some experiments directed towards the synthesis of *p*-(α-dimethylaminoethyl)styrene (IV). These experiments indicate the synthesis to be feasible, but it has not been completed because our interest in the final product has diminished.



I R = Br
II R = CN
III R = $COCH_3$
IV R = $CH{=}CH_2$
V R = COOH

The starting material was *p*-bromo-N,N,α-trimethylbenzylamine (I), prepared from *p*-bromoacetophenone by the Leuckart reaction (1). The original intention was to convert this to a Grignard reagent or organolithium compound, which would then be coupled with acetaldehyde, etc., but our initial efforts to prepare an organometallic compound by conventional methods were unsuccessful. Attention was then turned to the general synthetic route by means of which Marvel and Overberger (2) prepared *p*-vinylbenzyl *d*-*sec*-butyl ether. This involved the sequence aryl bromide → aryl nitrile → aryl methyl ketone → aryl methyl carbinol → aryl ethylene. Cuprous cyanide and I condensed well in the presence of a molar amount of pyridine (3) to give *p*-(α-dimethylaminoethyl)-benzonitrile (II); this procedure was superior to reaction in an excess of pyridine or quinoline. This nitrile reacted, on the first attempt, with methylmagnesium iodide in ether to give *p*-(α-dimethylaminoethyl)acetophenone (III), but later attempts to repeat this preparation were not fruitful for reasons which are not clear to us.

Some time later, the possibility of preparing an organolithium compound from I by halogen-metal interconversion was re-examined. Work by Gilman, Langham, and Moore (4, 5) has demonstrated that, although this is a general reaction for aryl bromides, the optimum conditions for reaction vary considerably according to the structure of the aryl bromide.

In our exploratory experiments on exchange of I with *n*-butyllithium, the reaction mixture was carbonated with the object of isolating the corresponding acid (V). For comparison purposes, *p*-(α-dimethylaminoethyl)benzoic acid (V) was prepared by hydrolysis of the nitrile II. The acid was quite soluble in water at every *p*H, but was isolated as its hydrochloride and as its picrate. The picrate formed readily in an aqueous medium, and was the form in which the acid was isolated in the following experiments.

In ethyl ether, and with an approximate 1:1 molar ratio of *n*-butyllithium to

I, there was no identifiable yield of V (as its picrate) from reaction for 30 minutes at −50°, one hour at −10°, or a half-minute at 24°. Modest yields were obtained from reaction for 15 minutes at 15° or 30 minutes at reflux, while a 66% yield of V (as picrate) was obtained when the reactants were refluxed for 1½ hours.

Thus suitable conditions for the preparation of an organolithium compound from I by halogen-metal interconversion have been found. It is to be expected that the synthesis of IV could be completed by the method originally chosen, but the synthesis is not being continued.

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EXPERIMENTAL[1]

p-(α-Dimethylaminoethyl)benzonitrile (II). Dry pyridine (3.96 g., 0.05 mole) was added to 4.5 g. (0.05 mole) of cuprous cyanide; heat was generated as the complex formed. To this was added 11.4 g. (0.05 mole) of p-bromo-N,N,α-trimethylbenzylamine (1), two drops of benzonitrile, and some crystals of cupric sulfate and the mixture was heated two hours in a bath at 225°. There was some refluxing. After some cooling the reaction mixture was poured into 60 ml. of 8 *M* ammonium hydroxide. The resulting mixture of oil, solid, and aqueous phases was extracted with ether. The aqueous layer (in which the solid remained in suspension) was filtered and the cake washed with water and ether. The aqueous layer was again extracted with ether and finally the combined ether extracts were repeatedly washed with very dilute ammonium hydroxide until the washings were no longer blue. This ether solution, after drying over magnesium sulfate, was evaporated to an oil which boiled at 140–145°/18 mm. Weight: 5.5 g.; n_D^{20} 1.5290. Since I has n_D^{20} 1.5462 (1) and the pure cyano compound (see below) has n_D^{20} 1.5281, this crude product contained about 5% of unreacted starting material. After correction for this, the yield is 60%.

Bubbling hydrogen chloride through an ether solution of this product caused the hydrochloride to precipitate; after recrystallization from isopropyl alcohol, it had m.p. 222–222.5°.

Anal. Calc'd for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; Cl, 16.83.

Found:[2] C, 62.25; H, 7.22; Cl, 16.92.

The product from another run was purified by recrystallization of its picrate, m.p. 167–168°. From the picrate, pure p-(α-dimethylaminoethyl)benzonitrile was regenerated and distilled (b.p. 152°/25 mm.); it had n_D^{20} 1.5281 and d_{20}^{20} 0.9935. Molecular refractivity was 54.04 (calc'd, 54.00).

p-(α-Dimethylaminoethyl)acetophenone (III). A solution of 0.074 mole of methylmagnesium iodide and 6.44 g. (0.037 mole) of II in 65 ml. of dry ether was refluxed for eight hours. The reaction mixture was poured over ice, made alkaline with sodium hydroxide, and steam-distilled. The distillate was extracted with ether and the extracts dried over magnesium sulfate. Distillation of these extracts yielded 4.05 g. (57.5%) of p-(α-dimethylaminoethyl)acetophenone, b.p. 151–156°/20 mm., as a viscous faintly yellow oil. The hydrochloride melted, after recrystallization, at 231°.

Anal. Calc'd for $C_{12}H_{18}ClNO$: C, 63.27; H, 7.97; Cl, 15.57.

Found:[2] C, 62.56; H, 7.61; Cl, 15.49.

Hydrolysis of p-(α-dimethylaminoethyl)benzonitrile (II). The nitrile (2 g.) was refluxed for two hours in 50 ml. of 20% hydrochloric acid. The solution was made alkaline with sodium hydroxide, extracted with ether, and then was adjusted to pH 7.0. The solution was evaporated to dryness and the residue extracted with ethanol. Sodium chloride was precipitated from the extract by saturating it with hydrogen chloride gas, after which

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[1] Melting points are uncorrected.

[2] Analyses for C and H by Dr. Carl Tiedcke, New York.

the extract was evaporated to dryness. The residue of *p*-(α-dimethylaminoethyl)benzoic acid hydrochloride was recrystallized from *n*-butyl alcohol. Powdery white crystals, m.p. 255.5–256°, resulted.

Anal. Calc'd for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02.
Found:[3] C, 57.85; H, 6.78.

Another similar preparation, after ether extraction of the alkaline solution, was made neutral and an aqueous solution of picric acid was added. *p*-(α-Dimethylaminoethyl)-benzoic acid picrate, which separated, was recrystallized from water, forming fine yellow crystals, m.p. 191–193°.

Anal. Calc'd for $C_{17}H_{18}N_4O_9$: C, 48.34; H, 4.30.
Found:[3] C, 48.35; H, 4.15.

Reaction of n-butyllithium with p-bromo-N,N,α-trimethylbenzylamine. Compound I (2 g.) was combined with slightly more than one equivalent of *n*-butyllithium (6) in a total of 22 ml. of ethyl ether. After refluxing for 1½ hours, the solution was poured over pulverized carbon dioxide. After the addition of aqueous alkali, the mixture was extracted with ether, adjusted to *p*H 7.0, and aqueous picric acid was added. The picrate (2.45 g., 66%) melted at 185–188°. Recrystallization raised the melting point to 192.5–194°, and a mixture melting point with the analytical sample of *p*-(α-dimethylaminoethyl)benzoic acid picrate was 192.5–193.5°.

SUMMARY

It has been found possible to convert *p*-bromo-N,N,α-trimethylbenzylamine to an organolithium compound. The nature of this compound has been indicated by its carbonation to *p*-(α-dimethylaminoethyl)benzoic acid (V) and comparison with authentic V.

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[3] Analyses by Clark Microanalytical Laboratories, Urbana, Illinois.