[Contribution from the Dyson Perrins Laboratory of Oxford University]

THE REACTION OF SOME ACID AZIDES WITH DIETHYLAMINOETHANOL

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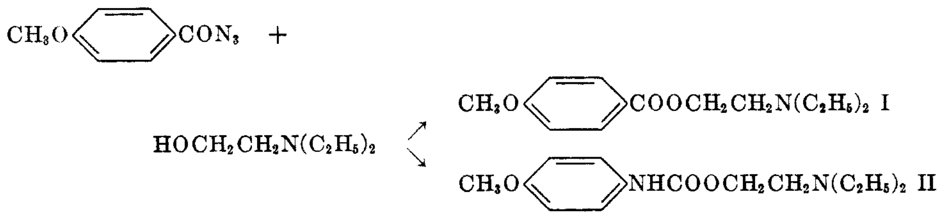
This investigation was begun as the result of the discovery that a compound, R.79, prepared by Robinson and Tomlinson (1) was fairly active as a local anaesthetic. It was hoped to prepare a group of similar compounds, all urethans of aminoalcohols, isomeric with the well known series of *p*-aminobenzoates of aminoalcohols, and to have their activity tested.

The compound R.79 was described as the picrate of 2-diethylaminoethyl *p*-anisylcarbamate (II) and was prepared by heating *p*-anisic azide with an excess of diethylaminoethanol,



evaporating excess diethylaminoethanol *in vacuo*, and converting to the picrate. The reaction was found, however, to yield a very messy product out of which it was rarely possible to isolate any pure compound; and moreover the compound obtained on one occasion, which had the same m.p. as R.79 was proved to be actually the picrate of the corresponding ester, 2-diethylaminoethyl *p*-anisate (I). In order to confirm this, the ester was prepared in an unambiguous manner from the acid chloride, and the ester, hydrochloride, and picrate resulting therefrom were found to be identical with those prepared from the azide. The true urethan (II) hydrochloride and picrate, which had quite different properties, were prepared (a) by heating the azide in an inert solvent to form the isocyanate, and (b) by forming the isocyanate from *p*-anisidine and phosgene, and reacting the isocyanate with diethylaminoethanol.

Five other azides were subjected to the same reaction, *i.e.* heating directly with diethylaminoethanol, with the following results:

Veratric azide gave a 50% yield of the *ester*.
2-Furoic azide gave a 33% yield of the *ester*.
p-Chlorbenzoic azide gave a 10% yield of the *ester*.
p-Toluic azide gave a 10% yield of the urethan.
p-Phenetic azide gave an 8% yield of the urethan.

In the majority of attempts, no pure solid compounds could be prepared, and though it was found possible by using a fair excess of diethylaminoethanol and avoiding too violent a reaction to obtain reasonable yields of the esters, there were only two occasions (out of a large number) on which urethans were obtained, and the yield was in both cases bad.

This behavior of azides is not altogether surprising in view of the fact that Curtius (2) found that the general reaction of an azide in alkaline solution is to lose hydrogen azide and give the same products as would an acid chloride.

$$RCON_3 + HOX \rightarrow RCOOX + HN_3$$

Ammonia, sodium hydroxide, hydrazine, aniline, and other amines behave in this way. On the other hand, in acid or in neutral solutions on heating, the azide undergoes the Curtius rearrangement with loss of nitrogen to give compounds derived from the isocyanate

$$RCON_3 \rightarrow RN{:}C{:}O + N_2(+ HOX) \rightarrow RNHCOOX + N_2$$

(compare the reactions with hydrogen chloride, bromine, water, and alcohol). This suggested that urethan hydrochlorides might be obtained from the hydrochlorides of aminoalcohols by heating with azides, and this proved to be the case (see Hutton, future paper) where a series of urethans were prepared by this and another method).

EXPERIMENTAL

THE REACTION BETWEEN *p*-ANISIC AZIDE AND 2-DIETHYLAMINOETHANOL

p-Anisic azide was prepared according to the method of Robinson and Tomlinson (1) in 95% yield. The azide (2.0 g.) was covered with diethylaminoethanol (2.0 g. = 1.5 × theoretical) and heated on steam-bath until evolution of nitrogen had ceased. After removal of excess diethylaminoethanol by distillation *in vacuo*, the product was taken up in hydrochloric acid and boiled with an alcoholic solution of picric acid until a yellow precipitate of the picrate was obtained. This was collected and re-crystallized from ethyl alcohol (1% solution). Yield: 0.2 g., m.p. 146–148°.

Anal. Calc'd for $C_{20}H_{24}N_4O_{10}$ (picrate of 2-diethylaminoethyl *p*-anisate (I): C, 50.0; H, 5.0; N, 11.8.

Calc'd for $C_{20}H_{25}N_5O_{10}$ (picrate of 2-diethylaminoethyl *p*-anisylcarbamate (II): C, 48.5; H, 5.1; N, 14.3.

Found: C, 49.8; H, 4.9; N, 11.8.

Robinson and Tomlinson gave m.p. 150–152° and "Found: C, 48.3; H, 5.1;" (misprinted as N, 5.1)". Attempts to prepare the hydrochloride either from the picrate or directly from the reaction mixture failed.

The experiment was repeated several times in order to see whether any urethan could be isolated from it. On no other occasion, however, could any pure compound be obtained, except for a very small quantity of di-*p*-anisyl urea (3). The proportion of diethylaminoethanol was then varied from 1 to 4 times the theoretical, and the reaction temperature controlled at temperatures between 80° and 160°. When a fourfold excess of aminoalcohol was used, and the temperature kept as low as possible (80°), a product was obtained which could be partially distilled on a Hyvac pump. From 9.0 g. of azide there was produced 7.0 g. of a clear pale yellow liquid, which was re-distilled, b.p. 162°/1 mm.

Anal. Calc'd for the ester (I) $C_{14}H_{21}NO_3$: N, 5.6. Found: N, 5.7.

Calc'd for the urethan (II) $C_{14}H_{22}N_2O_3$: N, 10.6.

This was converted into the hydrochloride m.p. 146° [as given by Rohmann and Scheurle (4) for the hydrochloride of I], and the picrate m.p. 148–151° (from 13% solution in acetone), unchanged by admixture with the picrate obtained above.

It was then confirmed that the above compounds were derivatives of the ester I and not of the urethan II, by preparing both I and II by unambiguous methods.

2-Diethylaminoethyl p-anisate (I). *p*-Anisoyl chloride (5) (12.5 g.) was added drop by drop with cooling to an ice-cold solution of diethylaminoethanol (8.0 g.) in sodium hydroxide solution (8.0 g. in 80 cc. of water), according to the method of Cook (6). The ester was immediately extracted with ether, dried and distilled, b.p. 161°/1 mm. This substance has been prepared in British Patent 487,824 (7) but not described. The hydrochloride m.p. 146° and the picrate m.p. 148–151°, were identical (mixture melting points) with the specimens obtained above.

2-Diethylaminoethyl p-anisylcarbamate hydrochloride (II). *p*-Anisyl isocyanate was prepared in a small yield by the method of Shriner, Horne, and Cox for *p*-nitrophenyl isocyanate (8), distilled b.p. 105–108°/17 mm., warmed with excess diethylaminoethanol and the excess removed, and the product converted into a hydrochloride m.p. 158–160° and a *picrate* m.p. 131°, which were both different (mixture melting points) from the specimens obtained above. As only very small amounts of the products were obtained by this method, further quantities were prepared by another method.

p-Anisic azide (4.0 g.) evolved the theoretical amount of nitrogen when heated under xylene (500 cc.), and, after warming with diethylaminoethanol (2.6 g. = theoretical amount), was cooled in ice and treated with dry hydrogen chloride. The precipitated hydrochloride crystallized from absolute alcohol (solubility 15 g./100 cc. of solvent) in large transparent rectangular plates m.p. 161°. Yield 4.4 g. (66%).

Anal. Calc'd for $C_{14}H_{23}ClN_2O_3$: N, 9.3. Found: N, 9.3.

Sekera, Urba, and Lebduska (9) record m.p. 171°. A portion of the hydrochloride was dissolved in alcohol (solubility 0.4% on boiling) and converted into the picrate, yellow needles m.p. 131°.

Anal. Calc'd for $C_{20}H_{25}N_5O_{10}$: N, 14.3. Found: N, 14.0.

The reaction between other azides and diethylaminoethanol. As was the case with *p*-anisic azide, the normal product of a reaction between diethylaminoethanol and each of five other azides was a dirty brown oil which could not be converted into a hydrochloride or a picrate. On a few occasions, however, pure compounds were isolated as follows:

Diethylaminoethyl veratrate hydrochloride. Veratric hydrazide (40 g.) (10), dissolved in glacial acetic acid (200 cc.), was cooled in ice and treated drop by drop with a 5% excess of sodium nitrite solution. After completing the precipitation by adding excess water, the *azide* was collected, well washed with water and dried *in vacuo.* Yield: 38 g. (90%), m.p. 72.5–73.5°. It is very soluble (*ca.* 25 g./100 cc. of solvent) in cold benzene, and a small portion was recrystallized for analysis from carbon tetrachloride (5 g./10 cc.), m.p. 74°.

Anal. Calc'd for $C_9H_9N_3O_3$: N, 20.3. Found: N, 20.4.

Veratric azide (4.8 g.) and diethylaminoethanol (5.0 g.) reacted together with only a fairly gentle evolution of gas when heated on a steam-bath. After removing excess aminoalcohol, taking up ether, filtering off a small amount of di-veratryl urea (10) and passing in dry hydrogen chloride, the hydrochloride was obtained as white needles (from acetone) m.p. 155°. Yield, 3.9 g. (50%).

Anal. Calc'd for $C_{15}H_{24}ClNO_4$: C, 56.8; H, 7.5, N, 4.4.
Found: C, 57.1; H, 7.2; N, 4.4.

Diethylaminoethyl 2-furoate hydrochloride. 2-Furoic azide (11) reacted vigorously under similar conditions, and on working up the product a red oil was obtained. This solidified on scratching with acetone, and on crystallization therefrom 3.3. g. of pale yellow prisms were obtained (from 6.25 g. of azide) m.p. 121–124°. It was difficult to purify further, but the m.p. was raised to 124–125° by recrystallization from acetone, dioxane, and ethyl acetate. Gilman (12) gave m.p. 127°.

Anal. Calc'd for $C_{11}H_{18}ClNO_3$: N, 5.6. Found: N, 5.6.

The *hydrochloride* was very soluble in absolute alcohol; attempts to form a picrate failed.

Diethylaminoethyl p-chlorobenzoate hydrochloride. p-Chlorbenzoic azide (4.9 g.) (13), when warmed cautiously with diethylaminoethanol (4.8 g.) so that the reaction only just proceeded, gave rise to a product which could not be converted into a hydrochloride, but which gave a picrate m.p. 163–167°, from a 6% solution in acetone. Yield 1.6 g. (10%). After two further recrystallizations from ethyl alcohol, it had a melting point of 165–168°, unchanged by admixture with an euthentic specimen prepared from the heating of *p*-chlorbenzoyl chloride with slightly less than the theoretical amount of diethylaminoethanol, for five hours in benzene.

Diethylaminoethyl p-phenetylcabamate hydrochloride. p-Phenetic azide. p-Phenetic hydrazide (3 g.) dissolved in glacial acetic acid (15 cc.) and cooled in ice, was treated with a solution of sodium nitrite (1 g.) in water (3 cc.) drop by drop with cooling and stirring. (The reaction is exothermic, and on the first occasion on which it was tried the azide separated out as an oil, which needed prolonged cooling before it set to a solid, m.p. 32°.) On this occasion the temperature was maintained throughout below 15° and the azide separated out as a solid. This was collected, washed well with water, and dried in a vacuum desiccator. Yield: 3 g. of a white powder (95%) m.p. 41°.

Anal. Calc'd for $C_9H_9N_3O_2$: N, 22.0. Found: N, 21.9.

Curtius (14) who used a different method for its preparation gave m.p. 31°, but no analysis.

p-Phenetic azide (4.9 g.) reacted very vigorously when heated with diethylaminoethanol (7.5 g.) on the steam-bath, and the product was a moist looking yellow solid part of which dissolved in ether. The residue dissolved in much hot methyl alcohol and was identified as *p*-phenetyl urea, prepared by Curtius (14).

Anal. Calc'd for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.7.
Found: C, 68.4; H, 6.7.

The ethereal solution on treatment with hydrogen chloride eventually gave a gelatinous precipitate which was recrystallized from acetone m.p. 163°. Yield: 0.4 g. (8% of theory).

Anal. Calc'd for $C_{15}H_{25}ClN_2O_3$: C, 56.9; H, 7.9.
Found: C, 57.1; H, 7.9.

German patent 272,529 (15) gave m.p. 167°. The corresponding ester hydrochloride (4) has m.p. 174°, and would require C, 60.0; H, 8.0. (Calc'd for $C_{16}H_{24}ClNO_3$.)

2-Diethylaminoethyl p-tolycarbamate hydrochloride. p-Toluic azide was prepared in a similar manner to the other azides in a 70% yield from the hydrazide, m.p. 33.5°.

Anal. Calc'd for $C_8H_7N_3O$: N, 26.1. Found: N, 26.2.

Naegeli, Tyabji, and Conrad (16) prepared *p*-toluic azide by the action of sodium azide on the acid chloride, and found m.p. 28°, but gave neither yield nor analysis.

p-Toluic azide (10.9 g.) and diethylaminoethanol (13.0 g.) reacted vigorously and gave 1.5 g. of the urea and 1.6 g. of the urethan hydrochloride. The latter was obtained as white needles m.p. 176°, with solubility in boiling absolute alcohol of 15 g./100 cc. of solvent.

Anal. Calc'd for $C_{14}H_{23}ClN_2O_2$: C, 58.5; H, 8.1; N, 9.8.
Found: C, 58.7; H, 8.0; N, 9.9.

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SUMMARY

The compound prepared by Robinson and Tomlinson (1) by heating *p*-anisic azide with 2-diethylaminoethanol and converting to the picrate, has been shown to be the picrate of 2-diethylaminoethyl *p*-anisate, and not that of 2-diethylaminoethyl *p*-anisylcarbamate as claimed. Three other azides also gave deriva-

tives of the ester on the occasions when crystalline products could be obtained, and although derivatives of the urethan were isolated in two further cases the yields were very small.

The reaction is evidently not suitable for preparing urethans from amino-alcohols.

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