211. *An Improved Synthesis of* o-2-*Bromoethylbenzyl Bromide.*

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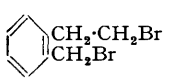
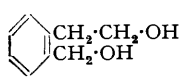
o-2-*Hydroxyethylbenzyl alcohol* has been prepared by the reduction of ethyl homophthalate with lithium aluminium hydride, and converted into *o*-2-bromoethylbenzyl bromide.

o-2-Bromoethylbenzyl bromide (I) was originally synthesised by von Braun and Zobel (*Ber.*, 1923, **56**, 2142) but a much improved synthesis, of five stages compared with the original twelve, was worked out by Holliman and Mann (*J.*, 1942, 737) who demonstrated the wide synthetic application of this substance (see also *J.*, 1943, 547, 550; 1945, 34, 37, 45). In spite of this improvement, the method was unsuitable for the synthesis of substituted analogues. Beeby and Mann (*J.*, 1949, 1799) sought to remedy this disadvantage and synthesised 5-nitro-2-2′-chloroethylbenzyl chloride and the corresponding dibromo-compound by introducing the halogenomethyl group into the 2-*p*-nitrophenylethyl halide by treatment with the *s*-dihalogenodimethyl ether in the presence of fuming sulphuric acid; however, in order that *ortho*-substitution may take place, the choice of substituent and its position in the aromatic nucleus is considerably restricted.

When the dibromide was originally synthesised (*J.*, 1942, 737), the possibility of synthesising the parent alcohol, o-2-*hydroxyethylbenzyl alcohol* (II) by reduction of homophthalic ester was not examined as the methods of reducing carbalkoxy- to hydroxymethyl groups then known were unsatisfactory when these groups were directly attached to the aromatic nucleus. Use



(I.)



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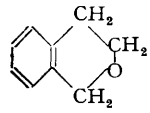

(III.)

of lithium aluminium hydride as a reducing agent for carboxyl and carbalkoxy-groups (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548) opened this route to (II) and its derivatives. Compounds of type (II) with two different alkyl or aryl substituents in the 1 position of the bromoethyl group were required for another problem in this laboratory, and, as a model synthesis, the preparation of (I) from homophthalic acid was undertaken.

Reduction of homophthalic anhydride by Nystrom and Brown's technique (*loc. cit.*) was unsatisfactory. Owing to the very slight solubility of the anhydride in ether, the reaction was very prolonged and, in large quantities, very tedious. Further, the reaction product contained *iso*chroman (III) (the internal ether of the desired alcohol), a high-boiling fraction which could not be further purified but which appeared to be the required alcohol, and a residue which did not distil at 300° under high vacuum. Even so, both the *iso*chroman fraction and the high-boiling fraction could be converted into (I) by heating them at 100° with a solution of hydrobromic acid in acetic acid. The overall yield from indene, which was used for the preparation of homophthalic acid (Fieser and Pechet, *J. Amer. Chem. Soc.*, 1946, **68**, 2577), was 30%, a considerable improvement on the earlier method of synthesis.

Attention was next directed to ethyl homophthalate. As it is miscible with ether, its introduction is a rapid process, and the reduction is noteworthy in that the ethereal solution remains clear throughout the reduction, no precipitate of the alcohol–metal complex separating as in reductions described by other workers. Pure o-2-*hydroxyethylbenzyl alcohol* was thus obtained

in 91% yield; it was characterised as the *di*-p-*nitrobenzoate* and *diphenylurethane*, and with an acetic acid solution of hydrogen bromide at 100° gave the dibromide in high yield, the overall yield from indene being again about 30%. Attempts to avoid the use of sealed tubes during conversion of the alcohol into the bromide proved unsuccessful.

Further work is being carried out on the application of this route to the synthesis of substituted derivatives of the type described above.

Experimental.

(M. p.s are uncorrected.)

Homophthalic acid (Fieser and Pechet, *loc. cit.*) was converted into the anhydride by acetic anhydride (cf. Dieckmann, *Ber.*, 1914, **47**, 1432) and into ethyl homophthalate by heating with ethyl alcohol in a current of dry hydrogen chloride. The lithium aluminium hydride used was prepared from lithium hydride (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1200).

Reduction of Homophthalic Anhydride.—Thoroughly dried homophthalic anhydride was placed in the thimble of a Soxhlet extractor attached to a three-necked flask fitted with a mechanical stirrer. An ethereal solution of lithium aluminium hydride (1·1 mols.; as obtained in the preparation from lithium hydride and containing *ca.* 2·5—3·0 g. of $LiAlH_4$ per 100 g.) in the flask was refluxed with stirring so that the anhydride was slowly washed in; addition of 30 g. of anhydride required about 24 hours. Initially, the entry of the anhydride solution caused the deposition of a yellow solid but in the later stages of the reaction a white solid was precipitated. When all the anhydride had been washed in, the mixture was chilled in ice-water whilst water was slowly added; after decomposition of the excess of reducing agent, dilute sulphuric acid was slowly added to dissolve the metal hydroxide. The aqueous mixture, separated from the ethereal layer, was continuously extracted with ether for 10 hours. The combined ethereal extracts were dried (K_2CO_3) and evaporated, and the residue was fractionated under reduced pressure.

In different experiments, the relative quantities of the various fractions varied somewhat. In one experiment, the ethereal solution directly from the reduction of 14 g. of anhydride was worked up separately from that obtained by continuous extraction of the aqueous layer. The former yielded 6·65 g. of a fraction, b. p. 176—192°/18 mm.; this was a cloudy, viscous oil from which no solid benzoyl derivative could be obtained by the Schotten–Baumann method; with hydrobromic acid in acetic acid, however, it yielded 8·3 g. of *o*-2-bromoethylbenzyl bromide and was therefore considered to be impure *o*-2-hydroxyethylbenzyl alcohol. The continuous extract of the aqueous layer yielded, on fractionation, an oil (3 g.), b. p. 96—118°/21 mm., and a non-volatile residue. From the b. p., it would seem that the former is *iso*chroman and with hydrobromic acid in acetic acid it yielded the dibromide (6·2 g.). The total yield of dibromide in this preparation was therefore 14·5 g. (67%).

In another experiment, 35 g. of homophthalic anhydride were reduced and the combined ethereal extracts worked up. Distillation of the reaction product at 25 mm. yielded 8·5 g. of *iso*chroman at 110°, 1·32 g. at 180—186°, 1·79 g. at 196—230°, and a non-volatile residue.

On another occasion, the crude product left after evaporation of the combined ethereal extracts was converted directly into the dibromide. From 11 g. of anhydride 6·21 g. of crude reduction product were obtained and thence 9·15 g. of dibromide (48·5% calc. on the anhydride).

Reduction of Ethyl Homophthalate.—In the usual type of apparatus (three-necked flask fitted with mechanical stirrer, reflux water-condenser, and dropping funnel) a solution of ethyl homophthalate (15 g.) in dry ether (200 c.c.) was slowly added to an ethereal solution of lithium aluminium hydride (3·1 g. in 230 c.c.; 1·3 mols.) at such a rate that gentle refluxing without external cooling was maintained. Although a small amount of yellow precipitate was formed in the early stages of the addition, the ethereal solution remained practically clear throughout. When addition of the ester was complete, the mixture was set aside overnight before treatment as above with water and sulphuric acid. The ethereal layer was separated and the aqueous layer continuously extracted with ether during 8 hours. The combined ethereal solutions were dried (K_2CO_3) and evaporated, and the residue was distilled under reduced pressure to yield a single fraction at 192—198°/15 mm. (8·8 g., 91%). Redistillation gave pure o-2-*hydroxyethylbenzyl alcohol*, b. p. 194—196°/15 mm. (Found: C, 70·6; H, 7·7. $C_9H_{12}O_2$ requires C, 71·0; H, 7·9%).

The alcohol was heated with *p*-nitrobenzyl chloride (2 mols.) in pyridine at 100° for 1 hour. After cooling, dilution with water, washing with 5% aqueous sodium hydroxide solution, and drying, three recrystallisations from alcohol gave the *di*-p-*nitrobenzoate*, m. p. 141—142·5° (Found: C, 60·45; H, 4·4; N, 6·5. $C_{23}H_{18}O_8N_2$ requires C, 61·32; H, 4·0; N, 6·2%).

The alcohol was treated with phenyl *iso*cyanate (2 mols.), and the mixture heated at 100° for 1 hour. On cooling, the thick viscous liquid slowly crystallised. Trituration with light petroleum (b. p. 65—75°) and two recrystallisations from benzene yielded the *diphenylurethane* which crystallised as long silky needles, m. p. 133—133·5°, containing one molecule of benzene of crystallisation (Found: C, 74·5; H, 6·0. $C_{23}H_{22}O_4N_2,C_6H_6$ requires C, 74·3; H, 6·0%). The solvent-free derivative was obtained by drying it at 120°/15 mm. for 6 hours; the m. p. was unchanged (Found: C, 69·5; H, 5·85; N, 7·4. $C_{23}H_{22}O_4N_2$ requires C, 70·6; H, 5·7; N, 7·2%).

o-2-*Bromoethylbenzyl Bromide.*—*o*-2-Hydroxyethylbenzyl alcohol was heated with a 50% w/v solution of hydrobromic acid in glacial acetic acid in a sealed tube at 100° for 4 hours. The dark oil, precipitated on addition to water, rapidly solidified when scratched. Recrystallisation (charcoal) from light petroleum (b. p. 35—50°) gave colourless crystals of *o*-2-bromoethylbenzyl bromide (85%).

Attempts to carry out the conversion by heating with aqueous hydrobromic acid (48%) in the presence of a trace of sulphuric acid failed; although the initial soluble alcohol was quite rapidly converted into a water-insoluble oil, the latter failed to crystallise even when refluxing had been carried on for some 5 hours. In the light of this experiment, where it was thought that only one of the alcoholic hydroxyls

was reacting, a stream of dry hydrogen bromide was passed through a boiling solution of the alcohol in glacial acetic acid : even after several hours, only an oil was obtained by pouring the reaction mixture on ice.

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