LXIX.—*Benzyl δ-Chlorobutyl Ether: A New Unsymmetrical Derivative of Tetramethylene Glycol.*

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The preparation of tetramethylene dibromide is no longer a very difficult matter (v. Braun and Lemke, *Ber.*, 1922, **55**, 3526; Marvel and Tanenbaum, *J. Amer. Chem. Soc.*, 1922, **44**, 2645), but unsymmetrical δ-substituted *n*-butyl halides, which have a special importance as synthetic reagents, have been obtained in only two instances and in poor yield. δ-Amyloxy-*n*-butyl bromide was isolated by Hamonet (*Bull. Soc. chim.*, 1905, **33**, 513) and used in a synthesis of pentamethylene dibromide, whilst δ-phenoxybutyl bromide appeared as a by-product in the conversion of δ-phenoxybutyl alcohol into tetramethylene dibromide described by Marvel and Tanenbaum (*loc. cit.*).

Being in need of an unsymmetrical αδ-disubstituted butane of this type, we decided to prepare δ-benzyloxybutyl chloride (benzyl δ-chlorobutyl ether), since the benzyl group has considerable advantages over both the phenyl and the amyl group in respect of the ease with which it is removed and of the fact that a free hydroxyl group is left in the process. This was a point so vital for the purpose we had in view (see succeeding paper) as to render comparatively unimportant our lower yield of δ-benzyloxybutyl alcohol as compared with that of phenoxybutyl alcohol obtained by Marvel and Tanenbaum.

Benzyl β-chloroethyl ether (Bennett, J., 1925, **127**, 1277) showed no tendency to combine with magnesium, an observation which was consistent with the statement by Hamonet (Wurtz, "Dictionnaire de Chimie," **2**, 751) that ethers of the type $RO{\cdot}CH_2{\cdot}CH_2X$ (where X is a halogen) do not yield Grignard reagents. Benzyl iodoethyl ether, however, combined readily with magnesium. The action of the resulting organo-magnesium compound on β-chloroethyl *p*-toluenesulphonate (compare Gilman and Beaber, *J. Amer. Chem. Soc.*, 1923, **45**, 839), on ethylene oxide and on ethylene chlorohydrin (compare Grignard, *Compt. rend.*, 1903, **136**, 1260; 1905, **141**, 44; Meisenheimer, *Annalen*, 1925, **442**, 180) was studied, but in no case did we isolate enough of the desired product for its identification with certainty, and experiments in this direction were abandoned after we had confirmed the original statements of Grignard.

The method of preparation finally adopted involved the reduction of ethyl γ-benzyloxybutyrate to the δ-benzyloxybutyl alcohol. The required ester was obtained in two ways: (*a*) from ethylene glycol through benzyl chloroethyl ether by the malonic ester method, and (*b*) from trimethylene glycol through its monobenzyl ether, benzyl chloropropyl ether and the corresponding nitrile, $CH_2Ph{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$. The practical success of each of these methods depends on the use of thionyl chloride in presence of dimethylaniline to replace the hydroxyl group by chlorine (Darzens, *Compt. rend.*, 1911, **152**, 1314). On the other hand, the corresponding reaction with thionyl bromide has proved less useful, for benzyl γ-hydroxypropyl ether was only partly converted by it into benzyl bromopropyl ether. As the yield was poor and the product impure, a valuable substance for use as an organo-magnesium compound remains inaccessible. With a cheap supply of trimethylene glycol available, the method (*b*) is the more economical, but the yields by the method (*a*) were good.

EXPERIMENTAL.

Benzyl γ-Hydroxypropyl Ether.—The dissolution of sodium metal in hot trimethylene glycol involves considerable charring and the reaction may become uncontrollable if the metal is allowed to melt (compare Noyes, *Amer. Chem. J.*, 1897, **19**, 766). The method recently used (J., 1925, **127**, 1279) with ethylene glycol is inadvisable, since trimethylene glycol forms a stable compound with sodium ethoxide (Parone, *Boll. Chim. Farm.*, 1905, **44**, 481). The required sodium compound was conveniently obtained as follows: To trimethylene glycol (240 g.), covered with dry xylene (200 c.c.) and heated to 130°, sodium (25 g.) was cautiously added in small pieces. The reaction was easily controlled and soon complete. To the mixture, cooled to 120°, benzyl chloride (150 g.) was added in small portions, and the reaction completed by boiling the whole for 15 minutes. After addition of benzene to increase the precipitation of the sodium chloride, the solution was filtered, washed with water and dried, the solvents were evaporated, and the product was distilled under diminished pressure. The residue of high b. p. containing the dibenzyl ether of the glycol was neglected. *Benzyl γ-hydroxypropyl ether* is an almost colourless oil, b. p. 155°/23 mm., 172°/43 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·0474, $n_{\alpha}^{20^\circ}$ 1·5128, whence $[R_L]_\alpha$ 47·77 (calc., 47·64). It is not miscible with water, but is soluble in alcohol and ether (Found : C, 71·8; H, 8·5. $C_{10}H_{14}O_2$ requires C, 72·2; H, 8·5%). The yield of this monobenzyl ether (128 g.; 70%) was reduced when the temperature of the reaction was higher than 120°. This is to be expected if, as is the case with ethylene glycol (Forcrand, *Compt. rend.*, 1891, **113**, 1048), the heat evolved in the replacement of the second atom of hydrogen by sodium is less than that for the first, since this will cause a redistribution of the equilibrium in the mixture in favour of the disodium compound as the temperature rises. Attempts to prepare a *p*-nitrobenzoate and a phenylurethane derivative of the substance yielded no crystalline products other than *p*-nitrobenzoic acid and diphenylcarbamide.

Benzyl γ-Chloropropyl Ether.—Thionyl chloride (120 g.) was added drop by drop to a mixture of benzyl hydroxypropyl ether (160 g.) and dimethylaniline (130 g.) below 60°. After ½ hour, the mixture was poured into dilute hydrochloric acid in excess, and the heavy oil which separated removed with chloroform. The extract was washed with dilute acid to remove dimethylaniline, then with water, and dried over sodium sulphate, the solvent evaporated, and the oil distilled. *Benzyl γ-chloropropyl ether* was at once obtained (153 g.; 83% yield) as a colourless oil, b. p. 129°/16 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·0706, $n_{\alpha}^{20^\circ}$ 1·5102, whence $[R_L]_\alpha$ 50·40 (calc., 50·96) (Found : Cl, 19·4. $C_{10}H_{13}OCl$ requires Cl, 19·2%).

γ-Benzyloxybutyronitrile, $CH_2Ph{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$.—A solution of benzyl chloropropyl ether (200 g.) and sodium cyanide (85 g.) in water (100 c.c.) and industrial spirit (125 c.c.) was boiled under reflux for 48—60 hours, any alcohol evaporating being replaced from time to time. Benzene was added when the mixture had cooled, and the sodium chloride was then filtered off and the upper layer of benzene was removed, dried over sodium sulphate and distilled in a Widmer vacuum fractionating flask (*Helv. Chim. Acta*, 1924, **7**, 59), a complete separation of the nitrile from any unchanged chloro-compound being thus readily secured; a second distillation gave the analytically pure *γ-benzyloxybutyronitrile*, a colourless oil of faint odour, b. p. 157°/12 mm., 166°/16 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·026, $n_{\alpha}^{20^\circ}$ 1·5005, whence $[R_L]_\alpha$ 50·27 (calc., 50·61) (Found : C, 75·2; H, 7·7. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5%). The yield of nitrile was 100—110 g. (57%) and 25—40 g. of chloropropyl ether were recovered (16%).

Ethyl γ-Benzyloxybutyrate, $C_7H_7{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$.—The nitrile (82 g.) was boiled under reflux with absolute ethyl alcohol (95 g.) and concentrated sulphuric acid (45 g.) for 8 hours, half the alcohol removed by distillation, and the residue poured into water. The precipitated oil was separated by means of ether, the extract washed with sodium carbonate solution, dried, and distilled. *Ethyl benzyloxybutyrate* (63—69 g.; 65% yield) was thus obtained as a straw-coloured oil, b. p. 160°/14 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·036, $n_\alpha^{20^\circ}$ 1·4930, whence $[R_L]_\alpha$ 62·10 (calc., 61·56) (Found: C, 70·5; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·2%).

Alternative Synthesis of Ethyl Benzyloxybutyrate.—A mixture of ethyl malonate (24 g.), benzyl β-chloroethyl ether (25·6 g.), and sodium ethoxide (from 3·5 g. of sodium) in absolute ethyl alcohol (50 c.c.) was heated in a soda-water bottle at 100° for 6 hours. The alcohol and any unchanged material were removed in a current of steam, the residual oil was separated in ether, and the extract was washed, dried and distilled; *ethyl β-benzyloxyethylmalonate,* $C_7H_7{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et)_2$ (17 g.), was then obtained as a colourless liquid of b. p. 213°/22 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·0795, $n_\alpha^{20^\circ}$ 1·4908, whence $[R_L]_\alpha$ 78·9 (calc., 77·00) (Found: C, 65·1; H, 7·5. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%).

This ester (40 g.) was carefully added to a solution of potassium hydroxide (22 g.) in ethyl alcohol (100 c.c.), and the mixture boiled for 2 hours. The alcohol was evaporated, and the solution was acidified with dilute sulphuric acid (22 g. of H_2SO_4 in 200 c.c. of water) and extracted with ether for 1 day in a continuous extractor. The residue after evaporation of the ether from the dried ethereal solution was heated at 170—180° until evolution of carbon dioxide ceased (2 hours); *γ-benzyloxybutyric acid* (25 g.) was then left as a syrupy liquid. This was at once esterified by boiling it for 7 hours with 10% alcoholic sulphuric acid (250 g.). The ester, isolated in the usual manner, had b. p. 163—166°/18 mm. (23 g.; overall yield from the dicarboxylic ester, 76%).

Reduction of Ethyl Benzyloxybutyrate.—The ester was reduced in toluene solution by sodium and ethyl alcohol as described by Marvel and Tanenbaum (*loc. cit.*) in a glass flask with two wide necks down one of which passed the stirrer and the delivery-tube of a dropping-funnel, whilst the other was fitted with the extra-wide metal tube of a long condenser. No difficulty was found in reducing the molten metal to a fine state of division when the stirrer (of the hollow T-piece pattern) was driven directly by an electric motor at high speed. On distillation of the final product, *benzyl δ-hydroxybutyl ether* was obtained (yield 37%) as a colourless oil, b. p. 157°/12 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·029, $n_\alpha^{20^\circ}$ 1·5107, whence $[R_L]_\alpha$ 52·46 (calc., 52·24). It is soluble in alcohol, ether or benzene, but insoluble in water (Found: C, 73·6, 73·5; H, 9·0, 9·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 9·0%). As was the case with the lower homologue (p. 474), the *p*-nitrobenzoate and phenylurethane of this substance could not be obtained crystalline.

Benzyl δ-Chlorobutyl Ether.—Thionyl chloride (6 g.) was gradually added to a well-shaken mixture of benzyl hydroxybutyl ether (9 g.) and dimethylaniline (6 g.), and the product (8 g.; 80% yield) isolated as was the analogous chloropropyl ether (p. 474). *Benzyl chlorobutyl ether* is a pale yellow oil, b. p. 135°/12 mm., $d_{4^\circ}^{20^\circ}$ (vac.) 1·0572, $n_{\alpha}^{20^\circ}$ 1·5083, whence $[R_L]_\alpha$ 56·10 (calc., 55·56) (Found: Cl, 17·5. $C_{11}H_{15}OCl$ requires Cl, 17·8%).

Benzyl β-Iodoethyl Ether.—Benzyl chloroethyl ether (60 g.) was heated for 30 hours in boiling methyl alcohol with sodium iodide (60 g.), the solvent was then evaporated, and the oil was precipitated by water, removed in ether, dried, and distilled under diminished pressure in a Widmer flask. *Benzyl iodoethyl ether* was thus isolated (yield 60%; some chloro-compound was recovered) as a heavy, colourless oil, b. p. 148—149°/14 mm. (Found: I, 48·0. $C_9H_{11}OI$ requires I, 48·4%).

Experiments with Magnesium β-Benzyloxyethyl Iodide.—Magnesium dissolved readily in an ethereal solution of benzyl iodoethyl ether. (No reaction was observed with the corresponding chloro-compound.) The resulting Grignard reagent was subjected to the action of β-chloroethyl *p*-toluenesulphonate (1 mol.) either in boiling ether or in boiling benzene, but the ester was largely recovered unchanged together with benzyl ethyl ether. The magnesium benzyloxyethyl iodide was also allowed to react in ethereal solution with ethylene oxide, the solution evaporated, and the residue heated; and, lastly, the Grignard reagent in question was added to a mixture of ethylene chlorohydrin with either magnesium phenyl bromide or magnesium ethyl bromide, and the mixture heated. In none of these experiments was benzyl hydroxybutyl ether identified with certainty among the products. In each case benzyl ethyl ether was obtained in quantity.

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