A NOTE ON THE ANAESTHETIC ACTIVITY OF SOME 1:3-PROPANEDIOLS

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The discovery is reported of the anaesthetic activity of 2-alkyl-substituted alkane-1 : 3-diols in mice. The preparation of some hitherto undescribed members of this class is reported.

2:2-Dialkyl-substituted propane-1:3-diols (for example, 2:2-diethylpropane-1:3-diol) are known to possess anticonvulsant activity[1-7], but although the muscle relaxant activity of 2-ethylpentane-1:3-diol has been reported[1], the anaesthetic activity does not seem to have been noted before in this series except in high doses[2]. It was found during another investigation that 2-ethylhexane-1:3-diol (I; R = *n*Pr; R′ = Et; R″ = H) produced general anesthesia after

$$R-CHOH\cdot CR'R''\cdot CH_2OH$$

(I)

intraperitoneal injection into mice. Several other compounds of this type were, therefore, tested and are listed in Table I.

TABLE I

ANAESTHETIC ACTIVITY AND TOXICITY OF COMPOUNDS EXAMINED

Compound	Reference	Formula (I) R	R′	R″	Dilution (in water) used (vol.)	ED50 (ml. compd./ kg. body wt.)	LD50 (ml. compd./ kg. body wt.)
2-Ethylpropane-1:3-diol[a] ..	12, 13	H	Et	H	1/2	3·7[e]	7·5[e]
2:2-Dimethylpropane-1:3-diol	*	H	Me	Me	1/1·5	†	8·0[f]
2-Methylpentane-1:3-diol ..	*	Et	Me	H	1/10	1·95[g]	4·2[g]
2:2-Diethylpropane-1:3-diol[b]	8, 9	H	Et	Et	1 g./12·5 ml.	0·8‡[e]	1·2‡[e]
2-Methyl-2-propylpropane-1:3-diol[c]	8, 10	H	Me	*n*Pr	1 g./30 ml.	0·4‡[h]	0·66‡[h]
2-Ethylpentane-1:3-diol ..	*d*	Et	Et	H	1/10	0·75[e]	1·5[e]
Heptane-1:3-diol	*d*	*n*Bu	H	H	1/10	0·5[i]	1·5[i]
2-Ethylhexane-1:3-diol ..	*	*n*Pr	Et	H	1/30	0·65[j]	1·2[j]
2-Ethylheptane-1:3-diol ..	*d*	*n*Bu	Et	H	1/100	0·3[j]	0·48[j]

a n_D^{20} 1·4495. b.p. 122 to 123° at 17 mm. *b* m.p. 61°. *c* m.p. 57° after crystallisation from light petroleum (b.p. 80 to 100°) and sublimation. Yale and others[8] quote m.p. 62 to 63°. *d* See text for preparation. *e–j* Conditions of test: *e* five mice at each of three dose levels; *f* ten mice at each of four dose levels; *g* ten mice at each of three dose levels; *h* five mice at each of five dose levels; *i* four mice at each of four dose levels; *j* ten mice at each of five dose levels. * Commercial material. † No anaesthetic effect detected. ‡ g./kg. body weight.

Most of the compounds tested are well-known and some were obtained from commercial sources. A convenient route to propane-1:3-diols, which are not alkyl-substituted at the terminal carbon atoms, is afforded by the reduction with lithium aluminium hydride of substituted malonic esters, and has been previously used for the preparation of (I; R = H; R′ = R″ = Et)[8,9]. 2-Methyl-2-propylpropane-1:3-diol was prepared by the reaction of formaldehyde and sodium hydroxide on 2-methylvaleraldehyde[10]. For propanediols substituted on the 3-carbon atom

(I; R = alkyl) the route chosen (cf.[8]) was the reduction by lithium aluminium hydride of esters of β-hydroxyacids, themselves prepared by the Reformatsky reaction.

The biological testing was carried out by the intraperitoneal injection of aqueous solutions into groups of mice. The criterion of activity was the production of anaesthesia and its maintenance for 30 minutes; from the results obtained, the median effective and median lethal doses were calculated. No ill effects were noted in the mice which recovered. The results are shown in Table I.

Since the number of compounds tested was small, it is not possible to relate the activity to the structure, except to note that the activity and toxicity are greatest in the compounds of higher molecular weight.

It is thought that 1:3-diols might be useful, under carefully controlled conditions, as anaesthetics for laboratory animals.

Preparation of Compounds

2-Ethylpentane-1:3-diol. A mixture of ethyl 2-bromo-*n*-butyrate (48·7 g.), propionaldehyde (17·4 g.), ether (20 ml.), and benzene (80 ml.) was cautiously added to a stirred suspension of zinc powder (22 g.), (previously washed in turn with 2 per cent v/v hydrochloric acid, water, ethanol, acetone, and ether, and dried at 60°), in ether (2 ml.) and benzene (18 ml.). The vigorous reaction was maintained under reflux by the application of heat and the continued addition of the ester–aldehyde mixture; the heating was continued for 30 minutes after the addition was complete. The mixture was poured into ice-cold 10 per cent v/v aqueous sulphuric acid and the organic layer was separated, washed with dilute sodium bicarbonate solution, and dried. The combined products of two such experiments were fractionated (12 in. packed column). No sharply-boiling fraction was obtained, and the crude ethyl 2-ethyl-3-hydroxyvalerate (20·5 g.), b.p. 97 to 105° at 13 mm., was collected separately. This material (19·1 g.) was reduced in ether (250 ml.) with lithium aluminium hydride (7·2 g.) and the product was distilled to give the crude diol (9·8 g.), b.p. 120 to 124° at 13 mm. Redistillation gave *2-ethylpentane-1:3-diol* as a viscous liquid, b.p. 124 to 125° at 14 mm., n_D^{20} 1·4505. (Found: C, 64·1; H, 11·9. $C_7H_{16}O_2$ requires C, 63·6; H, 12·2 per cent.)

Heptane-1:3-diol. Ethyl 3-hydroxyheptoate was prepared from valeraldehyde (48 g.), ethyl bromoacetate (95 g.), ether (20 ml.), benzene (100 ml.), and zinc powder (46·7 g.) by a similar process to that used for the preparation of ethyl 2-ethyl-3-hydroxyvalerate above. Ethyl 3-hydroxyheptoate (46 g.) was obtained as a fraction, b.p. 103 to 110° at 10 mm. [Adickes and Andressen[11] quote b.p. 94 to 96° at 5 mm.] On reduction with lithium aluminium hydride (12·7 g.) it gave a fraction (16·5 g.), b.p. 94 to 96° at 1 mm., which, on redistillation, gave the *diol* (14·8 g.) as a viscous liquid, b.p. 95° at 0·75 mm. (Found: C, 63·7; H, 11·8. $C_7H_{16}O_2$ requires C, 63·6; H, 12·2 per cent.)

2-Ethylheptane-1:3-diol. The reaction of valeraldehyde (26 g.), ethyl 2-bromo-*n*-butyrate (58·8 g.), and zinc powder (23 g.), carried out as described above for analogous reactions, gave a fraction (34·8 g.), b.p.

115 to 127° at 12 mm., a sample of which was redistilled to give *ethyl 2-ethyl-3-hydroxyheptoate*, b.p. 124° at 12 mm. (Found: C, 65·5; H, 10·9. $C_{11}H_{22}O_3$ requires C, 65·3; H, 10·9 per cent.) Reduction of the main portion of the fraction (28 g.) with lithium aluminium hydride (6·85 g.) in ether, gave the *diol* (13·5 g.), b.p. 140 to 143° at 12 mm., n_D^{20} 1·4515. (Found: C, 67·9; H, 12·6. $C_9H_{20}O_2$ requires C, 67·5; H, 12·6 per cent.)

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