SOME HYDROXYALKYL ETHERS OF *o*-TOLOXY- AND *p*-CHLOROPHENOXYPROPANE-2 : 3-DIOL

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FOLLOWING the discovery of the muscle-relaxing and anticonvulsant properties of 1-*o*-toloxypropane-2 : 3-diol (mephenesin)[1] and the antibacterial and antifungal activity of 1-*p*-chlorophenoxypropane-2 : 3-diol (chlorphenesin)[2], many related compounds were synthesised for pharmacological evaluation in this and other laboratories[3]. In addition, the preparation of some 1-aryloxy*iso*butane-2 : 3-diol derivatives was undertaken by Bradley, Forrest and Stephenson[4]. The formally related types (I), (II) and (III), however, have not hitherto been described in the literature and form the subject of the present communication.

$$ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}(CH_2)_n{\cdot}CHROH \quad (I)$$

$$ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2OH \quad (II)$$

$$ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2{\cdot}CH_2O{\cdot}CH_2{\cdot}CH_2OH \quad (III)$$

$$Cl{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2{\cdot}CH_2OH \quad (IV)$$

(Ar = *o*-tolyl or *p*-chlorophenyl)

6-Chloro-3-oxahexane-1 : 5-diol (IV), required for the synthesis of (I; $n = 1$; R = H), has been described by Kharasch and Nudenberg[5], who obtained it in 56 per cent. yield by reacting ethylene glycol (2 moles) with epichlorohydrin in the presence of concentrated sulphuric acid as catalyst. Though satisfactory on the molar scale, the method is not directly applicable to the preparation of (IV) in quantity, as the reaction tends to become strongly exothermic during the addition of the acid. We have, consequently, studied the formation of (IV) and now report an improved route to this intermediate.

Initial attempts to condense ethylene glycol (2 moles) with epichlorohydrin in the presence of a basic catalyst proved disappointing, only 26 per cent. of (IV) being isolated from the complex reaction mixture. In addition, some 3 : 7-dioxanonane-1 : 5 : 9-triol (VI) was obtained, presumably by the reaction sequence (i) to (iii), together with a smaller amount of 1 : 10-dichloro-4 : 7-dioxadecane-2 : 9-diol (VII; R = Cl), formed as indicated in (iv).

(i) $CH_2OH{\cdot}CH_2OH + CH_2{\cdot}CH{\cdot}CH_2Cl \rightarrow CH_2O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2Cl$ (IV)

(ii) (IV) + $CH_2{\cdot}CH{\cdot}CH_2Cl \rightarrow CH_2O{\cdot}CH_2{\cdot}CH{\cdot}CH_2 + CH_2Cl{\cdot}CHOH{\cdot}CH_2Cl$ (V)

(iii) (V) + $\begin{matrix}CH_2OH\\|\\CH_2OH\end{matrix}$ → $\begin{matrix}CH_2O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2\\|\qquad\qquad\qquad\qquad|\\CH_2OH\qquad\qquad\qquad CH_2OH\end{matrix}$

(VI)

(iv) $\begin{matrix}CH_2OH\\|\\|\\CH_2OH\end{matrix}$ + 2 $CH_2CH{\cdot}CH_2Cl$ (O) → $\begin{matrix}CH_2O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2R\\|\\CH_2O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2R\end{matrix}$

(VII)

The last compound was characterised by conversion to the bis-β-naphthyl ether (VII; R = β — $OC_{10}H_7$) and to the bis-piperidino derivative (VII; R = — NC_5H_{10}), which was isolated as the dihydrochloride. More complex high-boiling reaction products were not investigated.

Further study revealed the adverse effects of both basic and acidic catalysts upon this reaction. By simply heating epichlorohydrin with ethylene glycol (3 moles) at 120° to 150° C. for about 4 hours in the absence of catalysts, however, improved yields (70 per cent.) of (IV) were consistently obtained in both small and large scale experiments. In addition, the latter showed no signs of undue exothermic vigour. The yield of (IV) decreased considerably when less than 2 moles of ethylene glycol were used. Extension of the reaction to propylene glycol, diethylene glycol and glycerol furnished 1-chloro-4-oxaheptane-2:6-diol (VIII), 9-chloro-3:6-dioxanonane-1:8-diol (IX) and 1-chloro-4-oxaheptane-2:6:7-triol (X), respectively.

$Cl{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2{\cdot}\overset{Me}{\underset{|}{C}}HOH$ (VIII)

$Cl{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2{\cdot}CH_2OCH_2{\cdot}CH_2OH$ (IX)

$Cl{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2O{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2OH$ (X)

Condensation of (IV) with *o*-cresol and *p*-chlorophenol in alkaline solution furnished 6-*o*-toloxy (I; Ar = — C_7H_7; $n = 1$; R = H) and 6-*p*-chlorophenoxy-3-oxahexane-1:5-diol (I; Ar = — C_6H_4Cl; $n = 1$; R = H), respectively. The last two compounds were additionally prepared (*a*) by converting (IV) into 5:6-epoxy-3-oxahexan-1-ol and condensing the latter with the appropriate phenol in the presence of a basic catalyst: and (*b*) by direct reaction between the 1-aryloxy-2:3-epoxypropane (XI) and ethylene glycol at 140° to 180° C. or at *ca.* 100° C. in the presence of a basic catalyst as indicated in (v).

(v) $ArO{\cdot}CH_2{\cdot}CH(O){\cdot}CH_2 + (CH_2OH)_2 \rightarrow ArO{\cdot}CH_2{\cdot}CHOH{\cdot}CH_2OCH_2CH_2OH$

(XI)

(I; $n = 1$; R = Me), (I; $n = 2$; R = H), (II) and (III) were similarly obtained from (VIII), (IX) and (X), or by alternatives (*a*) and (*b*) (*vide supra*). Of these, (*b*) proved the most satisfactory on the preparative scale.

Dr. A. David has kindly examined the foregoing *o*-toloxy ethers for muscle-relaxing properties, but reports that none of them proved more active than mephenesin. In addition, Dr. S. W. F. Underhill has kindly

examined the *p*-chlorophenoxy derivatives for antifungal activity. His results show that the new compounds compare unfavourably with chlorphenesin.

EXPERIMENTAL

Melting points and boiling points are uncorrected.

Condensation of Epichlorohydrin with Ethylene Glycol.

(A) Epichlorohydrin (185 g.; 2 moles), ethylene glycol (248 g.; 4 moles) and pyridine (1 ml.) were heated at 140° C. until refluxing stopped (45 minutes) and then at 145° C. for 3 hours. Distillation at 0·3 mm. yielded—

Fraction (i) b.pt. 50° to 100° C., 253 g.
„ (ii) b.pt. 100° to 170° C., 108 g.
„ (iii) b.pt. 180° to *ca.* 200° C., 53·7 g.

Fraction (i) was redistilled at 0·3 mm. through a 24 inch Vigreux column and a bath temperature of 85° C. to give glycerol dichlorohydrin, b.pt. 36° to 44° C. which was converted into epichlorohydrin by treatment with solid potassium hydroxide. The rest of the fraction was unchanged ethylene glycol, b.pt. 50° to 52° C.

Fraction (ii) gave 1-chloro-4-oxahexane-2:6-diol (IV) (80 g.; 26 per cent.).

Fraction (iii) yielded 3:7-*dioxanonane*-1:5:9-*triol* (VI), b.pt. 160° to 162° C. at 0·4 mm. Found: C, 46·1; H, 8·9. $C_7H_{16}O_5$ requires C, 46·6; H, 9·0 per cent. The material slowly solidified. By heating a portion (3·5 g.) with *p*-nitrobenzoyl chloride (10·5 g.) at 100° C. for 4 hours and precipitating with benzene, the *tri*-p-*nitrobenzoate* was obtained as needles, m.pt. 125° to 127° C. after crystallisation from a large volume of ethanol. Found C, 53·2; H, 4·1; N, 6·8. $C_{28}H_{25}O_{14}N_3$ requires C, 53·6; H, 4·0; N, 6·7 per cent.

(B) Epichlorohydrin (185 g., 2 moles), ethylene glycol (124 g.; 2 moles) and pyridine (2 ml.) were heated at 130° to 150° C. for 5½ hours. Distillation at 0·3 mm. yielded—

Fraction (i), b.pt. 55° to 110° C., 136 g., a mixture containing ethylene glycol and glycerol dichlorohydrin.

Fraction (ii), b.pt. 120° to 150° C., 65 g., which was redistilled to give pure (IV) (50 g., 17 per cent.).

Fraction (iii), b.pt. up to *ca.* 200° C., 28 g.

Fraction (iii) was treated with piperidine and potassium hydroxide in aqueous ethanol on the steam bath. The mixture was extracted with chloroform and the extract freed from solvent and piperidine by heating under reduced pressure. Conversion to the hydrochloride furnished 1:10-*piperidino*-4:7-*dioxadecane*-2:9-*diol dihydrochloride* (7 g.), large nodules, m.pt. 180° to 182° C. Found: C, 51·7; H, 8·9; N, 6·6. $C_{18}H_{38}O_4N_2Cl_2$ requires C, 51·8; H, 9·2; N, 6·7 per cent., after purification from ethanol-ethyl acetate.

(C) Epichlorohydrin (92·5 g.; 1 mole) and ethylene glycol (186 g.; 3 moles) were heated at 105° to 140° C. for 1½ hours and then at 140° to 155° C. for 2½ hours. Distillation at 0·4 mm. yielded—

Fraction (i), b.pt. 50° C., 142 g., consisting of ethylene glycol and glycerol dichlorohydrin.

Fraction (ii), b.pt. 110° C., 106 g. (68·6 per cent.), which proved to be pure (IV). Found: C, 39·3; H, 7·2; Cl, 22·3. Calculated for $C_5H_{11}O_3Cl$: C, 38·8; H, 7·2; Cl, 22·9 per cent.

Fraction (iii), residue, 27 g., contained (VIII; R = Cl). A portion (5·4 g.) and 2-naphthol (5·4 g.) in sodium hydroxide (1·8 g.) and water (20 ml.) was warmed on the water bath, cooled, and the separated oil triturated with water to give a solid which was repeatedly crystallised from ethyl acetate-light petroleum (b.pt. 60° to 80° C.) to give 1:10-di(2-*naphthoxy*)-4:7-*dioxadecane*-2:9-*diol*, nodules, m.pt. 98° to 100° C. Found: C, 72·3; H, 6·5. $C_{28}H_{32}O_6$ requires C, 72·4; H, 6·9 per cent. A second portion (1·4 g.) of the residue was heated with *p*-nitrobenzoyl chloride (4·2 g.) at 120° C. for 10 minutes. Purification of the product from ethanol furnished 1:5:9-tri-*p*-nitrobenzoyloxy-3:7-dioxanonane, m.pt. 125° to 127° C., alone or in admixture with an authentic specimen (*vide supra*).

(D) As (C), but employing 2 moles of ethylene glycol, when 61·4 per cent. of (IV) was obtained.

5:6-*Epoxy*-3-*oxahexane*-1-*ol* (V): (IV) (30·9 g.), glycide 2-naphthyl ether (40 g.) and triethylamine (1 ml.) were distilled slowly through an efficient fractionating column under reduced pressure. The fraction b.pt. 86° to 95° C. at 1 mm. was redistilled giving 5:6-epoxy-3-oxahexane-1-ol, b.pt. 66° C. at 0·1 mm. Found: C, 50·6; H, 8·5. Calculated for $C_5H_{10}O_3$: C, 50·8; H, 8·6 per cent.

The epoxide (16·5 g.) was mixed with piperidine (11·9 g.) in benzene (25 ml.) with initial cooling, after which reaction was completed by heating at 100° C. for 1 hour. After removal of solvent, the product was distilled under reduced pressure to give 6-*piperidino*-3-*oxahexane*-1:5-*diol* (24 g.), b.pt. 154° C. at 1 mm. Found: N, 6·9. $C_{10}H_{21}O_3N$ requires N, 6·9 per cent.

1-*Chloro*-4-*oxaheptane*-2:6-*diol* (VIII): Epichlorohydrin (92·5 g., 1 mole) and propylene glycol (228 g., 3 moles) were heated at 140° to 150° C. for 4 hours and then at 180° C. for 1 hour. Distillation under reduced pressure furnished.

Fraction (i), b.pt. 50° C. at 0·4 mm., 178 g., consisting of unchanged propylene glycol and glycerol dichlorohydrin.

Fraction (ii), b.pt. 120° C. at 0·6 mm., 113 g. (67 per cent.), which was redistilled to give 1-*chloro*-4-*oxaheptane*-2:6-*diol*, b.pt. 95° C. at 0·2 mm. Found: C, 42·6; H, 7·7. $C_6H_{13}O_3Cl$ requires C, 42·7; H, 7·8 per cent.

When the reaction was performed using 2 moles of propylene glycol, 54 per cent. of (VIII) was obtained.

9-*Chloro*-3:6-*dioxanonane*-1:8-*diol* (IX): Epichlorohydrin (92·5 g., 1 mole) and diethylene glycol (212 g., 2 moles) were heated at 140° to 150° C. for 2½ hours and then at 180° C. for 3 hours. Distillation at 0·4 mm. yielded—

Fraction (i), b.pt. 100° to 134° C., 168 g.

Fraction (ii), b.pt. 134° to 140° C., 70 g., which was redistilled to give 9-*chloro*-3:6-*dioxanonane*-1:8-*diol*, b.pt. 126° to 130° C. at 0·4 mm. Found: C, 42·8; H, 7·4; Cl, 17·7. $C_7H_{15}O_4Cl$ requires C, 42·3; H, 7·6; Cl, 17·9 per cent.

1-*Chloro*-4-*oxaheptane*-2:6:7-*triol* (X): Epichlorohydrin (92·5 g., 1 mole) and glycerol (184 g., 2 moles) were heated at 100° to 130° C. for 1 hour with occasional shaking, when the mixture had become homogeneous. The temperature was then raised to 140° to 150° C. and there maintained for 1½ hours. Distillation at 0·3 mm. furnished a fraction (89·5 g., 48·6 per cent.), b.pt. 180° to 190° C., which was redistilled to give 1-*chloro*-4-*oxaheptane*-2:6:7-*triol*, b.pt. 170° C. at 0·3 mm. Found: C, 39·3; H, 6·8; Cl, 19·4. $C_6H_{13}O_4Cl$ requires C, 39·0; H, 7·1; Cl, 19·2 per cent.

6-o-*Toloxy*-3-*oxahexane*-1:5-*diol* (I; Ar = — C_7H_7; $n = 1$; R = H) (cf. reference 7) was prepared by heating ethylene glycol (62 g., 1 mole) and glycide *o*-tolyl ether (41 g., 0·25 mole) at 150° C. for 3 hours and distilling directly under reduced pressure. The fraction (40·5 g., 72 per cent.) b.pt. 150° to 155° C. at 0·3 mm. was redistilled giving the required *product*, b.pt. 146° C. at 0·2 mm. Found: C, 63·5; H, 7·9. Calculated for $C_{12}H_{18}O_4$: C, 63·7; H, 8·0 per cent.

1-o-*Toloxy*-4-*oxaheptane*-2:6-*diol* had b.pt. 150° C. at 0·3 mm. Found: C, 65·2; H, 8·3. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·4 per cent. It was obtained (82·5 per cent.) by heating glycide-*o*-tolyl ether (41 g., 0·25 mole) with propylene glycol (76 g., 1 mole) at 190° for 3 hours.

1-o-*Toloxy*-4-*oxaheptane*-2:7-*diol* (68 per cent.) had b.pt. 152° to 154° C. at 0·4 mm. Found: C, 65·4; H, 8·4. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·4 per cent.

9-o-*Toloxy*-3:6-*dioxanonane*-1:8-*diol* (III; R = — C_7H_7) had b.pt. 170° C. at 0·4 mm. Found: C, 62·3; H, 8·4. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2 per cent. It was prepared (80 per cent.) by heating glycide-*o*-tolyl ether (41 g.) and diethylene glycol (80 g.) at 160° to 200° C. for 2 hours and then at 200° C. for 4 hours.

1-o-*Toloxy*-4-*oxaheptane*-2:6:7-*triol* (II; Ar = — C_7H_7) had b.pt. 200° C. at 0·5 mm. Found: C, 60·8; H, 7·9. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·9 per cent. It was obtained (60 per cent.) by heating glycide-*o*-tolyl ether (32·8 g., 0·2 mole) with glycerol (50 g., 0·54 mole) and pyridine (4 drops) with shaking until homogeneous and then at 150° C. for 3 hours.

6-p-*Chlorophenoxy*-3-*oxahexane*-1:5-*diol* (I; Ar = C_6H_4Cl; R = H; $n = 1$), prepared (83 per cent.) by heating glycide *p*-chlorophenyl ether (92·3 g., 0·5 mole) and ethylene glycol (100 g., 1·6 mole) at 200° C. for 3 hours, had b.pt. 160° C. at 0·3 mm. After crystallisation from ethyl acetate-light petroleum it formed needles, m.pt. 75° to 77° C. Found: C, 53·7; H, 6·2; Cl, 14·7. $C_{11}H_{15}O_4Cl$ requires C, 53·5; H, 6·1; Cl, 14·4 per cent. The same compound was also obtained by (*a*) heating 5:6-epoxy-3-oxahexane-1-ol (11·8 g.) and *p*-chlorophenol (12·85 g.) in benzene (25 ml.) containing triethylamine (0·2 ml.) under reflux for 6 hours, followed by distillation under reduced pressure, yield 81 per cent., and (*b*) heating (IV) with equimolar *p*-chlorophenol in aqueous potassium hydroxide.

1-p-*Chlorophenoxy*-4-*oxaheptane*-2:7-*diol*, prepared (51 per cent.) by heating glycide *p*-chlorophenyl ether (46 g.) and trimethylene glycol (57 g.) at 190° to 195° C. for 2½ hours, had b.p. 172° C. at 0·3 mm. Found: C, 55·3; H, 6·5; Cl, 13·6. $C_{12}H_{17}O_4Cl$ requires C, 55·3; H, 6·6; Cl, 13·6 per cent.

6-*Phenoxy*-3-*oxahexane*-1:5-*diol* (I; Ar = — Ph; R = H; $n = 1$), (70 per cent.) had b.p. 140° C. at 0·4 mm. Found: C, 62·5; H, 7·6. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6 per cent.

Glycide 4-*chloro*-3:5-*xylyl ether*, prepared by condensing 4-chloro-3:5-xylen-1-ol (1 mole) with epichlorohydrin (1·5 mole) in aqueous alkaline solution (= 1·2 mole alkali, cf. reference 8) formed an oil, b.p. 110° C. at 0·2 mm. which solidified and after purification from light petroleum (b.p. 40° to 60° C.) was obtained as needles, m.p. 47° to 48° C. Found: C, 62·0; H, 6·3; Cl, 16·7. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·2; Cl, 16·7 per cent.

6(4-*Chloro*-3:5-*dimethylphenoxy*)-3-*oxahexane*-1:5-*diol*, prepared (90 per cent.) by heating the foregoing compound (53·1 g.; 0·25 mole) with ethylene glycol (62 g., 1·0 mole) for 5 hours at 150° C. had b.p. 166° C. at 0·1 mm. and after purification from ether-light petroleum (b.p. 40° to 60° C.) had m.p. 62°. Found: C, 56·5; H, 7·1. $C_{19}H_{19}O_4Cl$ requires C, 56·8; H, 7·0 per cent.

1(4-*Chloro*-3:5-*dimethylphenoxy*)-4-*oxaheptane*-2:6-*diol*, prepared (60 per cent.) by heating the glycide ether (21·3 g.) with propylene glycol (22·8 g.) at 180° C. for 3 hours, formed an oil, b.p. 178° to 182° C. at 0·3 mm. Found: C, 58·5; H, 7·7. $C_{14}H_{21}O_4Cl$ requires C, 58·2; H, 7·3 per cent.

1(4-*Chloro*-3:5-*dimethylphenoxy*)-4-*oxaheptane*-2:7-*diol* had b.p. 180° to 184° C. at 0·3 mm. Found: C, 57·9; H, 7·7. $C_{14}H_{21}O_4Cl$ requires C, 58·2; H, 7·3 per cent.

1-p-*Chlorophenoxy*-4-*oxaheptane*-2:6-*diol* had b.p. 164° C. at 0·3 mm. Found: C, 54·8; H, 6·8; Cl, 13·9. $C_{12}H_{17}O_4Cl$ requires C, 55·3; H, 6·6; Cl, 13·6 per cent.

Summary

1. Some hydroxyalkyl ethers of mephenesin and chlorphenesin have been prepared.

2. Examination of the two series for muscle-relaxing and antifungal activity, respectively, failed to reveal evidence of outstanding activity.

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