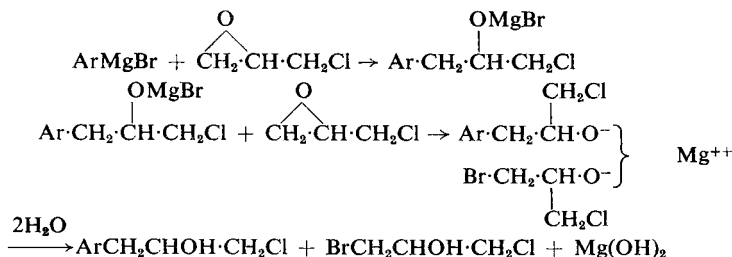


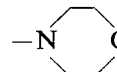
SOME 3-ARYLPROPANE-1:2-DIOLS.

We now find that by careful addition of two molar equivalents of 2:3-epoxypropyl chloride to a cooled ethereal solution of *o*-tolyl magnesium bromide, followed by heating the reaction mixture for two hours under reflux, the yield of 3-*o*-tolyl-2-hydroxypropyl chloride may be raised to > 70 per cent. 1-Bromo-3-chloroisopropanol (cf. 4), identified by conversion to 1:3-diphenoxisopropanol, was a by-product. The yield was not improved by further increase in the quantity of 2:3-epoxypropyl chloride used, but fell markedly when less than two molar equivalents were employed. These results indicate the reaction mechanism:



Conversion of the chlorohydrin (II; R = Cl, R' = *o*-Me) into the required glycol (II; R = OH, R' = *o*-Me) was achieved in excellent yield by heating for several hours with a slight excess of aqueous sodium carbonate (cf. Read and others⁵). The structure of the compound so obtained was confirmed by its alternate synthesis from *o*-allyl toluene by oxidation with peracetic acid followed by mild hydrolysis of the resulting glycol acetates (cf. Hershberg⁹). It reacted with phosgene in benzene solution in the presence of a tertiary base to give the dioxolone (III), which passed into 3-*o*-tolylpropane-1:2-diol 1-carbamate on reaction with concentrated aqueous ammonium hydroxide.

Short treatment of the chlorohydrin (II; R = Cl, R' = *o*-Me) with one equivalent of cold methanolic potash gave 1:2-epoxy-3-*o*-tolylpropane (IV), which was converted into 1-morpholino-3-*o*-tolylpropan-2-ol (II;

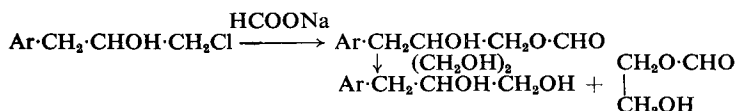
R = , R' = *o*-Me) on reaction with morpholine. 1-Piperidino-

and 1-pyrrolidino-3-*o*-tolylpropan-2-ol were similarly prepared. Reaction of the epoxide with succinimide in boiling ethanol in the presence of a basic catalyst¹⁰ gave the succinimido-derivative which was converted into 2-hydroxy-3-*o*-tolylpropylamine hydrochloride on hydrolysis with concentrated hydrochloric acid.

3-*o*-Alkoxyphenyl-, 3-*p*-chlorophenyl-, 3-*p*-tolyl- and 3-*p-n*-butoxyphenylpropane-1:2-diol were readily prepared by hydroxylation of the corresponding allyl-derivatives, and subsequently, by hydrolysis of the appropriate chlorohydrins. In contrast to 2-hydroxy-3-*o*-tolylpropyl chloride (above), attempted conversion of the chlorohydrins into the glycols with boiling aqueous sodium carbonate led to the formation of the corresponding epoxides. The diols were ultimately obtained, however,

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by heating the chlorohydrins with a slight excess of sodium formate or acetate in ethane-1:2-diol (cf. Brooks and Humphrey¹¹) when ester interchange occurred as indicated below:



Epoxide formation surprisingly did not take place under these experimental conditions as 6-aryl-3-oxa-hexane-1:5-diols, which would certainly be present in the reaction products through reaction of the epoxides with ethane-1:2-diol¹², were not isolated.

Two β -methyl analogues (V) were prepared by hydroxylation of the corresponding methallyl ethers.

Pharmacological study of the above compounds was kindly undertaken by Dr. A. David and his colleagues (Biological Laboratories, Godalming, Surrey).

EXPERIMENTAL

2-Hydroxy-3-o-tolylpropyl chloride^{7,8} (II; R = Cl, R' = *o*-Me). To a stirred solution of *o*-tolylmagnesium bromide (prepared from magnesium (14.6 g.) and *o*-bromotoluene (102.6 g.) in ether (700 ml.)), 1:2-epoxypropylchloride (111 g.) was added at such a rate that the mixture was kept refluxing gently. After addition was complete the mixture was heated under reflux for 2 hours, cooled in ice, and decomposed by careful addition of a solution of ammonium chloride (37 g.) in water (250 ml.) followed by just sufficient concentrated hydrochloric acid to break the resultant emulsion. The ether layer was separated, washed and dried and the ether removed by distillation. The residual oil was fractionated at 0.3 to 0.4 mm. to yield two main fractions (i) b.p. 42 to 49°, and (ii) b.p. 82 to 86°. Fraction (i) was redistilled. It had b.p. 95° at 15 mm. and proved to be 1-bromo-3-chloro-propan-2-ol. It formed a *phenyl urethane* which separated from light petroleum (b.p. 80 to 100°) in shining plates, m.p. 76 to 77°. Found: C, 41.5; H, 4.0; N, 4.5; Halogen, 39.5. C₁₀H₁₁O₂NCIBr requires C, 41.0; H, 3.8; N, 4.8; Halogen, 39.5 per cent. Fraction (ii) (80 g., 72 per cent yield) had b.p. 84 to 85° at 0.4 mm. on refractionation, and proved to be *2-hydroxy-3-o-tolylpropyl chloride*. Found: C, 65.1; H, 7.0; Cl, 19.2. Calc. for C₁₀H₁₃OCl: C, 65.0; H, 7.1; Cl, 19.2 per cent.

3-o-Tolyl-1:2-epoxypropane (IV). A solution of 2-hydroxy-3-*o*-tolylpropyl chloride (18.45 g.) in methanol (50 ml.) was treated with a solution of potassium hydroxide (5.6 g.) in methanol (75 ml.). The mixture was warmed on the steam bath for 10 minutes, the potassium chloride collected and the filtrate concentrated under reduced pressure. The residual oil was distilled at 0.1 mm. to yield the *product*, b.p. 49 to 51°. Found: C, 80.7; H, 8.3. C₁₀H₁₂O requires C, 81.0; H, 8.1 per cent.

SOME 3-ARYLPROPANE-1:2-DIOLS

N-(2-Hydroxy-3-*o*-tolyl)-propyl succinimide. A mixture of the foregoing epoxide (3.1 g.) and succinimide (1.4 g.) in the minimum of hot ethanol containing pyridine (3 drops) was heated on the steam bath for 8 hours. The *product* which separated on cooling had m.p. 148 to 149° after crystallisation from ethanol. Found: C, 67.8; H, 6.9; N, 5.8. $C_{14}H_{17}O_3N$ requires C, 68.0; H, 6.9; N, 5.7 per cent. Hydrolysis of the succinimide derivative with 6N hydrochloric acid (cf. ¹⁰) yielded 2-hydroxy-3-*o*-tolylpropylamine hydrochloride which had m.p. 183 to 184° after crystallisation from ethanol/ether. Found: C, 59.4; H, 7.9. $C_{10}H_{16}ONCl$ requires C, 59.5; H, 8.0 per cent.

3-*o*-Tolylpropane-1:2-diol (II; R = OH, R' = *o*-Me). (a) A suspension of 2-hydroxy-3-*o*-tolylpropylchloride (50 g.) in water (500 ml.) containing sodium carbonate (29 g.) was heated under reflux for 10 hours. The *product* (33g.), isolated with chloroform, had m.p. 77 to 78° after crystallisation from chloroform/light petroleum (b.p. 60 to 80°). Found: C, 72.1; H, 8.5. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5 per cent.

(b) To a solution of peracetic acid prepared from 30 per cent hydrogen peroxide (56 g.) and glacial acetic acid (150 ml.), *o*-allyl toluene (33 g.) was added with stirring over 30 minutes. Reaction was completed by heating at 80 to 85° for 2 hours. After cooling and dilution with water, the resultant oil was extracted with chloroform, the extracts washed with aqueous sodium carbonate and with water and the chloroform distilled off.

The residual oil after hydrolysis with methanolic potash and isolation with chloroform was distilled at 0.4 mm. to yield unchanged *o*-allyl toluene, b.p. 40°, and the *product* (20 g.) as an oil b.p. 120° which solidified rapidly. It had m.p. 76 to 78° after crystallisation from chloroform/light petroleum (b.p. 60 to 80°) and was identical with the compound prepared in experiment (a).

3-*o*-Tolylpropane-1:2-diol monocarbamate (II; R = O·CO·NH₂, R' = *o*-Me). To a solution of the foregoing diol (32.8 g.) in benzene (200 ml.) was added with stirring and water cooling, a solution of phosgene (20 g.) in benzene (200 ml.), followed by a solution of phenazone (37.6 g.) in the minimum volume of chloroform. After allowing to stand overnight, the phenazone hydrochloride was collected and the filtrate washed with iced water until neutral.

A portion of the filtrate was concentrated. The resultant solid, after crystallisation from benzene/light petroleum (b.p. 40 to 60°), yielded 4-*o*-tolylmethyldioxol-2-one, m.p. 48 to 49°. Found: C, 68.4; H, 6.2. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3 per cent.

The bulk of the original filtrate was stirred at room temperature with aqueous ammonia (300 ml., d = 0.880) for 6 hours, ammonia gas being passed into the mixture at intervals. The solid *carbamate* (22.7 g.) which separated was collected. It crystallised from ethyl acetate/light petroleum (b.p. 60 to 80°) in needles m.p. 97 to 100°. Found: C, 63.1; H, 7.4; N, 6.6. $C_{11}H_{15}O_3N$ requires C, 63.1; H, 7.2; N, 6.7 per cent.

1-Pyrrolidino-3-*o*-tolylpropan-2-ol was prepared by condensation of 2-hydroxy-3-*o*-tolylpropyl chloride with pyrrolidine (1 mole) in methanolic

potash (1 mole). It had b.p. 108 to 110° at 0.3 mm. Found: C, 76.3; H, 9.6; N, 5.9. $C_{14}H_{21}ON$ requires C, 76.7; H, 9.7; N, 6.4 per cent. The *hydrochloride*, m.p. 110° separated from ethyl acetate as a hygroscopic solid. Found: N, 5.5; Cl, 14.3. $C_{14}H_{22}ONCl$ requires N, 5.5; Cl, 13.9 per cent. The *salicylate* had m.p. 138 to 139° after crystallisation from ethyl acetate/ether. Found: C, 70.5; H, 7.7; N, 3.7. $C_{21}H_{27}O_4N$ requires C, 70.6; H, 7.6; N, 3.9 per cent.

1-*Piperidino-3-o-tolylpropan-2-ol* was prepared as for the pyrrolidino analogue. The *hydrochloride*, after crystallisation from ethyl acetate/methanol, had m.p. 190 to 191°. Found: C, 66.3; H, 8.9; N, 4.8. $C_{15}H_{24}ONCl$ requires C, 66.8; H, 9.0; N, 5.2 per cent.

1-*Morpholino-3-o-tolylpropan-2-ol* had m.p. 138 to 139° after crystallisation from ethyl acetate/ether. Found: C, 61.6; H, 8.1; N, 4.8; Cl, 13.4. $C_{14}H_{22}O_2NCl$ requires C, 61.8; H, 8.2; N, 5.2; Cl, 13.1 per cent.

3-*p-Tolylpropane-1:2-diol* (II; R = OH, R' = *p*-Me), prepared by heating *p*-allyl toluene with peracetic acid at 70° for 7 hours followed by hydrolysis of the mixed acetate esters with methanolic potash, had b.p. 120 to 125° at 0.4 mm. and m.p. 45°. Found: C, 72.5; H, 8.3. Calc. for $C_{10}H_{14}O_2$, C, 72.3; H, 8.5 per cent.

3-*p-Chlorophenylpropane-1:2-diol* (II; R = OH, R' = *p*-Cl), prepared by hydroxylation of *p*-chloroallylbenzene with peracetic acid, had b.p. 145° at 0.5 mm. and m.p. 45°. Found: C, 57.5; H, 6.0; Cl, 19.0. $C_9H_{11}O_2Cl$ requires C, 57.9; H, 5.9; Cl, 19.0 per cent.

2-*Methyl-3-o-tolylpropane-1:2-diol*, obtained by the action of peracetic acid on 2- β -methallyl toluene, had m.p. 58 to 60° after crystallisation from light petroleum (b.p. 60 to 80°). Found: C, 73.1; H, 8.6. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.9 per cent.

2-*Hydroxy-3-(o-methoxyphenyl)propyl chloride* (II; R = Cl, R' = *o*-MeO) prepared by reaction of 2:3-epoxypropyl chloride with *o*-methoxyphenyl magnesium bromide in ethereal solution, had b.p. 106 to 108° at 0.4 mm. Found: C, 60.2; H, 6.7; Cl, 18.1. $C_{10}H_{13}O_2Cl$ requires C, 59.8; H, 6.5; Cl, 17.7 per cent.

3-*o-Methoxyphenylpropane-1:2-diol* (II; R = OH, R' = *o*-MeO). The foregoing chlorohydrin (16 g.) was dissolved in ethane diol (35 ml.) and sodium formate (8.25 g.) added. The mixture was stirred and heated under gentle reflux for 6 hours when it was cooled, diluted with water and the separated oil extracted with ethylene dichloride. After washing with salt solution the solvent was removed and the residual oil distilled at 0.2 mm. Unchanged chlorohydrin (2 g.) was obtained followed by the *product*, b.p. 126 to 128° at 0.2 mm. (9.7 g., 76 per cent yield allowing for unchanged material). Found: C, 65.9; H, 8.2. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7 per cent.

2-*Hydroxy-3-(o-ethoxyphenyl)propylchloride* (II; R = Cl, R' = *o*-EtO), prepared in 60 per cent yield by reaction of *o*-ethoxyphenyl magnesium bromide with 2 mole equivalents of 2:3-epoxypropyl chloride in ethereal solution, had b.p. 109 to 110° at 0.4 mm. and solidified in hexagonal plates on standing. Found: C, 61.8; H, 7.1; Cl, 16.3. $C_{11}H_{15}O_2Cl$ requires C, 61.5; H, 7.0; Cl, 16.5 per cent.

SOME 3-ARYLPROPANE-1:2-DIOLS

3-o-Ethoxyphenylpropane-1:2-diol (II; R = OH, R' = *o*-EtO). The foregoing chlorohydrin (16.7 g.) was dissolved in ethane diol (27 g.), sodium formate (7.9 g.) added and the mixture heated with stirring to gentle reflux for 5 hours. It was then cooled, diluted with water, and the product isolated with chloroform. After removal of the chloroform the residual oil was distilled at 0.4 mm. to yield the *product* (60 per cent) as an oil, b.p. 136 to 138°. Found: C, 67.4; H, 7.9. C₁₁H₁₆O₃ requires C, 67.3; H, 8.2 per cent.

The same product was obtained, but only in 35 per cent yield, by the action of peracetic acid (2 mole) on *o*-ethoxyallylbenzene, followed by hydrolysis of the resultant acetate esters with a suspension of sodium carbonate in boiling ethanol.

2-Hydroxy-3-o-propoxyphenylpropyl chloride (II; R = Cl; R' = *o*-PrO) had b.p. 102° at 0.1 mm. and solidified on standing. Found: C, 62.6; H, 7.1. C₁₂H₁₇O₂Cl requires C, 63.0; H, 7.5 per cent.

3-o-Propoxyphenylpropane-1:2-diol (II; R = OH, R' = *o*-PrO), prepared by heating the foregoing chlorohydrin (19.5 g.) with sodium formate (8.84 g.) in ethane diol (30 g.) for 7 hours, had b.p. 131 to 134° at 0.2 mm. Found: C, 68.5; H, 8.5. C₁₂H₁₈O₃ requires C, 68.5; H, 8.6 per cent.

o-Propoxybromobenzene, prepared by reaction of *n*-propyl bromide with the sodium salt of *o*-bromophenol in *n*-propanol, had b.p. 72° at 0.5 mm. Found: C, 50.6; H, 5.4; Br, 37.0. C₉H₁₁OBr requires C, 50.3; H, 5.2; Br, 37.2 per cent.

o-Propoxyallylbenzene had b.p. 84 to 85° at 1.4 mm. Reaction with peracetic acid and subsequent hydrolysis yielded *3-o-propoxyphenylpropane-1:2-diol*, identical with the product described earlier.

o-Butoxybromobenzene had b.p. 75° at 0.5 mm. Found: C, 52.0; H, 5.8; Br, 34.6. C₁₀H₁₃OBr requires C, 52.4; H, 5.7; Br, 34.9 per cent. Reaction of its Grignard reagent with 2:3-epoxypropyl chloride yielded *2-hydroxy-3-o-butoxyphenylpropylchloride* (II; R = Cl, R' = *o*-BuO), b.p. 124° at 0.4 mm.

3-o-Butoxyphenyl-1:2-epoxypropane, b.p. 90° at 0.1 mm. was obtained when the foregoing chlorohydrin was heated under reflux for several hours with aqueous sodium carbonate in an attempt to prepare the diol. Found: C, 75.9; H, 8.6. C₁₃H₁₈O₂ requires C, 75.7; H, 8.8 per cent.

3-o-Butoxyphenylpropane-1:2-diol (II; R = OH, R' = *o*-BuO) was obtained (a) in small yield by hydrolysis of the foregoing epoxide (5 g.) in water (50 ml.) containing concentrated sulphuric acid (1 drop) at reflux temperature for 4 hours.

(b) In 76 per cent yield by heating the chlorohydrin (24.2 g.) with sodium formate (10.2 g.) in ethane diol (35 g.) for 6 hours. The diol crystallised from light petroleum (b.p. 60 to 80°) in needles, m.p. 67 to 69°. Found: C, 69.6; H, 9.0. C₁₃H₂₀O₃ requires C, 69.6; H, 9.0 per cent.

(c) In 40 per cent yield by the action of peracetic acid on *o-butoxyallylbenzene*. The latter compound had b.p. 64 to 66° at 0.2 mm. Found: C, 82.5; H, 9.7. C₁₃H₁₈O requires C, 82.0; H, 9.5 per cent.

3-*p*-Butoxyphenylpropane-1:2-diol (II; R = OH, R' = *p*-BuO₂) obtained by the action of peracetic acid on *p*-butoxyallyl benzene, had b.p. 155° at 0.5 mm. and m.p. 53° after crystallisation from light petroleum (b.p. 60 to 80°). Found: C, 69.8; H, 9.0. C₁₃H₂₀O₃ requires C, 69.6; H, 9.0 per cent.

o-Amyloxyallyl benzene had b.p. 92 to 93° at 0.8 mm. Found: C, 82.2; H, 9.5. C₁₄H₂₀O requires C, 82.3; H, 9.9 per cent.

3-*o*-Amyloxyphenylpropane-1:2-diol (II; R = OH, R' = *o*-AmO) was obtained as an oil, b.p. 160° at 0.7 mm. by the action of peracetic acid on the foregoing allyl compound. Found: C, 70.8; H, 9.0. C₁₄H₂₂O₃ requires C, 70.5; H, 9.3 per cent.

o-Propoxymethylphenylbenzene prepared from *o*-methallylphenol had b.p. 74 to 75° at 0.3 mm. Found: C, 82.2; H, 9.7. C₁₃H₁₈O requires C, 82.0; H, 9.5 per cent. On reaction with peracetic acid it was converted into 3-*o*-propoxyphenyl-2-methylpropane-1:2-diol (V; R = Pr) (in 40 per cent yield), b.p. 118 to 119° at 0.3 mm. Found: C, 69.8; H, 9.0. C₁₃H₂₀O₃ requires C, 69.6; H, 9.0 per cent.

o-Butoxymethylphenylbenzene had b.p. 92 to 93° at 0.6 mm. Found: C, 82.7; H, 9.9. C₁₄H₂₀O requires C, 82.3; H, 9.9 per cent. On treatment with peracetic acid at 70° for 3 hours it yielded 3-*o*-butoxyphenyl-2-methylpropane-1:2-diol (V; R = Bu), obtained as a viscous oil, b.p. 132 to 134° at 0.4 mm. Found: C, 70.1; H, 9.1. C₁₄H₂₂O₃ requires C, 70.5; H, 9.3 per cent.

3-cyclohexylpropane-1:2-diol, prepared from allylcyclohexane, had b.p. 120° at 0.5 mm. Found: C, 68.6; H, 11.5. C₉H₁₈O₂ requires C, 68.3; H, 11.5 per cent.

REFERENCES

1. Berger and Bradley, *Brit. J. Pharmacol.*, 1946, **1**, 265.
2. Berger and Bradley, *Lancet*, 1947, **252**, 97.
3. Berger and Bradley, *Nature, Lond.*, 1947, **159**, 813.
4. Gaylord and Becker, *Chem. Rev.*, 1951, **49**, 413.
5. Gilman, Hofferth and Honeycutt, *J. Amer. chem. Soc.*, 1952, **74**, 1594.
6. Hofferth, *Iowa State Coll. J. Sci.*, 1952, **26**, 219.
7. Fourneau and Tiffeneau, *Bull. Soc. Chim.*, 1907 [4], **1**, 1227.
8. Read, Lathrop and Chandler, *J. Amer. chem. Soc.*, 1927, **49**, 3116.
9. Herschberg, *Helv. Chim. Acta.*, 1934, **17**, 351.
10. Petrow and Stephenson, *J. Pharm. Pharmacol.*, 1953, **6**, 359.
11. Brooks and Humphrey, *J. Industr. Engng Chem.*, 1917, **9**, 750.
12. Petrow and Stephenson, *J. Pharm. Pharmacol.*, 1955, **7**, 198.