RESEARCH PAPERS

SOME DERIVATIVES AND ANALOGUES OF MEPHENESIN

BY V. PETROW, O. STEPHENSON AND A. M. WILD

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The preparation of some miscellaneous types formally related to mephenesin is reported.

RECENT publications from this laboratory have dealt with hydroxyalkyl ethers[1], ureas[2] and 3-arylpropane-1,2-diols[3] related to 3-*o*-tolyloxypropane-1,2-diol ("Mephenesin", I; R = H, R′ = OH). The preparation of some further types formally derived from (I; R = H, R′ = OH) is herein reported.

Mephenesin α-carbamate[4,5] (I; R = H, R′ = $OCONH_2$) has been shown to possess a lower acute toxicity and longer duration of action than mephenesin. We therefore prepared the β-carbamate (I; R = $CONH_2$, R′ = OH) for comparison. This was effected by controlled acid hydrolysis of mephenesin α-acetate-β-carbamate (I; R = $CONH_2$, R′ = O.CO.Me), itself obtained by reaction of the α-acetate (I; R = H, R′ = O·CO·Me) with phosgene followed by ammonia.

β-Mephenesin[6] (II; R = R′ = H) was obtained as a water-soluble oil by reduction of the corresponding diethyl malonate with lithium aluminium hydride. It was converted into the crystalline dicarbamate (II; R = $CONH_2$, R′ = H). The dicarbamate of the ethyl analogue (II); R = $CONH_2$, R′ = Et) was similarly prepared.

With the object of obtaining derivatives of mephenesin with longer duration of action, some esters derived from aliphatic, aromatic and heterocyclic carboxylic acids were prepared by reaction of 1,2-epoxy-3-*o*-tolyloxypropane (III) with the appropriate acid in the presence of a basic catalyst. The glycollate ester (I; R = H, R′ = $O{\cdot}CO{\cdot}CH_2OH$) was obtained by an alternative route which involved heating mephenesin with ethyl glycollate.

In addition, a series of 1,3-dioxolanes (IV) were prepared by reaction of mephenesin with ethyl orthoformate, aldehydes, acetals and ketones using toluene-*p*-sulphonic acid or hydrogen chloride as condensing agents.

Several 3-aryloxy-2-hydroxypropyl chlorides[7] (cf. I; R = H, R′ = Cl) were converted into their carbamates.

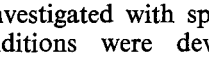
2-Hydroxy-3-*o*-tolyloxy and 3-*o*-chlorophenoxy-2-hydroxypropyl chloride were converted into the corresponding fluorohydrins by reaction with anhydrous potassium fluoride in ethanediol. The main by-product in this reaction was the hydroxyethyl ether[1] (I; R = H, R′ = $O{\cdot}CH_2{\cdot}CH_2OH$), but this was readily removed by fractional distillation under reduced pressure. The fluorohydrins were characterised by the preparations of phenylurethanes. The *o*-tolyloxy analogue was converted into the carbamate.

The preparation of chlorohydrins (V; R = alkyl, aralkyl, alicyclic or heterocyclic, R′ = H, R″ = Cl) by reaction of the appropriate alcohols with 2,3-epoxypropyl chloride using stannic chloride as catalyst[8] was reinvestigated with special emphasis upon tertiary alcohols. Optimum conditions were developed for the preparation of 3-t-butoxy-2-hydroxypropyl chloride (V; R = Me_3C, R′ = H, R″ = Cl). Highest yields of chlorohydrin were obtained with a two to four molar excess of the alcohol. With less than two moles of the alcohol the yield of secondary product (V; R = Me_3C, R′ = $CH_2{\cdot}CHOH{\cdot}CH_2Cl$, R″ = Cl) increased appreciably. The t-butoxy chlorohydrin was converted into its ethyl and guaiacyl ethers. A few of the new chlorohydrins obtained by this method were hydrolysed to the corresponding 1,2-diols using sodium formate in ethanediol as described previously[3].

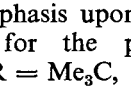
Condensation of 1,2-epoxy-3-*o*-tolyloxypropane (III) and of the corresponding *p*-chlorophenoxy epoxide with butane-2,3-diol, hexane-2,5-diol and hexyne-2,5-diol were carried out using conditions described earlier[1] to yield compounds of type (VI).

Reaction of 1,2-epoxy-3-*o*-tolyloxypropane (III) with sodium acetylide in liquid ammonia furnished the novel acetylide (I; R = H, R′ = C ≡ CH). The corresponding *o*-chlorophenoxy derivative was similarly obtained.

Dicarbamates were prepared from 1,1-bishydroxymethylcyclopentane and 4,4-bishydroxymethylcyclohex-1-ene[9].



(I)



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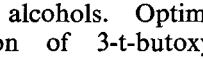

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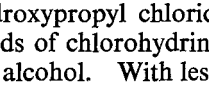

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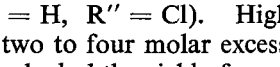

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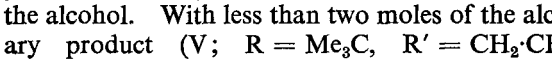

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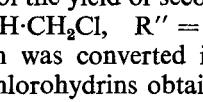

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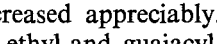

2-Amino-2-methylpropane-1,3-diol was converted into 4-methyl-4-hydroxymethyl oxazolid-2-one (VII; R = OH) by reaction with ethyl carbonate in the presence of sodium ethoxide[2]. This intermediate was transformed into the carbamate (VII; R = O·CO·NH_2) using dioxan as solvent as it proved to be too insoluble in benzene-chloroform for the normal preparative procedure to be employed.

The discovery by Okamoto[10] that some basically substituted 1,3-diaryloxypropan-2-ols possessed useful anticonvulsant and muscle-relaxant properties led us to prepare two derivatives of type (I; Ar = *o*-tolyloxy or *o*-methoxyphenoxy, R = H and R′ = *o*-aminophenoxy). These were obtained by reaction of the appropriate epoxide (*cf.* III) with *o*-acetamidophenol using a basic catalyst, or alternatively by reaction of 1,2-epoxy-3-*o*-acetamidophenoxypropane with *o*-cresol or with guaiacol, followed by acid hydrolysis of the acetamido-group.

The above compounds were kindly examined for muscle relaxant properties by Dr. A. David and his colleagues. Although slight activity was shown by many of the products, only 2-ethoxy-5-*o*-tolyloxymethyl-1,3-dioxolane, 2-methyl-5-*o*-tolyloxymethyl-1,3-dioxolane, mephenesin β-carbamate and 2-(4,5-dihydroxy-2-oxapentyl)5,6-benz-1,4-dioxan approached mephenesin in potency.

EXPERIMENTAL

Mephenesin β-carbamate

(*β*) *Mephenesin α-acetate-β-carbamate.* To a solution of 1-acetoxy-2-hydroxy-3-*o*-tolyloxypropane (mephenesin α-acetate, 36·9 g.) in benzene (150 ml.) was added a solution of phenazone (16·4 g.) in the minimum of chloroform, followed by a solution of phosgene (16·4 g.) in benzene (100 ml.), added in portions with shaking and cooling. The mixture was left at room temperature for 30 minutes and was then filtered. The filtrate was cooled in ice, saturated with ammonia gas, concentrated to half-bulk and diluted with light petroleum (b.p. 60° to 80°). The *product* (29·6 g.) had m.p. 95° to 97° after crystallisations from benzene-light petroleum (b.p. 60° to 80°) and then from methanol. Found: C, 58·4; H, 6·1; N, 4·7. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4;; N, 5·2 per cent.

(*b*) The foregoing compound (10 g.) dissolved in ethanol (30 ml.) was treated with concentrated hydrochloric acid (10 drops) and the solution heated on the steam bath for 30 minutes with slight concentration. Dilution with water furnished the *product* which had m.p. 117° to 118° after crystallisation from benzene. Found: C, 58·7; H, 6·7; N, 6·1. $C_{11}H_{15}O_4N$ requires C, 58·6; H, 6·7; N, 6·2 per cent.

Diethyl α-o-tolyloxymalonate. *o*-Cresol (38 g.) was added to a solution of sodium (7·7 g.) in ethanol (250 ml.) and the resulting solution treated with diethyl α-chloromalonate (65 g.) added in portions with shaking. The mixture was heated under reflux for 3 hours, cooled, acidified with acetic acid and diluted well with water. The *product* (47·8 g.) isolated with chloroform had b.p. 114° at 0·1 mm. Found: C, 63·4; H, 6·9. Calc. for $C_{14}H_{18}O_5$: C, 63·1; H, 6·8 per cent. When the foregoing ester

(2 g.) in ethanol was treated with ammonia solution (20 ml., d = 0·880) and the solution heated on the steam bath for 1 hour, α-o-*tolyloxymalondiamide* separated in high yield. It had m.p. 241° to 242° after crystallisation from ethanol. Found: C, 57·8; H, 6·2; N, 13·4. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5 per cent.

2-*o-Tolyloxypropane*-1,3-*diol.* A solution of the foregoing ester (41·5 g.) in anhydrous ether (200 ml.) was added in portions to a stirred solution of lithium aluminium hydride (9·5 g.) in the same solvent (500 ml.) Reaction was completed at reflux temperature for 1 hour. After the addition of ethyl acetate and dilute hydrochloric acid the aqueous portion was saturated with sodium chloride and extracted with five portions of chloroform. The combined ether and chloroform extracts were dried over anhydrous sodium sulphate, the solvents removed and the *diol* (21·4 g.) obtained as an oil, b.p. 120° at 0·1 mm. Found: C, 65·6; H, 7·5. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·8 per cent.

The diol (1·2 g.) was melted with *p*-nitrobenzoyl chloride (2·4 g.) until evolution of hydrogen chloride ceased. The *bis*-p-*nitrobenzoate* had m.p. 120° to 121° after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 60·1; H, 4·4; N, 5·8. $C_{24}H_{20}O_9N_2$ requires C. 60·0; H, 4·2; N, 5·8 per cent.

1,3-*Dicarbamoyloxy*-2-o-*tolyloxypropane.* A mixture of the foregoing diol (9·1 g.) and phenazone (20·7 g.) in chloroform (150 ml.) was added in portions with shaking to a solution of phosgene (11 g.) in toluene (250 ml.) at − 10° over about 5 minutes. The mixture was then left at room-temperature for 16 hours, filtered, the filtrate cooled in ice and treated with a slight excess of ammonia gas. The *product* which separated on short standing formed needles, m.p. 123° to 125° on crystallisation from water. Found: C, 54·1; H, 6·2; N, 10·2. $C_{12}H_{16}O_5N_2$ requires C, 53·7; H, 6·0; N, 10·4 per cent.

Diethyl α-ethyl-α-o-tolyoxymalonate. Diethyl α-*o*-tolyloxymalonate (77·7 g.) was added to a solution of sodium (6·7 g.) in ethanol (200 ml.) and the resultant solution treated with ethyl iodide (68·5 g.) added in portions. Reaction was completed at reflux temperature for 3 hours, when the solution was diluted with water and the oil extracted with chloroform. The *product* (68·5 g.) was isolated as an oil, b.p. 114° at 0·3 mm. which solidified on standing. Found: C, 65·4; H, 7·5. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·6 per cent. It was reduced to 2-*ethyl*-2-o-*tolyloxypropane*-1,2-*diol*, b.p. 130° to 132° at 0·3 mm. with ethereal lithium aluminium hydride as described earlier. The diol furnished a *dicarbamate hemihydrate*, m.p. 116° after crystallisation from aqueous methanol. Found: C, 55·4; H,7·1; N, 9·4. $C_{14}H_{20}O_5N_2$; $\frac{1}{2}$ H_2O requires C, 55·0; H, 6·9; N, 9·2 per cent.

Mephenesin α-glycollate. A mixture of mephenesin (45·5 g.) and ethyl glycollate (26 g.) containing toluene-*p*-sulphonic acid (1 g.) was heated on the steam bath for 4 hours; a slight vacuum was applied at intervals to remove volatile materials. The residue was dissolved in chloroform, the extract washed with aqueous sodium bicarbonate then with water,

the solvent removed and the residual oil distilled under reduced pressure. The *glycollate* was obtained as an oil, b.p. 175° at 0·5 mm. after refractionation. Found: C, 59·9; H, 6·6. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7 per cent.

Mephenesin α-benzoate. A mixture of 1,2-epoxy-3-*o*-tolyloxypropane (55 g.) and benzoic acid (41 g.) in benzene (100 ml.) was treated with pyridine (6 drops) and the mixture heated at reflux temperature for 12 hours. It was diluted with benzene (100 ml.), washed with aqueous sodium bicarbonate then with water, the solvent removed and the residual oil distilled under reduced pressure to yield the *benzoate* b.p. 178° at 0·2 mm. after refractionation. Found: C, 70·9; H,6·4. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3 per cent.

Other α-esters were prepared similarly but solvent was omitted when a homogeneous mixture could be obtained on the steam bath.

The *formate* had b.p. 118° at 0·1 mm. The *acetate*, b.p. 124° at 0·2 mm. (n_D^{18} 1·5112). The *palmitate* was a low melting solid, b.p. 215° at 0·1 mm. Found: C, 73·9; H, 10·3. $C_{26}H_{44}O_4$ requires C, 74·2; H, 10·6 per cent. The *phenylacetate* had b.p. 176° at 0·1 mm. Found: C, 72·3; H, 6·8. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7 per cent. The *furoate* had b.p. 176° at 0·3 mm. Found: C, 65·2; H, 5·9. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8 per cent.

1-*Carbamoyloxy*-3-o-*chlorophenoxypropan*-2-*ol.* (*a*) The diol (39 g.) was dissolved in benzene (260 ml.) and a solution of phosgene (20·5g.) in benzene (190 ml.) added with stirring. The solution was left for 1 hour at room temperature and then treated with a solution of dimethylaniline (24 g.) in benzene (100 ml.) and allowed to stand overnight at room temperature. Ice-water (500 ml.) was added and the benzene layer separated. Evaporation of an aliquot furnished 4-*o*-*chlorophenoxymethyldioxol*-2-*one* in shining plates, m.p. 109° to 110° after crystallisation from benzene-light petroleum (b.p. 60 to 80°). Found: C, 52·4; H, 4·3; Cl, 15·1. $C_{10}H_9O_4Cl$ requires C, 52·5; H, 4·0; Cl, 15·5 per cent.

(*b*) The rest of the benzene solution was cooled to 5°, stirred with ammonia solution (450 ml., d = 0·880) for 6 hours and saturated at intervals with ammonia gas. The *product* which separated had m.p. 96° to 98°, after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 49·0; H, 4·9; N, 6·0; Cl, 14·2. $C_{10}H_{12}O_4NCl$ requires C, 48·9; H, 4·9; N, 5·7; Cl, 14·5 per cent.

4-*o*-*Methoxyphenoxymethyldioxol*-2-*one* had m.p. 70° to 71° after crystallisation from aqueous methanol. Found: C, 59·1; H 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4 per cent.

3-o-*Methoxyphenoxypropane*-1,2-*diol α-monocarbamate* separated from benzene-light petroleum (b.p. 60° to 80°) in needles, m.p. 95° to 97°. Found: C, 54·8; H, 6·2; N, 5·7. $C_{11}H_{15}O_5N$ requires C, 54·8; H, 6·3; N, 5·8 per cent. The *dicarbamate* had m.p. 163° to 165° (from ethanol). Found: N, 9·8. $C_{12}H_{16}O_6N_2$ requires N, 9·9 per cent.

2-*Ethoxy*-4-o-*tolyloxymethyl*-1,3-*dioxolane*. A mixture of mephenesin (45·5 g.) and ethyl orthoformate (56 g.) was warmed until homogeneous when toluene-*p*-sulphonic acid was added as catalyst. The mixture was heated on the steam bath for 30 minutes, ethanol being allowed to distil off. Excess of volatile material was removed under reduced pressure, the residue dissolved in chloroform, washed with dilute aqueous sodium iodide, dilute aqueous sodium bicarbonate then with water. After removal of the chloroform the residue was distilled under reduced pressure to yield the *product* (57 g.) as an oil, b.p. 102° at 0·5 mm. Found: C, 65·1; H, 7·6. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6 per cent.

4-*Chloromethyl*-2-*ethoxy*-1,3-*dioxolane* had b.p. 40° at 0·2 mm. Found: C, 42·8; H, 6·5; Cl, 21·5. $C_6H_{11}O_3Cl$ requires C, 43·2; H, 6·7; Cl, 21·3 per cent.

4-p-*Chlorophenoxymethyl*-2-*ethoxy*-1,3-*dioxolane*, prepared from 3-*p*-chlorophenoxypropane-1,2-diol ("Chlorphenesin") (50·5 g.) and ethyl orthoformate (56 g.) using hydrogen chloride (2 g.) in ethanol (10 ml.) as catalyst, formed an oil, b.p. 120° at 0·4 mm. Found: C, 55·9; H, 5·7. $C_{12}H_{15}O_4Cl$ requires C, 55·7; H, 5·9 per cent.

2-*Ethoxy*-4-o-*methoxyphenoxymethyl*-1,3-*dioxolane*, had b.p. 128° at 0·4 mm. Found: C, 61·5; H, 7·0. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1 per cent.

4-o-n-*Butoxyphenoxymethyl*-2-*ethoxy*-1,2-*dioxolane* had b.p. 140° at 0·2 mm. Found: C, 64·3; H, 8·1. $C_{16}H_{24}O_5$ requires C, 64·8; H, 8·2 per cent.

4-o-*Tolyloxymethyl*-1,3-*dioxolane*. To a mixture of mephenesin (45·5 g.) and paraformaldehyde (15 g.) in benzene (200 ml.) was added toluene-*p*-sulphonic acid and the solution heated in a Dean-Stark apparatus for 3 hours. The solution was washed with aqueous sodium bicarbonate then with water, the benzene distilled off and the residue distilled at reduced pressure to yield the *product* as an oil, b.p. 80° at 0·5 mm. Found: C, 68·5; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3 per cent.

2-*Methyl*-4-o-*tolyloxymethyl*-1,3-*dioxolane* prepared by reaction of mephenesin with acetal using toluene-*p*-sulphonic acid as catalyst, had b.p. 85° at 0·4 mm. Found: C, 69·2; H, 7·6 $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·8 per cent.

2-*Chloromethyl*-4-o-*tolyloxymethyl*-1,3-*dioxolane* formed a low melting solid, b.p. 114° at 0·5 mm. Found: C, 59·8; H, 6·1; Cl, 15·0. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·2; Cl, 14·6 per cent.

2-*Dichloromethyl*-4-o-*tolyloxymethyl*-1,3-*dioxolane* had b.p. 130° at 0·5 mm. Found: C, 52·3; H, 5·1; Cl, 25·1. $C_{12}H_{14}O_3Cl_2$ requires C, 52·0; H, 5·1; Cl, 26·6 per cent.

2-*Methyl*-2-*phenyl*-4-o-*tolyloxymethyl*-1,3-*dioxolane* prepared by condensation of mephenesin with acetophenone in benzene solution using toluene-*p*-sulphonic acid as catalyst, was an oil b.p. 128° at 0·05 mm. Found: C, 76·2; H, 7·2. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1 per cent.

2-*Carbamoyloxy*-3-o-*tolyloxypropyl chloride* prepared by reaction of 2-hydroxy-3-*o*-tolyloxypropyl chloride with phosgene then with ammonia, had m.p. 87° to 89° after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 54·4; H, 5·7; N, 5·6; Cl, 14·7. $C_{11}H_{14}O_3NCl$ requires C, 54·2; H, 5·8; N, 5·8; Cl, 14·6 per cent.

2-*Carbamoyloxy*-3-m-*tolyloxypropyl chloride* had m.p. 91° to 94° after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 54·6; H, 5·6; N, 5·7; Cl, 14·5 per cent.

2-*Carbamoyloxy*-3-p-*tolyloxypropyl chloride* had m.p. 79° after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 53·9; H, 5·3; N, 6·1; Cl, 14·7 per cent.

2-*Carbamoyloxy*-3-o-*methoxyphenoxypropyl chloride* had m.p. 107° to 108° after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 51·2; H, 5·2; N, 5·2; Cl, 13·3. $C_{11}H_{14}O_4NCl$ requires C, 50·9; H, 5·4; N, 5·4; Cl, 13·7 per cent.

2-*Carbamoyloxy*-3-m-*methoxyphenoxypropyl chloride*, had m.p. 80° to 82° after crystallisation from aqueous methanol. Found: C, 51·3; H, 5·4; N, 5·1; Cl, 13·7 per cent.

2-*Carbamoyloxy*-3-o-*chlorophenoxypropyl chloride*, had m.p. 79° to 80° after crystallisation from benzene-light petroleum (b.p. 60° to 80°). Found: C, 45·6; H, 4·2; N, 5·4; Cl, 26·6. $C_{10}H_{11}O_3NCl_2$ requires C,45·4; H, 4·2; N, 5·3; Cl, 26·9 per cent.

2-*Hydroxy*-3-o-*tolyloxypropyl fluoride*. A mixture of 2-hydroxy-3-*o*-tolyloxypropyl chloride (100·3 g.) and potassium fluoride (44 g.) in ethane diol (100 ml.) was heated with stirring at 185° to 190° for 2 hours. The mixture was poured into water, the oil isolated with choroform and distilled under reduced pressure. The *product* obtained formed an oil b.p. 84° to 86° at 0·25 mm. Found: C, 65·5; H, 7·0. $C_{10}H_{13}O_2F$ requires C, 65·2; H, 7·1 per cent. It formed a *phenylurethane*, m.p. 128° to 129° (needles from ethanol). Found: C, 66·9; H, 6·1; N, 4·8. $C_{17}H_{18}O_3NF$ requires C, 67·3; H, 6·0; N, 4·6 per cent.

The *fluorohydrin* (18·4 g.) was dissolved in benzene (75 ml.) and a solution of phenazone (18·8 g.) in chloroform (30 ml.) added. A solution of phosgene (10 g.) in benzene (90 ml.) was added to the stirred solution which was left at room temperature overnight. The solid was collected and the filtrate cooled slightly and treated with a slight excess of ammonia gas. The *carbamate* which separated was purified by crystallisation from benzene-light petroleum (b.p. 60° to 80°). It had m.p. 80° to 82°. Found: C, 58·2; H, 6·2; N, 6·2. $C_{11}H_{14}O_3NF$ requires C, 58·1; H, 6·2; N, 6·2 per cent.

3-o-*Chlorophenoxy*-2-*hydroxypropyl fluoride* had b.p. 94° at 0·2 mm. Found: C, 53·2; H, 5·2. $C_9H_{10}O_2ClF$ requires C, 52·8; H, 4·9 per cent. It formed a *phenylurethane* which separated from light petroleum (b.p. 80° to 100°) in needles, m.p. 102° to 103°. Found: C, 59·6; H, 4·9; N, 4·0. $C_{16}H_{15}O_3NClF$ requires C, 59·3; H, 4·7; N, 4·3 per cent.

3-*t-Butoxy-2-hydroxypropyl chloride.* t-Butanol (296 g.) containing stannic chloride (2 ml.) was stirred at room temperature and 2,3-epoxypropyl chloride (92·5 g.) added slowly over 25 minutes, slight water-cooling being applied to control the exothermic reaction. The reaction was completed by heating at reflux temperature for 1 hour, and a slight excess of ammonia solution ($d = 0{\cdot}880$) then added. The mixture was filtered to remove inorganic material, the filtrate concentrated and the residual oil distilled under reduced pressure to yield the *product* (81 per cent), b.p. 36° at 0·3 mm. Found: C, 50·4; H, 9·2; Cl, 21·0. $C_7H_{15}O_2Cl$ requires C, 50·4; H, 9·1; Cl ,21·3 per cent. When 3, 2 and 1·5 mole. equivs. of t-butanol were used in the reaction, yields of product were 74·4, 71·4 and 62·1 per cent respectively. A by-product, presumably 6-*t-butoxy*-1-*chloro*-5-*chloromethyl*-2-*hydroxy*-4-*oxa-hexane*, (Found: C, 46·6; H, 7·9; C., 28·3. $C_{10}H_{20}O_3Cl_2$ requires C, 46·3; H, 7·8; Cl, 27·4 per cent) was isolated as an oil, b.p. 105° at 0·3 mm. in the experiments where smaller amounts of t-butanol were used. 3-t-Butoxy-2-hydroxypropyl chloride reacted with piperazine in ethanol containing an equivalent of potassium hydroxide to yield NN′-*bis*(3-*t-butoxy*-2-*hydroxypropyl*) *piperazine*, which separated from light-petroleum (b.p. 40° to 60°) in needles, m.p. 91° to 92°. Found C, 62·3; H, 10·8; N, 8·0. $C_{18}H_{38}O_4N_2$ requires C, 62·4; H, 11·0; H, 8·1 per cent.

3-*t-Butoxy*-1-*ethoxypropan*-2-*ol.* The foregoing chlorohydrin (28 g.) was added to a solution of sodium (4·2 g.) in ethanol (100 ml.) and the mixture heated under reflux for 3 hours. The sodium chloride was removed, the filtrate concentrated and the *product* obtained as an oil, b.p. 38° at 0·15 mm. Found: C, 60·9; H, 11·1. $C_9H_{20}O_3$ requires C, 61·3; H, 11·4 per cent.

1-*t-Butoxy*-3-o-*methoxyphenoxypropan*-2-*ol* was obtained in 66 per cent yield by condensation of 3-t-butoxy-2-hydroxypropyl chloride with the sodium salt of guaiacol in ethanolic solution. It formed an oil, b.p. 124° at 0·4 mm., $n_D^{18} - 1{\cdot}5065$. Found: 66·0; H, 8·8. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7 per cent.

3-*t-Pentyloxy*-2-*hydroxypropyl chloride* was obtained in 75 per cent yield as an oil, b.p. 45° at 0·1 mm. by condensation of 2,3-epoxypropyl chloride with t-pentyl alcohol (2·5 mole. equivs.) using stannic chloride as catalyst. Found: Cl, 20·2. $C_8H_{17}O_2Cl$ requires Cl, 19·7; per cent.

1-*Chloro*-2-*hydroxy*-5,5-*dimethyl*-4-*oxahept*-6-*yne*, was prepared (70 per cent) by condensation of 2-methylbut-3-yn-2-ol (2·5 moles) with 2,3-epoxypropyl chloride using stannic chloride as catalyst. It formed an oil, b.p. 41° at 0·05 mm. Found: C, 54·3; H, 7·4; Cl, 20·5. $C_8H_{13}O_2Cl$ requires C, 54·4; H, 7·4; Cl, 20·1 per cent. The compound yielded polymeric material on reaction with sodium methoxide in methanol.

3-*Cyclohexyloxy*-2-*hydroxypropyl chloride* (*cf.*[11]) was obtained (83 per cent) as an oil, b.p. 90° at 0·6 mm. by condensation of cyclohexanol (2 moles) with 2,3-epoxypropyl chloride employing stannic chloride as catalyst.

3-*Cyclohexyloxypropane*-1,2-*diol*.—Sodium formate (25·5 g.) was added to a solution of the foregoing chlorohydrin (48·2 g.) in ethanediol (100 ml.) and the mixture heated under reflux for 3 hours, with stirring. The mixture was diluted with water, the oil isolated with chloroform and the product obtained in 75 per cent yield as an oil, b.p. 98° at 0·1 mm. Found: C,61·9; H, 10·2. $C_9H_{18}O_3$ requires C, 62·0; H, 10·4 per cent.

3-*Benzyloxy*-2-*hydroxypropyl chloride*, obtained in 76 per cent yield as an oil, b.p. 104° at 0·1 mm. (Found: Cl, 17·6. $C_{10}H_{13}O_2Cl$ requires Cl, 17·7 per cent) was converted into 3-*benzyloxypropane*-1,2-*diol*. (Found: C, 66·3; H, 8·2. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7 per cent), b.p. 120° at 0·2 mm., by hydrolysis with sodium formate in ethanediol.

1-*Chloro*-2-*hydroxy*-7-*phenyl*-4-*oxahept*-6-*ene* was obtained as an oil, b.p. 130° at 0·3 mm., by condensation of cinnamyl alcohol with 2,3-epoxypropyl chloride and stannic chloride catalyst. Found: C, 63·4; H, 6·3; Cl, 15·9. $C_{12}H_{15}O_2Cl$ requires C, 63·5; H, 6·7; Cl, 15·7 per cent.

2-(5-*Chloro*-4-*hydroxy*-2-*oxapentyl*)-5,6-*benz*-1,4-*dioxan* was obtained (62 per cent) by condensation of 2-hydroxymethyl-5,6-benz-1,4-dioxan with 2,3-epoxypropyl chloride in toluene using stannic chloride as catalyst. It formed an oil, b.p. 152° at 0·3 mm. Found: C, 56·1; H, 6·0; Cl, 14·1. $C_{12}H_{15}O_4Cl$ requires C, 55·7; H, 5·8; Cl, 13·7 per cent. Its hydrolysis with sodium formate in ethanediol furnished 2-(4,5-*dihydroxy*-2-*oxapentyl*)-5,6-*benz*-1,4-*dioxan* (65 per cent) as an oil, b.p. 176° at 0·3 mm. Found: C, 59·8; H, 6·9. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7 per cent.

cis-2-*Hydroxy*-3-o-*phenylcyclohexyloxypropyl chloride* b.p. 126° at 0·1 mm. (Found: C, 66·8; H, 7·9; Cl, 13·1. $C_{15}H_{21}O_2Cl$ requires C, 67·0; H, 7·9; Cl, 13·2 per cent) was formed (40 per cent) by condensation of *cis*-2-phenylcyclohexanol (2 moles) with 2,3-epoxypropyl chloride. A by-product from the reaction was 1-*chloro*-5-*chloromethyl*-2-*hydroxy*-6-o-*phenylcyclohexyl*-4-*oxahexane* an oil, b.p. 180° at 0·2 mm. Found: C, 60·3; H, 7·2; Cl, 19·4. $C_{18}H_{26}O_3Cl_2$ requires C, 59·8; H, 7·3; Cl, 19·7 per cent.

Hydrolysis of the primary chlorohydrin with sodium formate-ethanediol yielded 3-o-*phenylcyclohexyloxypropane*-1,2-*diol*, b.p. 152° at 0·3 mm., in 78 per cent yield. Found: C, 71·9; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9 per cent.

3-*Methyl*-7-o-*tolyloxy*-4-*oxaheptane*-2,6-*diol* prepared (70 per cent) by heating butane-2,3-diol (3 moles) with 3-*o*-tolyloxy-1,2-epoxypropane at 180° to 190° for 15 hours had b.p. 154° at 0·5 mm. Found: C, 65·9; H, 8·7. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7 per cent.

7-p-*Chlorophenoxy*-3-*methyl*-4-*oxaheptane*-2,6-*diol*, (71 per cent), had b.p. 158° at 0·2 mm. and m.p. 66° to 68° [from benzene-light petroleum (b.p. 60° to 80°)]. Found: C, 56·9; H, 6·7. $C_{13}H_{19}O_4Cl$ requires C, 56·8; H, 7·0 per cent.

9-p-*Chlorophenoxy*-5-*methyl*-6-*oxanonane*-2,8-*diol*, an oil, b.p. 182° to 184° at 0·4 mm. was obtained (82 per cent) by reaction of hexane-2,5-diol

(3 moles) with 3-*p*-chlorophenoxy-1,2-epoxypropane at 205° to 210° for 8 hours. Found: C, 59·1; H, 7·7; Cl, 11·6. $C_{15}H_{23}O_4Cl$ requires C, 59·5; H, 7·7; Cl, 11·7 per cent.

9-p-*Chlorophenoxy-5-methyl-6-oxanon-3-yne-2,6-diol*, was obtained in poor yield as an oil, b.p. 184° to 188° at 0·4 mm., by condensation of 3-hexyne-2,5-diol with 3-*p*-chlorophenoxy-1,2-epoxypropane at 190° to 200° for 6 hours. Found: C, 59·7; H, 6·7; Cl, 12·3. $C_{15}H_{19}O_4Cl$ requires C, 60·3; H, 6·4; Cl, 11·9 per cent.

1-o-*Tolyloxypent-4-yn-2-ol.* Acetylene was passed slowly into liquid ammonia (500 ml.) and sodium (11·5 g.) added in small portions with stirring. Stirring was continued for 30 minutes after the addition was complete when 1,2-epoxy-3-*o*-tolyloxypropane (62 g.) was added dropwise, the current of acetylene being maintained during the addition. Excess of ammonia was allowed to evaporate at room temperature, the residue was treated with iced-water then with a solution of tartaric acid (40 g.) in water, and the oil isolated with ether. The ether extracts were washed with aqueous sodium bicarbonate, then with water, the ether removed and the residual oil distilled under reduced pressure to yield a main fraction (47 g.) b.p. 100° at 0·5 mm. to 120° at 0·8 mm. This was purified in the following way. The oil (40 g.) was dissolved in ethanol (200 ml.) and treated with a solution of silver nitrate (40 g.) in water (100 ml.). The heavy white precipitate was collected and washed with 70 per cent ethanol. The salt was decomposed by the addition of a solution of sodium cyanide (40 g.) in water (200 ml.) and the resultant oil isolated and distilled as above to give the *product*, b.p. 110° at 0·6 mm. Found: C,75·6; H, 7·5. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4 per cent.

1-o-*Chlorophenoxypent-4-yn-2-ol*, had b.p. 130° at 2 mm. Found: Cl, 16·9. $C_{11}H_{11}O_2Cl$ requires Cl, 16·9 per cent.

1,3-*Dicarbamoyloxy-2-methylpentane* had m.p. 113° after crystallisation from water. Found: C, 46·8; H, 7·7; N, 13·8. $C_8H_{16}O_4N_2$ requires C, 47·0; H, 7·9; N, 13·7 per cent.

1,3-*Dicarbamoyloxy-2-ethylhexane* m.p. 114° (from water). Found: C, 51·6; H, 8·6; N, 12·0. $C_{10}H_{20}O_4N_2$ requires C, 51·7; H, 8·7; N, 12·1 per cent.

1,2-*Dicarbamoyloxyoctane* m.p. 145° (from water). Found: C, 51·3; H, 8·5; N, 12·5. $C_{10}H_{20}O_4N_2$ requires C, 51·7; H, 8·7; N, 12·1 per cent.

1,5-*Dicarbamoyloxy-6-o-tolyloxy-3-oxahexane*, prepared from the diol[1], had m.p. 127° to 129° after crystallisation from aqueous ethanol. Found: C, 54·0; H, 6·3; N, 9·2. $C_{14}H_{20}O_6N_2$ requires C, 53·8; H, 6·5; N, 9·0 per cent.

1,1-*Bishydroxymethylcyclopentane.* A solution of 1,1-bisethoxycarbonylcyclopentane (42·8 g.) in ether (50 ml.) was added dropwise with stirring to a solution of lithium aluminium hydride (10 g.) in ether (200 ml.). When the vigorous reaction had subsided, ether (150 ml.) was added to facilitate stirring. The mixture was cooled, decomposed by

careful addition of dilute hydrochloric acid, the ether extract separated and the aqueous fraction saturated with salt and re-extracted with ether. The combined ether extracts were washed with saturated salt solution and dried with anhydrous sodium sulphate. After removal of the ether the *product* crystallised from benzene-light petroleum (b.p. 60° to 80°) in needles, m.p. 95° to 96°. Found: C, 64·9; H, 10·6. $C_7H_{14}O_2$ requires C, 64·6; H, 10·8 per cent. The diol formed a bis-*p*-nitrobenzoate which separated from benzene-light petroleum (b.p. 60° to 80°) in nodules, m.p. 163°. Found: C, 59·4; H, 5·0; N, 6·7. $C_{21}H_{20}O_8N_2$ requires C, 58·9; H, 4·7; N, 6·5 per cent. The diol formed a *dicarbamate* which crystallised from aqueous ethanol in needles, m.p. 167°. Found: C, 49·8; H, 7·3; N, 12·0. $C_9H_{16}O_4N_2$ requires C, 50·0; H, 7·5; N, 13·0 per cent.

4,4-*Biscarbamoyloxymethylcyclohex*-1-*ene* prepared from the diol[9] had m.p. 104° after crystallisation from water. Found: N, 12·4. $C_{10}H_{16}O_4N_2$ requires N, 12·3 per cent.

4-*Hydroxymethyl*-4-*methyloxazolid*-2-*one*. A solution of 2-amino-2-methylpropane-1,3-diol monohydrate (24·6 g.) in ethanol-benzene was concentrated to remove water. Ethyl carbonate (47·2 g.) was added followed by a solution of sodium ethoxide prepared from sodium (0·5 g.) in ethanol (10 ml.). The mixture was heated on the steam bath for 2 hours, water was added to clarify it and it was neutralised with acetic acid and solvent removed at reduced pressure. The residual solid crystallised from ethanol-benzene to yield the *product* (23 g.) in colourless prisms, m.p. 120°. Found: C, 45·8; H, 6·5; N, 10·7. $C_5H_9O_3N$ requires C, 45·8; H, 6·9; N, 10·7 per cent.

4-*Carbamoyloxymethyl*-4-*methyloxazolid*-2-*one*. A solution of phosgene (4 g.) in dioxan (80 ml.) was added in portions to a solution of the oxazolidone (5·2 g.) in dioxan (100 ml.). The mixture was allowed to stand overnight, heated to 50° for 1 hour then aspirated to remove excess of hydrogen chloride and phosgene. Treatment of the mixture with excess of ammonia gas furnished the *carbamate* which had m.p. 117° after crystallisation from ethyl acetate-light petroleum (b.p. 60° to 80°). Found: C, 41·5; H, 5·7; N, 16·3. $C_6H_{10}O_4N_2$ requires C, 41·4; H, 5·8; N, 16·1 per cent.

1-o-*Acetamidophenoxy*-3-p-*acetamidophenoxypropan*-2-*ol*. A solution of *p*-acetamidophenol (7·55 g.) and 1,2-epoxy-3-*o*-acetamidophenoxypropane (10·35 g.) in ethanol (50 ml.) containing pyridine (3 drops) was heated under reflux for 8 hours. The *product* (14·8 g., 83 per cent) separated on cooling and had m.p. 178° after crystallisation from ethanol. Found: C, 64·0; H, 6·3; N, 8·2. $C_{19}H_{22}O_5N_2$ requires C, 63·7; H, 6·2; N, 7·8 per cent. Hydrolysis of the foregoing compound (10 g.) in ethanol (10 ml.) containing conc. hydrochloric acid (20 ml.) for 3 hours under reflux furnished 1-o-*aminophenoxy*-3-p-*aminophenoxypropan*-2-*ol dihydrochloride* which separated from ethanol-ethyl acetate in nodules, m.p. 228° (decomp.). Found: C, 52·3; H, 5·7; N, 7·8; Cl, 19·8. $C_{15}H_{20}O_3N_2Cl_2$ requires C, 51·8; H, 5·8; N,8·1; Cl, 20·4 per cent.

1-o-*Aminophenoxy*-3-o-*tolyloxypropan*-2-*ol hydrochloride.* A mixture of *o*-acetamidophenol (30·2 g.), 1,2-epoxy-3-*o*-tolyloxypropane (32·8 g.) and pyridine (5 drops) in ethanol (200 ml.) was heated under reflux for 10 hours. The mixture was concentrated to half bulk, conc. hydrochloric acid (40 ml.) added and heating continued for 2 hours. The *product* (60 g.) separated on cooling and crystallised from ethanol-ethyl acetate in needles, m.p. 181°. Found: C, 62·3; H, 6·5; N, 4·4. $C_{16}H_{20}O_3NCl$ requires C, 62·0; H, 6·5; N, 4·5 per cent. The same product was obtained by condensation of *o*-cresol with 3-*o*-acetamidophenoxy-1,2-epoxypropane followed by hydrolysis with aqueous-ethanolic hydrochloric acid.

1-o-*Aminophenoxy*-3-o-*methoxyphenoxypropan*-2-*ol*, separated from ethyl acetate-light petroleum (b.p. 60° to 80°) in needles, m.p. 103° to 104°. Found: C, 66·0; H, 6·6; N, 4·9. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6; N, 4·8 per cent. The *hydrochloride* crystallised from ethanol in needles m.p. 194° to 196°. Found: C, 58·9; H, 6·5; N, 4·2. $C_{16}H_{20}O_4NCl$ requires C, 59·0; H, 6·2; N, 4·3 per cent.

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