ANALGESICS. PART III. SALICYLAMIDE DERIVATIVES

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The synthesis of some derivatives of 3-(*o*-aminocarbonylphenoxy)-propan-1:2-diol, 1-aryloxy-3-(*o*-aminocarbonylphenoxy)-propan-2-ol and *NN'*-bis-(3-*o*-aminocarbonylphenoxy-2-hydroxypropyl)-piperazine is described.

WHILE the work described in Parts I and II was in progress, Way and others[1] published a paper on the pharmacology of some eighty congeners of salicylamide containing small substituent groups in the phenyl ring, on the phenolic hydroxyl group or on the amido-nitrogen. Many of these compounds showed central nervous depressant, hypnotic, antipyretic and analgesic activity. We therefore extended our studies to the preparation of some 3-(*o*-aminocarbonylphenoxy)-propan-1:2-diol derivatives formally related to salicylamide.

The preparation of 3-aminocarbonylphenoxy-1:2-epoxypropane (IV; R = H), required as an intermediate for types (I) and (III), was first examined. Condensation of salicylamide with one or two molar equivalents of 2:3-epoxypropyl chloride in aqueous alkaline solution at room temperature under the conditions used previously for the preparation of 3-aryloxy-1:2-epoxypropanes[2] (see also Part I), led to the formation of 1:3-bis-(*o*-aminocarbonylphenoxy)-propan-2-ol (III; R = R' = $CONH_2$) as major product. The required epoxide (IV; R = H) was ultimately obtained in about 43 per cent yield by using a large excess (5 to 6 molar equivalents) of 2:3-epoxypropyl chloride in the reaction, but even then formation of the bis-compound was not completely suppressed.

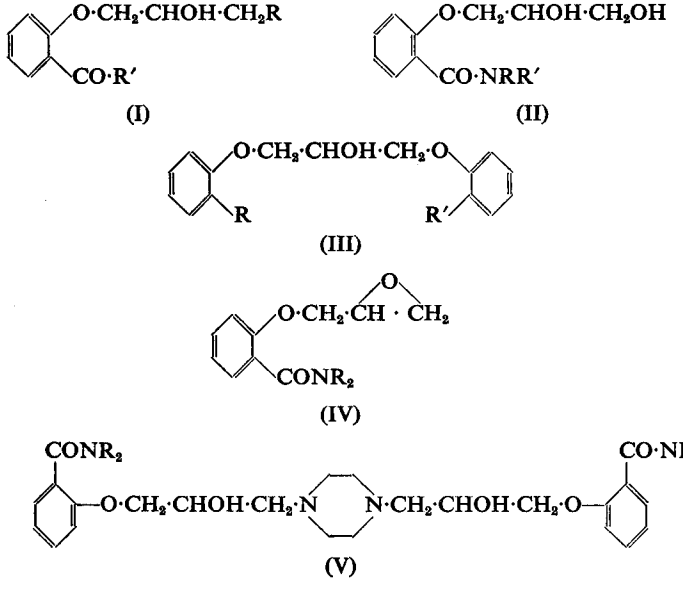
Alkaline hydrolysis of the diamide (III; R = R' = $CONH_2$) yielded the corresponding dicarboxylic acid (III; R = R' = CO_2H). The last compound was also prepared by reaction between sodium salicylate and 2:3-epoxypropyl chloride in aqueous alkaline solution and was purified *via* its dimethyl ester.

Condensation of the epoxide (IV; R = H) with piperidine and with piperazine yielded 3-(*o*-piperidinocarbonylphenoxy)-propane-1:2-diol (I; R = piperidino, R' = NH_2) and *NN'*-bis-(2-hydroxy-3-*o*-aminocarbonylphenoxypropyl)-piperazine (V; R = H), respectively. Reaction of (IV; R = H) with succinimide and with phthalimide in the presence of a basic catalyst gave the succinimido- (I; R = succinimido, R' = NH_2) and phthalimido- (I; R = phthalimido, R' = NH_2) derivatives. The former gave 3-(*o*-carboxyphenoxy)-2-hydroxypropylamine (hydrochloride) (I; R = NH_2·HCl, R' = OH) on hydrolysis with concentrated hydrochloric acid. The phthalimido-compound, on reaction with hydrazine hydrate, followed by careful treatment with hydrochloric acid, furnished 3-(*o*-aminocarbonylphenoxy-2-hydroxypropylamine (hydrochloride) (I; R = NH_2·HCl, R' = NH_2).

Condensation of salicyldiethylamide with excess 2:3-epoxypropyl chloride in alkaline solution yielded the epoxide (IV; R = Et) together with 3-(*o*-diethylaminocarbonylphenoxy)-propane-1:2-diol (II; R = R′ = Et). Reaction of the epoxide (IV) with piperazine gave *NN*′-bis-(3-*o*-diethylaminocarbonylphenoxy-2-hydroxypropyl)-piperazine (V; R = Et).

3-(*o*-Aminocarbonylphenoxy)-propane-1:2-diol (II; R = R′ = H) was readily obtained by condensation of salicylamide with 2:3-dihydroxypropyl chloride in aqueous alkaline solution. Its preparation from salicylamide and 2:3-epoxypropan-1-ol in the presence of a basic catalyst proved less satisfactory, though this method was useful for the preparation of the substituted amides (II; R = H, R′ = Et; R = H, R′ = Bu; R = R′ = Et and NRR′ = piperidino).

Some unsymmetrical bis-compounds (III) were prepared by condensing the appropriate epoxide (IV) with various phenols or alternatively by the reaction of 3-*o*-aryloxy-1:2-epoxypropanes with the substituted salicylamide. The condensation of methyl salicylate with 3-*o*-toloxy-1:2-epoxypropane and with 2:3-epoxypropyl chloride was also examined (see Experimental).



Experimental

Melting points are uncorrected.

Condensation of salicylamide with 2:3-epoxypropyl chloride. To a stirred suspension of salicylamide (34·5 g.) and 2:3-epoxypropyl chloride (138·8 g., 6 mole equiv.) in water (100 ml.) was added a solution of sodium hydroxide (10 g.) in water (20 ml.) and stirring continued for 24 hours. The solid which separated was collected, drained and dissolved in boiling

ethanol (200 ml.). The solution on cooling deposited white fluffy needles (11 g.) of 1:3-*bis*-(o-*aminocarbonylphenoxy*)-*propan*-2-*ol* (III; R = R′ = $CONH_2$), m.p. 213 to 215° after a further crystallisation from ethanol. Found: C, 62·1; H, 5·5; N, 8·4. $C_{17}H_{18}O_5N_2$ requires C, 61·8; H, 5·5; N, 8·5 per cent.

A second product (7·9 g., m.p. 108 to 110°) separated from the ethanolic mother liquors after concentration and cooling. Extraction of the original aqueous mother liquors with chloroform followed by recrystallisation from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) gave a second crop (12·6 g.) of this material which on purification had m.p. 108 to 110° and proved to be 3-(o-*aminocarbonylphenoxy*)-1:2-*epoxypropane* (IV; R = H). Found: C, 61·7; H, 5·5; N, 7·1. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3 per cent.

The foregoing diamide (6 g.) was suspended in water (100 ml.) containing sodium hydroxide (5 g.) and heated under reflux for 7 hours. Acidification with hydrochloric acid furnished 1:3-*bis*-(o-*carboxyphenoxy*)-*propan*-2-*ol* (III; R = R′ = CO_2H) which separated from ethanol in white needles, m.p. 170 to 171°. Found: C, 61·3; H, 5·0. $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·9 per cent.

Condensation of sodium salicylate with 2:3-*epoxypropyl chloride in alkaline solution.* 2:3-Epoxypropyl chloride (28 g., 0·6 mole) was added to a solution of salicylic acid (69 g.) in water (200 ml.) containing sodium hydroxide (40 g., 2 moles). A little ethanol was added to make the mixture homogeneous when it was allowed to stand at room temperature for 2 days. Acidification with concentrated hydrochloric acid yielded a crude solid which could not be readily purified. It was collected, washed and dried at 100°.

Crude dry solid (93 g.) was dissolved in methanol (500 ml.) hydrogen chloride (10 g.) added and the solution heated under reflux for 4 hours to complete esterification.

The cooled reaction mixture was poured into water, extracted with chloroform, the extract washed acid-free and concentrated. The residue was heated at 100° at 0·1 mm. to remove methyl salicylate (34 g.). The high boiling residue weighed 48 g. An 18 g. portion of this was hydrolysed by heating on the steam bath with water (250 ml.) containing potassium hydroxide (9·3 g.). After cooling and acidification the solid was collected and washed with water, it had m.p. 168 to 170°, not depressed on admixture with a sample of the aforementioned dicarboxylic acid.

N-(2-*Hydroxy*-3-o-*aminocarbonylphenoxypropyl*)-*piperidine* (I; R = piperidino, R′ = NH_2). Piperidine (2·5 ml.) was added to a solution of 3-(*o*-aminocarbonylphenoxy)-1:2-epoxypropane (4·8 g.) in benzene (30 ml.) and the solution heated on the steam bath for 30 minutes. Slight dilution with light petroleum (b.p. 60 to 80°) furnished the *product* (5·5 g.) which crystallised from aqueous methanol in flat white needles, m.p. 167 to 168°. Found: C, 65·0; H, 8·0; N, 10·1. $C_{15}H_{22}O_3N_2$ requires C, 64·7; H, 8·0; N, 10·1 per cent.

The *hydrochloride dihydrate* separated from a mixture of ethanol and ethyl acetate in small deliquescent needles, m.p. 140 to 150°. Found:

C, 50·8; H, 7·2; N, 7·6. $C_{15}H_{23}O_3N_2Cl$; $2H_2O$ requires C, 51·3; H, 7·8; N, 8·0 per cent.

NN′-*bis*-(2-*Hydroxy*-3-o-*aminocarbonylphenoxypropyl*)-*piperazine* (V; R = H) was prepared by condensation of piperazine hexahydrate with 2 mole equivalents of 3-(*o*-aminocarbonylphenoxy)-1 : 2-epoxypropane in ethanolic solution. It separated from aqueous ethylene glycol in small white needles, m.p. 215 to 218°. Found: C, 60·7; H, 6·7; N, 11·8. $C_{24}H_{32}O_6N_4$ requires C, 61·0; H, 6·8; N, 11·9 per cent.

The *dihydrochloride* separated from 95 per cent ethanol in small white needles, m.p. 232 to 233°. Found: C, 52·8; H, 6·3; N, 10·4; Cl, 13·2. $C_{24}H_{34}O_6N_4Cl_2$ requires C, 52·8; H, 6·3; N, 10·3; Cl, 13·0 per cent.

N-(2-*Hydroxy*-3-o-*aminocarbonylphenoxypropyl*)-*succinimide* (I; R = succinimido, R′ = H). A solution of 3-(*o*-aminocarbonylphenoxy)-1 : 2-epoxypropane (15·5 g.) and succinimide (8·8 g.) in ethanol (30 ml.) containing pyridine (5 drops) was heated under reflux for 5 hours. The product (22 g.) separated on cooling. It crystallised from ethanol in small white needles, m.p. 175 to 177°. Found: C, 57·3; H, 5·4; N, 9·6. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5; N, 9·8 per cent.

The foregoing product (18 g.) was dissolved in a mixture of ethanol 50 ml.) and concentrated hydrochloric acid (50 ml.) and heated under reflux for 12 hours. After removal of the solvent under reduced pressure, the residue was dissolved in water (50 ml.) and washed with two 50 ml. portions of ethyl acetate. The aqueous portion was again concentrated under reduced pressure and the residue crystallised from a mixture of ethanol and ethyl acetate to yield (2-*hydroxy*-3-o-*carboxyphenoxypropyl*)-*amine hydrochloride* (I; R = NH_2·HCl, R′ = OH) in white needles, m.p. 150 to 154°. Found: C, 48·1; H, 5·7; N, 5·4; Cl, 14·3. $C_{10}H_{14}O_4NCl$ requires C, 48·5; H, 5·7; N, 5·7; Cl, 14·3 per cent.

N-(2-*Hydroxy*-3-o-*aminocarbonylphenoxypropyl*)-*phthalimide* (I; R = phthalimido, R′ = H) was prepared as for the corresponding succinimido compound. It separated from ethanol in small white feathery crystals, m.p. 183°. Found: C, 63·3; H, 4·8; N, 8·3. $C_{18}H_{16}O_5N_2$ requires C, 63·5; H, 4·7; N, 8·2 per cent.

Treatment of the foregoing compound (23 g.) with 50 per cent hydrazine hydrate (8·5 g.) in boiling ethanol (250 ml.) for 1 hour yielded on cooling an intermediate which had m.p. 201 to 202° after collecting and washing with boiling ethanol (cf.[2]). Found: N, 15·2. $C_{18}H_{20}O_5N_4$ requires N, 15·1 per cent.

(2-*Hydroxy*-3-o-*aminocarbonylphenoxypropyl*)-*amine hydrochloride* (I; R = NH_2·HCl, R′ = NH_2). The foregoing hydrazide was suspended in hot ethanol (250 ml.), concentrated hydrochloric acid (9 ml.) added and the mixture heated to boiling for a few minutes. After cooling the separated phthalyl hydrazine (10 g.) was removed. The filtrate was concentrated under reduced pressure and the solid residue crystallised from ethanol and then from a mixture of ethanol and ethyl acetate to yield small plates of 2-hydroxy-3-*o*-aminocarbonylphenoxypropylamine hydrochloride m.p. 162 to 166° (12 g.). Found: N, 11·3; Cl, 13·9. $C_{10}H_{15}O_3N_2Cl$ requires N, 11·4; Cl, 14·4 per cent.

Treatment of the foregoing hydrochloride with dilute sodium hydroxide and benzoyl chloride by the Schotten-Baumann method yielded N-(2-*hydroxy*-3-o-*aminocarbonylphenoxypropyl*)-*benzamide* (I; R = NHCOPh, R′ = NH_2) which separated from aqueous ethanol in small white needles, m.p. 162 to 163°. Found: C, 65·4; H, 6·0; N, 8·9. $C_{17}H_{18}O_4N_2$ requires C, 65·0; H, 5·8; N, 8·9 per cent.

Salicylethylamide (cf.[3]). To a cooled solution of phenyl salicylate (107 g., 0·5 mole) in benzene (100 ml.) a solution of ethylamine (45 g., 1·0 mole) in benzene (100 ml.) was added cautiously in portions. After the vigorous reaction had subsided the mixture was heated on the steam bath for 1 hour. Removal of the solvent and excess of amine, followed by distillation of the residual oil under reduced pressure yielded the *product* as an oil, b.p. 112° at 0·1 mm., which solidified and was crystallised from light petroleum (b.p. 60 to 80°) containing a little ethyl acetate, forming crystals, m.p. 62 to 63°. Found: C, 65·2; H, 6·5; N, 8·6. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7; N, 8·5 per cent.

Salicyl morpholineamide prepared by the method of Van Allan[3], crystallised from ethanol in needles, m.p. 181 to 183°. Found: C, 63·6; H, 6·3; N, 6·7. $C_{11}H_{13}O_3N$ requires C, 63·7; H, 6·3; N, 6·8 per cent.

Condensation of 2:3-*epoxypropyl chloride with salicyldiethylamide.* Salicyldiethylamide (65 g.) was dissolved in 2:3-epoxypropyl chloride (185 g., 6 mole equiv.) and a solution of sodium hydroxide (13·4 g., 1 mole equiv.) in water (200 ml.) added with stirring. Stirring at $< 20°$ was continued for 22 hours.

The oil was extracted with chloroform, the extract washed with water and concentrated under reduced pressure to remove excess of chloroform and 2:3-epoxypropyl chloride. A portion of the residue was distilled at 0·3 mm. yielding, (*a*) 3-(*diethylaminocarbonylphenoxy*)-1:2-*epoxypropane* (III; R = Et) as a pale yellow oil, b.p. 154°. Found: C, 67·1; H, 7·9; N, 5·7. $C_{14}H_{19}O_3N$ requires C, 67·4; H, 7·7; N, 5·6 per cent and (*b*) 3-(*diethylaminocarbonylphenoxy*)-*propan*-1:2-*diol* (II; R = R′ = Et), as a pale yellow viscous oil, b.p. 180°. Found: C, 63·1; H, 7·4; N, 5·6. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2 per cent. A 10 g. portion of the original residue was dissolved in ethanol (10 ml.) and treated with a solution of piperazine hexahydrate (3·9 g.) in ethanol (10 ml.). After heating under reflux for 1 hour the solution was acidified with hydrochloric acid and the solvent removed under reduced pressure. The residual gum solidified slowly in a mixture of ethanol and ethyl acetate. On crystallisation from the same solvent mixture it yielded *NN′-bis*-(2-*hydroxy*-3-o-*diethylaminocarbonylphenoxypropyl*)-*piperazine dihydrochloride* (V; R = Et) in small needles, m.p. 213 to 214°. Found: C, 58·0; H, 7·8; N, 8·9; Cl, 10·7. $C_{32}H_{50}O_6N_4Cl_2$ requires C, 58·4; H, 7·7; N, 8·5; Cl, 10·8 per cent.

3-(o-*Aminocarbonylphenoxy*)-*propan*-1:2-*diol* (cf.[1]). To a stirred solution of salicylamide (68·5 g., 0·5 mole) in water (120 ml.) containing sodium hydroxide (20 g., 0·5 mole) was added 2:3-dihydroxypropyl chloride (60·5 g., 0·55 mole). Stirring at 20 to 25° was continued for 2 hours and then for 30 minutes at 50°. The *product* separated after cooling

to 0° for some hours. It crystallised from ethanol in needles, m.p. 140 to 142°. Found: C, 56·8; H, 6·4; N, 6·7. Calc. for $C_{10}H_{13}O_4N$: C, 56·9; H, 6·2; N, 6·6 per cent.

The same product was prepared by heating salicylamide (6·9 g.) with 2:3-epoxypropan-1-ol (4·5 g.) in benzene (10 ml.) containing pyridine (1 drop) for 16 hours.

3-(*Ethylaminocarbonylphenoxy*)-*propan*-1:2-*diol* (II; R = H, R′ = Et). A mixture of salicylethylamide (20·6 g.) and 2:3-epoxypropanol (9·2 g.) containing pyridine (1 drop) was heated on the steam bath for 6 hours and then at 110° for 1 hour. Direct distillation under reduced pressure yielded the *product* (18·5 g.) as a viscous oil, b.p. 215° at 0·1 mm. which solidified on standing. Found: C, 60·3; H, 7·0; N, 5·8. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·2; N, 5·9 per cent.

3-(*n-Butylaminocarbonylphenoxy*)-*propan*-1:2-*diol* (II; R = H, R′ = *n*-Bu) separated from a mixture of ethylacetate and ether in small nodules, m.p. 85 to 87°. Found: C, 63·5; H, 7·9; N, 4·9. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2 per cent.

3-(o-*Diethylaminocarbonylphenoxy*)-*propan*-1:2-*diol* (II; R = R′ = Et) was prepared by condensation of salicyldiethylamide with 2:3-epoxypropanol and obtained as a water-soluble, viscous oil, b.p. 180 to 185° at 0·3 mm. Found: C, 62·5; H, 8·0. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9 per cent. 3-(o-*Piperidinocarbonylphenoxy*)-*propan*-1:2-*diol* (II; NRR′ = piperidino) formed an orange-coloured viscous liquid, b.p. 216° at 0·3 mm. Found: C, 64·9; H, 7·4; N, 5·3. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·6; N, 5·0 per cent.

1 - (o - *Aminocarbonylphenoxy*) - 3 - (o - *diethylaminocarbonylphenoxy*) - *propan*-2-*ol* (III; R = $-CONH_2$, R′ = $-CONEt_2$). To a solution of 3-(*o*-aminocarbonylphenoxy)-1:2-epoxypropane (5 g.) and salicyldiethylamide (5 g.) in benzene (15 ml.) was added pyridine (2 drops) as catalyst and the solution heated on the steam bath for 3 hours. The solvent was removed and the gummy residue triturated with ethyl acetate. The solid obtained (8 g.) crystallised from a mixture of ethanol and ethyl acetate in fawn needles, m.p. 182 to 183°. Found: C, 65·1; H, 6·7; N, 7·2. $C_{21}H_{26}O_5N_2$ requires C, 65·3; H, 6·8; N, 7·3 per cent.

1 - (o - *Aminocarbonylphenoxy*) - 3 - (o - *morpholinocarbonylphenoxy*) - *propan*-2-*ol* (III; R = $-CONH_2$, R′ = $CO{\cdot}\overset{\frown}{N\ O}$). This was prepared by condensation of 3-(*o*-aminocarbonylphenoxy)-1:2-epoxypropane with salicoylmorpholine as described in the previous example. It crystallised from a mixture of methanol and ethyl acetate in small, hard prisms, m.p. 152 to 153°. Found: C, 62·7; H, 6·1; N, 6·8. $C_{21}H_{24}O_6N_2$ requires C, 63·0; H, 6·0; N, 7·0 per cent.

1-(o-*Aminocarbonylphenoxy*)-3-o-*toloxy-propan*-2-*ol* (III; R = $CONH_2$, R′ = Me). It was prepared by condensation of 3-(*o*-aminocarbonylphenoxy)-1:2-epoxypropane with *o*-cresol, or by the condensation of 3-*o*-toloxy-1:2-epoxypropane with salicylamide. It separated from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) in needles,

m.p. 108 to 110°. Found: C, 68·1; H, 6·2; N, 4·5. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·7 per cent.

1-(o-*Diethylaminocarbonylphenoxy*)-3-o-*toloxy-propan*-2-*ol* (III; R = $CONEt_2$; R′ = Me) was prepared by condensation of 3-*o*-toloxy-1:2-epoxypropane with salicyldiethylamide employing pyridine as catalyst. It was obtained in high yield as a viscous oil, b.p. 210° at 0·1 mm. Found: C, 70·3; H, 7·5; N, 3·6. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6; N, 3·9 per cent.

1-(o-*Piperidinocarbonylphenoxy*)-3-o-*toloxypropan*-2-*ol* (III; R =  , R′ = Me) was obtained as a very viscous liquid of b.p. 236° at 0·2 mm. Found: C, 71·6; H, 7·2; N, 3·6. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·4; N, 3·8 per cent.

1-(o-*Aminocarbonylphenoxy*)-3-p-*chlorophenoxypropan*-2-*ol* crystallised from a mixture of ethyl acetate and light petroleum (b.p. 60 to 80°) in small, hard white crystals, m.p. 118 to 120°. Found: C, 59·8; H, 5·1; N, 4·4; Cl, 10·9. $C_{16}H_{16}O_4NCl$ requires C, 59·7; H, 5·0; N, 4·4; Cl, 11·0 per cent.

1-(o-*Methoxycarbonylphenoxy*)-3-o-*toloxy-propane*-2-*ol* (III; R = CO_2Me, R′ = Me). A mixture of 3-*o*-toloxy-1:2-epoxypropane (82 g.), methyl salicylate (76 g.) and pyridine (10 drops) was heated at 150° for 3 hours. After removal of unchanged material (125 g.) by distillation, the product (26 g.) was obtained as a viscous oil, b.p. 210° at 0·5 mm. Found: C, 68·7; H, 6·4. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4 per cent.

2-*Hydroxy*-3-o-*methoxycarbonylphenoxypropyl chloride* (I; R = Cl, R′ = OMe). A mixture of methyl salicylate (152 g.) and 2:3-epoxypropyl chloride (278 g., 3 mole equiv.) containing piperidine hydrochloride (4 g.) was heated on the steam bath for 24 hours (cf.[4]). Excess of 2:3-epoxypropyl chloride, methyl salicylate and 1:3-dichloro-propan-2-ol were removed by heating on the steam bath at 1 mm. pressure. The residual oil was dissolved in an equal volume of chloroform and shaken with concentrated hydrochloric acid (20 ml.) for 1 minute with cooling. The chloroform extract was washed with water until neutral, the extract concentrated and the residual oil distilled under reduced pressure. The *product* (106·5 g.) was obtained as a fluorescent oil, b.p. 128° at 0·1 mm. Found: Cl, 14·3. $C_{11}H_{13}O_4Cl$ requires Cl, 14·5 per cent. High boiling products were formed in the reaction.

3-(o-*Methoxycarbonylphenoxy*)-*propane*-1:2-*diol* (I; R = H, R′ = OMe). A mixture of methyl salicylate (38 g.) and 2:3-epoxypropanol (18·5 g.) containing pyridine (3 drops) was heated on the steam bath for 16 hours. Distillation under reduced pressure yielded the *product* (18 g.), b.p. 160° at 0·5 mm. Found: C, 58·2; H, 5·8. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2 per cent.

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