The Condensation of Epichlorohydrin with Monohydric Phenols and with Catechol.

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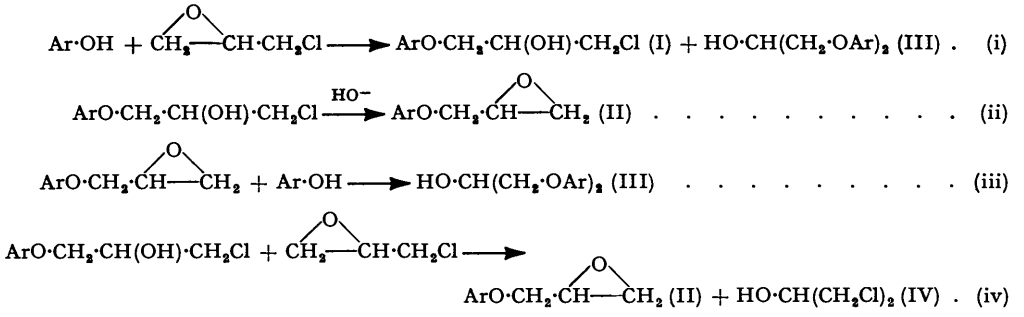
The method described earlier (*J.*, 1951, 1589) for the preparation of 1-aryloxy-3-chloropropan-2-ols has been improved to give increased yields. The condensation of catechol with epichlorohydrin in the presence of basic catalysts has been investigated and the hitherto unknown bisglycide ether (VIII) obtained.

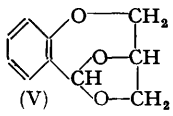
THE preparation of 1-aryloxy-3-chloropropan-2-ols (I) by condensation of phenols with epichlorohydrin in the presence of basic catalysts (cf. i) has been described by Bradley, Forrest, and Stephenson (*J.*, 1951, 1589). The method, however, is not entirely satisfactory as optimum yields of products are only obtained by leaving reaction mixtures at room temperature for periods exceeding one month. For this reason and because of the increasing importance of the products as intermediates, their preparation has been studied further and an improved procedure developed.



It was already known that phenols and epichlorohydrin in equimolar amounts in the presence of a basic catalyst give an aryloxychlorohydrin (I) [reaction (i)] in 50—70% yield, together with smaller quantites of the glyceryl αα′-diaryl ether (III); the latter is also obtained by way of the aryl glycide ether (II) [reactions (ii) and (iii)]. Further study of reaction (i) revealed that formation of (III) is virtually suppressed by employing excess of epichlorohydrin. When the chlorohydrin (I) is heated with 3 mols. of epichlorohydrin and a suitable basic catalyst for some hours on the water-bath, glycerol dichlorohydrin (IV) and an equivalent amount of aryl glycide ether (II), together with unchanged chlorohydrin (I), are obtained [cf. (iv); Bradley *et al.*, *loc. cit.*]. The foregoing experiments showed clearly that reaction of phenols with excess of epichlorohydrin leads to the formation of (I), (II), and (IV) with exclusion of (III). A basis for an improved route to aryloxychlorohydrins (I) was thus presented as the glycide (II) was known to pass into the

chlorohydrin with great facility on treatment with hydrochloric acid. The procedure finally adopted is given on p. 1573.

An attempt to extend this reaction to salicylaldehyde gave much polymeric material, a crystalline product $C_{10}H_{10}O_3$, and a small quantity of the desired ether (VI; R = Cl). The last compound with sodium hydroxide at room temperature gave the glycide ether (VII), which reacted smoothly with piperazine and *p*-chlorophenol.



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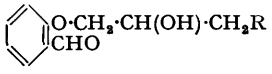

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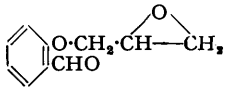
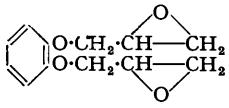
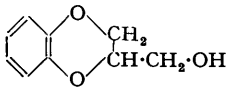


(VII)

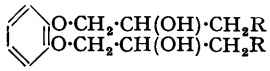
The structure (V) is assigned to the product $C_{10}H_{10}O_3$, on the following evidence: (i) The compound does not possess a free aldehyde group as it fails to react with hydroxylamine or semicarbazide under the usual experimental conditions; (ii) the ultra-violet absorption spectrum fails to reveal a carbonyl group associated with an aromatic nucleus; (iii) no free hydroxyl or alkali-sensitive groups are present as the material is recovered unchanged after treatment with alkali, phenyl *iso*cyanate, or boiling acetic anhydride; and (iv) with dinitrophenylhydrazine in ethanolic mineral acid it gives a dinitrophenylhydrazone identical with that from authentic (VI; R = OH), which is conveniently prepared from salicylaldehyde and glycidol.



(VIII)



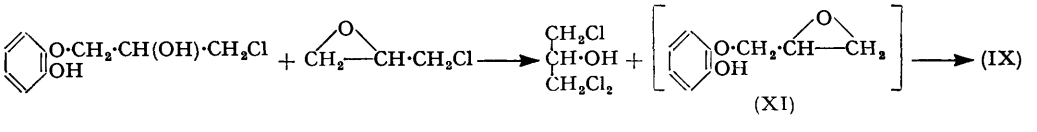
(IX)



(X)

The bisglycidyl ethers of resorcinol and quinol have been prepared by Werner and Farenhorst (*Rec. Trav. chim.*, 1948, **67**, 438) by reaction of the dihydric phenols with epichlorohydrin in aqueous alkaline solution, but attempts to obtain the corresponding catechol derivative (VIII) have not hitherto been successful. Thus Lindemann (*Ber.*, 1891, **24**, 2149) heated catechol with two equivalents of epichlorohydrin in aqueous potassium hydroxide at 120° and obtained a product which he claimed was (VIII). However, Fourneau (*Chem. Zent.*, 1910, I, 1134) showed that this was 2-hydroxymethylbenzodioxen (IX); this is indistinguishable from (VIII) by analysis, but is found to differ from authentic (VIII) now obtained for the first time.

Direct conversion of catechol into (VIII) could not be achieved, but an indirect approach *via* the bischlorohydrin (X; R = Cl) was successful. The last compound was first obtained, although in low yield, by condensing equivalent weights of catechol and epichlorohydrin on the steam-bath, with pyridine as catalyst. Fractionation of the product yielded the monochlorohydrin (I; Ar = C_6H_4·OH) in 35—45% yield, somewhat increased by use of excess of catechol, together with the diether (X; R = Cl) and the biscatechol ether (III; Ar = C_6H_4·OH). The monochlorohydrin yielded the benzodioxen (IX), *o*-(3-amino-2-hydroxypropyl)phenol, and *o*-(2-hydroxy-3-piperidinopropyl)phenol on treatment with an alkaline reagent, ammonia solution, and piperidine, respectively. Reaction with ammonia also yielded appreciable amounts of the benzodioxen by intramolecular reaction from the intermediate monoglycide ether (XI). Attempts to improve



(XI)

the yield of diether (X; R = Cl) by increasing the proportion of epichlorohydrin proved only partly successful: using two equivalents and heating the mixture for *ca.* 6 hr. on the water-bath gave a 20% yield of (X; R = Cl); the benzodioxen (IX) was the major product, being

evidently formed by interaction of the monochlorohydrin with excess of epichlorohydrin as indicated. Employing four mols. of epichlorohydrin in the presence of piperidine hydrochloride and leaving the mixture for *ca.* 40 days at room temperature, however, completely suppressed this reaction and the diether (X; R = Cl) was obtained in 74% yield. Heating this reaction mixture at *ca.* 95° for 10 hr. gave the benzodioxen and smaller quantities of epoxides and chlorohydrins of unestablished structure. In one experiment catechol was condensed with epichlorohydrin (2·2 mols.) in the presence of concentrated aqueous sodium hydroxide for 12 days at room temperature, yielding a mixture of the mono- and di-ethers without formation of high-boiling products. It seems certain therefore that with a larger excess of epichlorohydrin this reaction could be adapted to give an optimum yield of diether (X; R = Cl).

Careful reaction of the diether (X; R = Cl) with alkali gave the required bisglycide ether (VIII) as a liquid of b. p. 132—140°/0·2 mm. which slowly crystallised, leaving an oily residue which may have contained a stereoisomer (cf. Werner and Farenhorst, *loc. cit.*).

Experimental

The following illustrates the general method for preparation of the aryloxychlorohydrins (I). The phenol is heated with 3 mols. of epichlorohydrin for 4—6 hr. at *ca.* 100° in the presence of a catalytic quantity of piperidine or other base (see below). After removal of excess of epichlorohydrin by distillation under reduced pressure on the water-bath, the residue is cooled, dissolved in an equal volume of chloroform, and shaken with excess of concentrated hydrochloric acid to convert glycide ether into chlorohydrin. The whole is then washed with water to remove excess of acid and glycerol dichlorohydrin, the solvent is removed at reduced pressure, and the residue distilled *in vacuo*. Pyridine, piperidine, piperidine acetate, or piperidine hydrochloride is about equally effective as catalyst. Piperidine (2 ml./mole of phenol) was employed for convenience. The yields obtained were uniformly 70—85% (see Table 1).

Reaction between 1-Chloro-3-p-methoxyphenoxypropan-2-ol and Epichlorohydrin.—A solution of 1-chloro-3-*p*-methoxyphenoxypropan-2-ol (54·1 g.) in epichlorohydrin (69·4 g.) containing pyridine (0·5 ml.) was heated at 95° for 10 hr., after which excess of epichlorohydrin was removed under reduced pressure. Fractionation of the residue under reduced pressure yielded unchanged aryloxychlorohydrin, crude glycerol dichlorohydrin (6·8 g.) and a fraction (12 g.) of b. p. *ca.* 150°/15 mm. Refractionation of the latter oil gave a solid (6 g.) which on crystallisation from ether formed colourless prisms of glycide *p*-methoxyphenyl ether, m. p. and mixed m. p. 48° (Found: C, 66·8; H, 6·6. Calc. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·7%).

Condensation of Salicylaldehyde with Epichlorohydrin.—Salicylaldehyde (122 g.), epichlorohydrin (278 g.), and pyridine (4 ml.) were heated on the steam-bath for 6 hr., slight initial cooling being applied to keep the temperature below 110°. The excess of epichlorohydrin was removed at reduced pressure and the residue fractionated *in vacuo* to yield: (i) 60 g., b. p. 48—56°/0·5 mm., which on redistillation at atmospheric pressure yielded glycerol dichlorohydrin (40·2 g.), b. p. 174—178°, (ii) 70 g., b. p. 110—130°/0·5 mm., and (iii) 66 g., b. p. 180°/0·5 mm., of crude chlorohydrin. Distillation was stopped at this point as the residue had begun to decompose. Fraction (ii) was purified by crystallisation from ether–light petroleum (b. p. 40—60°), forming white needles (47·6 g.) of the acetal, 4 : 7-*epoxy*-2 : 3-*benzo*-1 : 5-*dioxa*cyclo*octene* (V), m. p. 65° (Found: C, 67·5; H, 5·6. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). This formed a 2 : 4-*dinitrophenylhydrazone* (in alcoholic mineral acid) which separated from ethanol in sparingly soluble orange-red needles, m. p. 208—209° (Found: C, 51·3; H, 4·3; N, 15·3. $C_{16}H_{16}O_7N_4$ requires C, 51·1; H, 4·3; N, 14·9%). Fraction (iii) on redistillation yielded a main fraction, b. p. 164°/0·1 mm., of o-(3-*chloro*-2-*hydroxypropyl*)*benzaldehyde* (Found: C, 56·5; H, 5·2; Cl, 15·7. $C_{10}H_{11}O_3Cl$ requires C, 55·9; H, 5·2; Cl, 16·5%). The 2 : 4-*dinitrophenylhydrazone* separated from alcoholic hydrochloric acid in dark-red plates, m. p. 188° (Found: C, 48·2; H, 3·8; N, 14·4; Cl, 8·7. $C_{16}H_{15}O_6N_4Cl$ requires C, 48·7; H, 3·8; N, 14·1; Cl, 9·0%).

Condensation of Salicylaldehyde with Glycidol.—To a mixture of salicylaldehyde (24·4 g.) and glycidol (14·8 g.) was added pyridine (5 drops) and the solution heated on the steam-bath for 5 hr. o-(2 : 3-*Dihydroxypropylbenzaldehyde* (23 g.) separated on cooling. After crystallisation from ethyl acetate–light petroleum (b. p. 60—80°), it formed light yellow needles, m. p. 85° (Found: C, 61·3; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%). The 2 : 4-*dinitrophenylhydrazone*, prepared in acetic acid, formed orange crystals, m. p. 206—208° (Found: C, 50·8;

H, 4·1; N, 14·6. $C_{16}H_{16}O_7N_4$ requires C, 51·1; H, 4·3; N, 14·9%), not depressed on admixture with the material prepared from (V).

Conversion of o-(3-*Chloro*-2-*hydroxypropyl*)*benzaldehyde into Glycidyl* o-*Formylphenyl Ether* (VII).—The crude chlorohydrin (VI; R = Cl) was stirred vigorously for 3 hr. with N-sodium hydroxide. The product was extracted with chloroform, the extract washed and concentrated,

TABLE 1. *Yields of* 1-*aryloxy*-3-*chloropropan*-2-*ols.*

No.	Ar	Mols. of epichlorohydrin per mol. of phenol	Catalyst *	Catalyst (g./mole of phenol)	Yield (%) of (I)
1	Phenyl	1·5	B	2	63
		3·0	C	2	78
2	*o*-Tolyl	1·5	B	2	56
		,,	,,	4	53
		,,	,,	8	56
		,,	C	2	55
		,,	,,	4	55
		3·0	,,	2	75
		,,	A	2	81
3	*m*-Tolyl	1·5	B	2	61
		3·0	C	2	80
4	*p*-Tolyl	1·5	B	2	61
		3·0	C	2	90
5	*o*-Methoxyphenyl	1·05	B	1	34
		,,	,,	2	50
		1·5	,,	2	56
		,,	,,	4	62
		3·0	C	2	82
6	*m*-Methoxyphenyl	1·05	B	1	37
		1·5	,,	2	62
		3·0	C	2	81
7	*p*-Methoxyphenyl	1·05	B	1	40
		,,	A	1	41
		1·5	B	2	60
		3·0	C	2	76
8	*o*-Chlorophenyl	1·5	B	2	75
		,,	,,	4	72
		,,	NH_4Cl	2	67
		,,	C	2	73
		3·0	,,	2	84
9	*p*-Chlorophenyl	1·5	B	2	71
		3·0	C	2	85
		,,	,,	2	87
10	*o*-Bromophenyl	3·0	C	2	89
11	*p*-Bromophenyl	3·0	A	2	81
12	o-*Iodophenyl*	3·0	A	2	76
13	o-*Nitrophenyl*	1·5	B	2	69
		3·0	,,	8	73
		,,	A	2	76
14	m-*Nitrophenyl*	3·0	A	2	76
15	*p*-Nitrophenyl	1·5	B	2	59
		3·0	A	2	83
16	2 : 4 : 6-Tribromophenyl	3·0	C	2	68
17	2 : 4-Dichlorophenyl	3·0	B	2	82
18	p-*Cyanophenyl*	3·0	A	3	80
19	o-*Formylphenyl*	3·0	D	2	*ca.* 18
20	p-*Formylphenyl*	3·0	C	1	68
21	p-*Ethoxycarbonylphenyl*	3·0	C	4	77
22	α-Naphthyl	3·0	A	2	85
23	β-Naphthyl	3·0	A	2	78
24	Thymyl	3·0	A	2	65
25	Carvacryl	3·0	A	2	68
26	4-Chloro-3-methylphenyl	3·0	A	2	86
27	2 : 6-*Dichloro*-4-*ethoxycarbonylphenyl*	6·0	D	1·5	73

* A = Piperidine. B = Piperidine acetate. C = Piperidine hydrochloride. D = Pyridine.

and the resultant oil distilled *in vacuo*, yielding o-(2 : 3-*epoxypropyl*)*benzaldehyde* (VII), b. p. 118°/0·5 mm. (Found: C, 67·2; H, 5·9. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%).

Reactions. (i) The glycide ether (11·3 g.) was treated with piperazine hexahydrate (6·2 g.) in ethanol (10 ml.), an exothermic reaction occurring, after which it was left overnight. Dilution with water yielded a gum which was converted into the hydrochloride which separated from

90% ethanol in small white crystals, m. p. 236—237° (decomp.), of 1 : 4-*di*-(3-o-*formylphenoxy*-2-*hydroxypropyl*)*piperazine dihydrochloride* (Found : C, 56·0; H, 6·3; N, 5·2; Cl, 13·5. $C_{24}H_{32}O_6N_2Cl_2$ requires C, 55·9; H, 6·3; N, 5·4; Cl, 13·8%).

(ii) The glycide ether (6·05 g.) and *p*-chlorophenol (4·4 g.) were melted together, pyridine (2 drops) was added, and the mixture heated on the steam-bath for 6 hr. The resultant gum solidified on trituration with dilute aqueous sodium hydroxide and separated from aqueous methanol in pale-yellow prisms of 1-p-*chlorophenoxy*-3-o-*formylphenoxypropan*-2-*ol*, m. p. 97—99° (Found : C, 62·7; H, 5·0; Cl, 11·8. $C_{16}H_{15}O_4Cl$ requires C, 62·6; H, 4·9; Cl, 11·6%).

Condensation of p-*Hydroxybenzaldehyde with Epichlorohydrin.*—This yielded 1-chloro-3-*p*-formylphenoxypropan-2-ol which formed a 2 : 4-*dinitrophenylhydrazone* in alcoholic hydrochloric acid. This separated from glacial acetic acid in small, dark-red shining plates, m. p. 209—212° (Found : N, 14·5; Cl, 9·4. $C_{16}H_{15}O_6N_4Cl$ requires N, 14·1; Cl, 9·0%).

TABLE 2. 1-*Aryloxy*-3-*chloropropan*-2-*ols* (I).

No.	B. p. (°/mm.)	n_D^{20}	Formula	Required (%) C	H	Cl	Found (%) C	H	Cl
1	178/15	1·5413	$C_9H_{11}O_2Cl$	57·9	6·0	19·0	58·5	6·4	18·5
2	104/0·3	1·5363	$C_{10}H_{13}O_2Cl$	59·8	6·5	17·7	59·7	6·5	17·2
3	200/30—35	1·5360					—	—	17·6
4	192/20	1·5349					60·2	6·5	17·4
5	194/15	—	$C_{10}H_{13}O_3Cl$	55·4	6·1	16·4	55·2	6·2	16·6
6	144/0·5	1·5431					55·6	6·1	16·3
7	200/15	1·5413					55·8	6·1	16·4
8	200/20	1·5518	$C_9H_{10}O_2Cl_2$	48·8	4·6	32·1	49·5	4·6	31·5
9	216/30	1·5540					49·4	4·5	—
10	128/0·3	—	$C_9H_{10}O_2ClBr$	40·6	3·8	43·5 *	41·1	4·3	42·5 *
11	138/0·3	1·5723					40·8	3·8	44·1 *
12	130/0·1	—	$C_9H_{10}O_2ClI$	34·6	3·2	52·0 *	35·1	3·4	51·2 *
13	160/0·5	1·5650	$C_9H_{10}O_4NCl$ [a]	46·6	4·4	15·3	46·5	4·5	15·4 *
15	176/0·2	1·5900					46·9	4·4	15·3
16	172/0·1	—	$C_9H_8O_2ClBr_3$	25·5	1·9	65·1 *	26·3	2·3	64·8 *
17	148/0·6	1·5641	$C_9H_9O_2Cl_3$	42·3	3·5	41·7	42·4	3·5	—
18	166/0·3	—	$C_{10}H_{10}O_2NCl$ [b]	56·7	4·8	16·8	56·9	4·6	—
19	164/0·1	—	$C_{10}H_{11}O_3Cl$	55·9	5·2	16·5	56·5	5·2	15·7
20	178/0·3	—					56·3	5·5	16·2
21	158/0·1	—	$C_{12}H_{15}O_4Cl$	55·7	5·9	13·7	55·3	5·6	13·6
22	158/0·1	—	$C_{13}H_{13}O_2Cl$	65·9	5·5	15·0	65·4	5·5	15·5
23	174/0·2	—					66·4	5·4	—
24	106/0·1	1·5231	$C_{13}H_{19}O_2Cl$	64·3	7·9	14·6	64·7	7·8	14·3
25	120/0·1	1·5222					—	—	14·4
26	136/0·5	—	$C_{10}H_{12}O_2Cl_2$	51·0	5·2	30·2	51·1	5·3	30·1
27	190/1·0	—	$C_{12}H_{13}O_4Cl_3$	44·0	4·0	32·5	44·6	3·9	31·7

* Total halogen. [a] Found : N, 6·3 (no. 13), 6·0 (no. 15). Reqd. : N, 6·1%. [b] Found : N, 6·2. Reqd. : N, 6·6%.

Condensation of Catechol with Epichlorohydrin.—(i) *With* 1 *mol. of epichlorohydrin.* (a) To a hot solution of catechol (110 g.) in epichlorohydrin (92·5 g.), pyridine (1 ml.) was added and the solution heated on the steam-bath for 2 hr., with cooling to keep the temperature below 105°. The mixture was distilled directly *in vacuo*, yielding the following fractions : (*a*) 13·5 g. of crude glycerol dichlorohydrin, b. p. <70°/0·2 mm., (*b*) 20 g. of unchanged catechol, b. p. 80—90°/0·1—0·2 mm., (*c*) 97·5 g., b. p. 120—140°/0·1—0·3 mm., (*d*) 31·5 g., b. p. 180°/0·2—0·3 mm., and (*e*) 10 g., b. p. >220°/0·2—0·5 mm. The residue was beginning to decompose.

Fraction (*c*) solidified and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), yielding white needles of o-(3-*chloro*-2-*hydroxypropyl*)*phenol*, m. p. 88—90° (Found : C, 53·6; H, 5·6; Cl, 17·7. $C_9H_{11}O_3Cl$ requires C, 53·3; H, 5·5; Cl, 17·5%). This (10·1 g.) was refluxed in water (50 ml.) containing potassium carbonate (6·9 g.) for 4 hr. After cooling, the oil was extracted with chloroform, and the extract washed, concentrated, and diluted with light petroleum (b. p. 60—80°), yielding 5-hydroxymethylbenzodioxen (5·7 g.), m. p. 86—92°, not depressed on admixture with an authentic specimen (see below). Acetylation of the chlorohydrin (20 g.) with acetic anhydride (50 ml.) under reflux for 2 hr. yielded the *diacetyl* derivative (20 g.), b. p. 138—140°/0·25 mm. (Found : Cl, 12·1. $C_{13}H_{15}O_5Cl$ requires Cl, 12·4%).

Fraction (*d*) consisted mainly of the bischlorohydrin (X; R = Cl) (see below).

Fraction (*e*) set to a glass which crystallised on remelting. After recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) and then from aqueous methanol, 1 : 3-*di*-o-

hydroxyphenoxypropan-2-ol was obtained as plates, m. p. 172° (Found: C, 65·0; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%).

(b) In a similar experiment the reaction product was dissolved in chloroform, shaken with concentrated hydrochloric acid, and washed with much water to remove excess of catechol. After working up as before a 36% yield of the pure monochlorohydrin, b. p. 140°/0·2 mm., was obtained.

(ii) *With 0·86 mol. of epichlorohydrin.* A mixture of catechol (2·45 mol.), epichlorohydrin (2 mol.), and piperidine acetate (2 g.) was heated at 95° for 6 hr. (initial cooling to keep the temperature below 115°). Treatment as in (i,a) yielded (*a*) 184 g. (46%) of pure monochlorohydrin, b. p. 140°/0·2 mm., (*b*) 18 g. of (X; R = Cl), b. p. 180°/0·2 mm., and (*c*) 70 g., b. p. >220°/0·2 mm., which yielded (III; Ar = C_6H_4·OH) (18 g.) and non-crystalline complex products which were not investigated further.

(iii) *With 2 mols. of epichlorohydrin.* A mixture of catechol (33 g.) and epichlorohydrin (55·5 g.) containing pyridine (0·5 ml.) was heated on the steam-bath for 4 hr. (max. temp. 103°). Low-boiling material was removed at reduced pressure and the residue distilled *in vacuo*, yielding (*a*) 26 g. (50%), b. p. 120°/0·1 mm., and (*b*) 20 g. (23%), b. p. 186°/0·1 mm. Fraction (*a*) crystallised from ethyl acetate–light petroleum (b. p. 60—80°) and then from benzene–light petroleum (b. p. 40—60°), yielding 2-hydroxymethylbenzodioxen in white prismatic needles, m. p. 90—92° (Found: C, 65·2; H, 6·1. Calc. for $C_9H_{10}O_3$: C, 65·0; H, 6·1%), m. p. strongly depressed on admixture with the monochlorohydrin. Fraction (*b*), on redistillation, had b. p. 166°/0·05 mm. Crystallisation from benzene–light petroleum (b. p. 60—80°) and then from ether–light petroleum (b. p. 40—60°) yielded o-*di*-(3-*chloro*-2-*hydroxypropyl*)*benzene* (X; R = Cl) in needles, m. p. 79° (Found: Cl, 23·8. $C_{12}H_{16}O_4Cl_2$ requires Cl, 24·1%). When this was stirred vigorously for 30 min. with a slight excess of aqueous-alcoholic potassium hydroxide it was converted into o-*di*-(2 : 3-*epoxypropyl*)*benzene*, obtained after two distillations *in vacuo* as an oil, b. p. 132—140°/0·2 mm. (Found: C, 64·6; H, 6·5. $C_{12}H_{14}O_4$ requires C, 64·8; H, 6·4%). The oil solidified gradually and then crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 44—46°. This ether (6·7 g.) was condensed with *n*-butylamine (5·25 g.) by warm benzene–light petroleum (b. p. 60—80°), giving o-(3-n-*butylamino*-2-*hydroxypropyl*)*benzene*, needles (from ethyl acetate), m. p. 120° (Found: C, 64·9; H, 9·7; N, 8·2. $C_{20}H_{36}O_4N_2$ requires C, 65·2; H, 9·9; N, 7·6%).

(iv) *With 4 mols. of epichlorohydrin.* (a) When a solution of catechol (55 g.) in epichlorohydrin (185 g.) containing piperidine hydrochloride (0·5 g.) was left at room temperature for 39 days and the product distilled *in vacuo*, the diether (X; R = Cl) was obtained in 74% yield, b. p. 180°/0·1 mm.

(b) The mixture used in the preceding example was heated on the steam-bath for 20 hr. After removal of excess of epichlorohydrin at reduced pressure, distillation of the residue *in vacuo* yielded the benzodioxen (43 g., 52%), b. p. 126—128°/0·5 mm., m. p. 90—92° [from benzene–light petroleum (b. p. 40—60°)], a complex mixture of epoxides and chlorohydrins (20·2 g.), b. p. 164°/0·5 mm., and the diether (X; R = Cl) (15·5 g.), b. p. 194°/0·5 mm.

(v) *With 2·2 mols. of epichlorohydrin, and sodium hydroxide as catalyst.* A solution of catechol (55 g.) in epichlorohydrin (102 g.) was treated with sodium hydroxide (0·5 g.) dissolved in a few drops of water, and the mixture left in an atmosphere of nitrogen for 12 days. After washing and concentration at reduced pressure, the resultant residue was distilled *in vacuo*, yielding the monochlorohydrin (34·4 g., 34%), b. p. 164°/0·5 mm., identified by conversion into (IX), and the bischlorohydrin (71·7 g., 49%), b. p. 194°/0·5 mm., m. p. and mixed m. p. 78—79° after crystallisation as previously.

Reaction of o-(3-*Chloro*-2-*hydroxypropyl*)*phenol with Bases.*—A solution of the chlorohydrin (15 g.) in ethanol (50 ml.) was treated with aqueous ammonia (*d* 0·880; 60 ml.) and the solution refluxed gently for 3 hr., then concentrated at reduced pressure. Water (50 ml.) was added and the mixture extracted with chloroform (3 × 50 ml.). The aqueous extract was acidified with concentrated hydrochloric acid (25 ml.) and evaporated on the steam-bath. The pink crystalline material which separated (6 g.; m. p. *ca.* 168°) was collected and washed with cold ethanol. Repeated crystallisation from ethanol–light petroleum (b. p. 60—80°) yielded needles of o-(3-*amino*-2-*hydroxypropyl*)*phenol hydrochloride*, m. p. 177—180° (Found: C, 48·9; H, 6·2; N, 6·5; Cl, 16·2. $C_9H_{14}O_3NCl$ requires C, 49·2; H, 6·4; N, 6·4; Cl, 16·2%). The original chloroform extract was washed, concentrated to *ca.* 25 ml., and diluted with light petroleum (b. p. 60—80°). The solids which separated (6 g.) were purified by crystallisation from benzene–light petroleum (b. p. 40—60°), to give needles of the benzodioxen (IX), m. p. and mixed m. p. 90—92°.

A solution of the monochlorohydrin (10·1 g.) and piperidine (12·75 g.) in ethanol (20 ml.) was

refluxed for 8 hr. After concentration at reduced pressure the gummy residue was converted into the hydrochloride. Crystallisation from methanol–ethyl acetate gave o-(2-*hydroxy*-3-*piperidinopropyl*)*phenol hydrochloride* (6·5 g.) as fawn-coloured needles (Found: N, 4·7; Cl, 12·5. $C_{14}H_{22}O_3NCl$ requires N, 4·9; Cl, 12·3%).

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