RESEARCH PAPERS

ARYLOXYPROPANE DERIVATIVES

PART I. THE SYNTHESIS OF 1-*p*-CHLORO- AND 1-*p*-NITROPHENOXY-3-DICHLOROACETAMIDOPROPAN-2-OL

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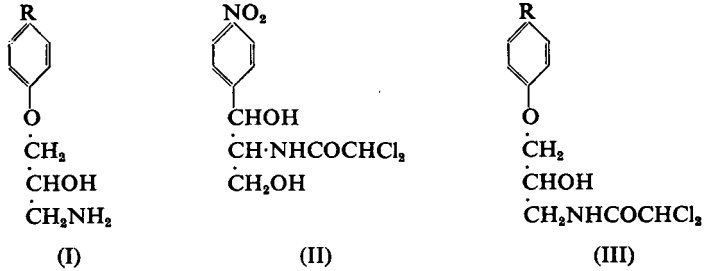
THE synthesis of aryloxypropanol derivatives of potential chemotherapeutic value has been the subject of systematic study in these laboratories during the past few years. Early work, initiated by Dr. W. Bradley, led to the preparation and pharmacological examination of numerous aryloxypropanediol derivatives and resulted in the discovery of the muscle-relaxing properties of 1-*o*-toloxypropane-2:3-diol (mephenesin)[1,2] and the antibacterial and antifungal properties of 1-*p*-chlorophenoxypropane-2:3-diol (chlorphenesin)[3]. In extending these observations we selected the 1-aryloxy-3-aminopropan-2-ol structure (I; R=H) for prior study.

Our first objective was the preparation of 1-*p*-chlorophenoxy-3-dichloroacetamidopropan-2-ol (III; R = Cl), an analogue of chlorphenesin which also bears a formal structural resemblance to the antibiotic chloramphenicol (II). To this end glycide *p*-chlorophenyl ether was condensed with aqueous ethanolic ammonium hydroxide (cf. Boyd[4]) to give 3-amino-1-*p*-chlorophenoxypropan-2-ol (I; R = Cl) admixed with the corresponding secondary base which separated from the mixture on cooling. By removal of the latter, followed by addition of concentrated hydrochloric acid, 3-amino-1-*p*-chlorophenoxypropan-2-ol hydrochloride



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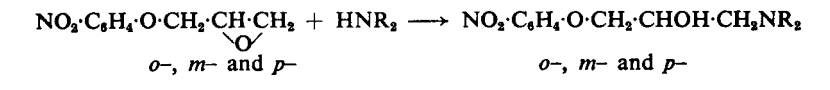

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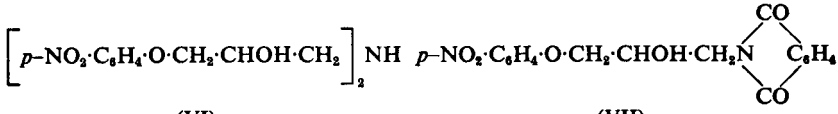

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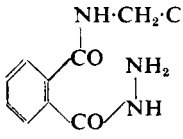

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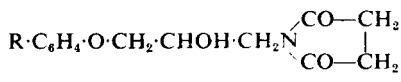

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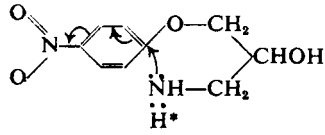

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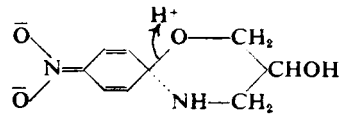

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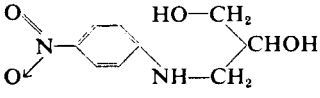

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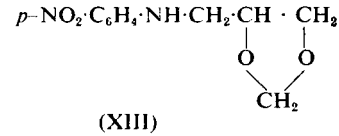

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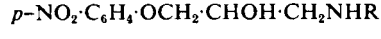

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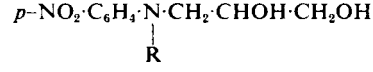


(XV)

was obtained in a yield of 28 per cent. The constitution assigned to this compound was confirmed by reaction with aqueous sodium cyanate when 1-*p*-chlorophenoxy-2-hydroxypropylurea was formed in excellent yield. Basification of the hydrochloride furnished the free amine, which was converted into the desired 1-*p*-chlorophenoxy-3-dichloroacetamido-propan-2-ol (III; R = Cl) by reaction with methyl dichloroacetate. 1-*o*-Chlorophenoxy-, 1-*p*-bromophenoxy-, 1-*p*-iodophenoxy, 1-*p*-cyano-phenoxy-, 1-*o*-toloxy- and 1-phenoxy-3-dichloro acetamidopropan-2-ol were obtained in a similar way.

We next turned our attention to the preparation of 3-dichloroace-tamido-1-*p*-nitrophenoxypropan-2-ol (III; R = NO_2; cf. II). By reacting glycide *p*-nitrophenyl ether[5] (IV; R = *p*-NO_2) with ammonia, however, a bright yellow crystalline *product A* was obtained which, though bearing the right empirical formula for (V; R = H) was clearly not the required compound. Thus attempted dichloroacetylation with methyl dichloro-acetate proved unsuccessful, even when the components were heated together for 40 hours at 140° C. The more vigorous dichloroacetylating agent pentachloroacetone[6] was likewise without effect. Boiling acetic anhydride gave a product which appeared to be the triacetyl and not the expected diacetyl-derivative. Hydrogen chloride in ethanolic solution gave a deep yellow coloured hydrochloride which failed to pass into a urea derivative on treatment with sodium cyanate and largely reverted into the original base on drying at 90° C. The bright yellow colour of the material was likewise difficult to reconcile with (V; R = H) as both 3-dimethylamino- (V; R = Me; Fourneau[7]) and 3-piperidino-1-*p*-nitrophenoxypropan-2-ol (V; R_2 = : C_5H_{10}) (see exptl.; also prepared

independently by Ing and Ormerod[8]) are only faintly yellow. Similar results were obtained employing glycide *o*-nitrophenyl ether[9], reaction with ammonia leading to formation of an orange *product B*, $C_9H_{12}O_4N_2$, which was clearly the *o*-nitro-analogue of *product A* (above). Glycide *m*-nitrophenyl ether, in contrast, behaved in the expected manner to give 3-amino-1-*m*-nitrophenoxypropan-2-ol (V; R = H), readily converted into 3-dichloroacetamido-1-*m*-nitrophenoxypropan-2-ol. Reaction of *p*-nitro (IV) with only one equivalent of ammonia led to the formation of the pale yellow secondary base (VI) in *ca.* 50 per cent. yield.

An alternative route to aryloxypropanolamines of type (V) had previously been described by Ing and Ormerod[8] who employed phthalimido-derivatives (cf. VII) as intermediates for their preparation. By heating glycide *p*- nitrophenyl ether (IV) with phthalimide in ethanolic solution in the presence of pyridine as catalyst (cf. Bradley, Forrest and Stephenson[10]), 2-hydroxy-1-*p*-nitrophenoxy-3-phthalimidopropane (VII) was obtained. Reaction with hydrazine (cf. Ing and Manske[11]) led to the formation of the substituted hydrazide (VIII) which was converted by acidolysis into the hydrochloride of the required 3-amino-1-*p*-nitrophenoxypropan-2-ol (V; R = H).

A more convenient synthesis of (V) was later discovered in which glycide *p*-nitrophenyl ether is condensed with succinimide to give the succinimido-derivative (IX; R = *p*-NO_2) which, on submission to acidolysis, gives the hydrochloride of (V; R = H) in excellent yield. The method appears to have wide applicability and was extended in the present series to the substituted succinimides listed in Table V. Reaction of (IX) with hydrazine led to the formation of the substituted hydrazide analogous to (VIII) which, on acidolysis, passed into the corresponding amine (cf. V; R = H), and succinoyl hydrazide. Separation of these two components offered difficulty, however, and direct acidolysis of (IX) to (V; R = H) is preferred.

The constitution assigned to *p*-NO_2 (V; R = H) hydrochloride was confirmed by treatment with sodium cyanate when 2-hydroxy-1-*p*-nitrophenoxypropyl urea was obtained and by condensation with anisaldehyde when *p*-methoxybenzylidene-2-hydroxy-3-*p*-nitrophenoxypropylamine was formed. Reaction with methyl dichloroacetate furnished 3-dichloroacetamido-1-*p*-nitrophenoxypropan-2-ol (III; R = NO_2). The corresponding *o*-nitro analogue was similarly prepared through (IX; R = *o*-NO_2).

During unsuccessful attempts to prepare (III; R = NO_2), Caldwell and Schweiker[12] nitrated 2-acetoxy-3-phthalimido-1-phenoxypropane, obtaining the mixed 1-*p*-nitrophenoxy- and 1-*o*-nitrophenoxy derivative (cf. VII). Fission of the mixture with hydrazine, followed by acidolysis, however, failed to give (V; *p*- and *o*-), products identical with our *products A* and *B* being obtained. To these the constitution of *p*-nitro- (XII) and *o*-nitro-2:3-dihydroxypropyl aniline was independently assigned, their formation from (VII; *o*- and *p*-nitro-) being interpreted as proceeding *via* a Smiles rearrangement. We fully concur with this conclusion and in support thereof find that *products A* and *B* may be

obtained by the condensation of *p*- and *o*-nitroaniline with glycidol, a reaction which, *inter alia*, establishes their structure. In addition, the ultra-violet absorption spectra of the compounds closely resemble those of *p*- and *o*-nitroaniline, but differ sharply from those of the corresponding nitrophenols (see Table VI). *Product A* passes into the dioxolane (XIII) on treatment with formaldehyde.

The Smiles rearrangement is known to be catalysed by alkaline reagents which, in the present case, would effect removal of the hydrogen atom in (X) marked with an asterisk (*) to give the mesomeric cation (XI) and thence (XII). Formation of the "abnormal" *product A* (XII) from (V; R = H), (VII) or (IX) under the action of alkaline reagents thus receives a satisfactory explanation.

In contrast to its behaviour with ammonia when (XII) is obtained (*vide supra*), reaction of glycide *p*-nitrophenyl ether (IV) with methyl-, ethyl- and *n*-butylamine leads directly to the formation of the *p*-nitrophenoxy-*N*-alkyl propanolamines (XIV; R = Me, Et and *n*-Bu) owing to stabilisation of these structures by the + I effects of the alkyl groups. By treatment with traces of alkali, however, the compounds readily undergo the Smiles rearrangement to give the corresponding *p*-nitro-2:3-dihydroxypropyl alkyl anilines (XV; R = Mr, Et and *n*-Bu) in nearly quantitative yield.

Experimental

M.pts. are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

The glycide aryl ethers were prepared by the following improved procedure[5,6,13]:

Epichlorhydrin (1·5 g. mole) was added at <20° C. to a solution of the phenol (1 g. mole) in water (1 l.) containing sodium hydroxide (1·2 g. mole) and the mixture stirred vigorously for 10 to 20 hours at room temperature. The product was extracted with chloroform (× 3), the extracts bulked, treated with a few drops of acetic acid, and washed thoroughly with water. After removal of the solvent, the residues were purified by distillation under reduced pressure and crystallisation from light petroleum or ether-light petroleum.

The *products* obtained are listed in Table I.

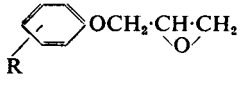


TABLE I

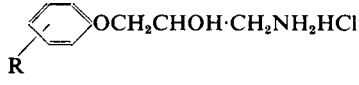
R	M.pt. ° C.	Formula	Found C per cent.	Found H per cent.	Found per cent.	Theory C per cent.	Theory H per cent.	Theory per cent.
p-Cl	32	$C_9H_9O_2Cl$	58·6	4·9	Cl, 19·3	58·5	4·9	Cl, 19·2
o-Cl	b.pt. 118°/1 mm.	$C_9H_9O_2Cl$	58·2	4·9		58·5	4·9	
p-Br	51 to 52	$C_9H_9O_2Br$	47·0	4·0	Br., 35·4	47·1	4·0	Br., 34·9
p-I	72 to 73	$C_9H_9O_2I$	38·9	3·3	I, 46·3	39·1	3·3	I, 46·0
p-CN	67	$C_{10}H_9O_2N$	68·4	5·1	N, 7·8	68·6	5·2	N, 8·0
m-NO_2	62	$C_9H_9O_4N$	55·9	4·7	N, 6·9	55·4	4·7	N, 7·2
p-NHAc	122	$C_{11}H_{13}O_3N$	63·9	6·3	N, 6·8	63·8	6·3	N, 6·8

Conversion of the glycide aryl ethers into the corresponding *aryloxypropanolamines* was achieved as indicated in the following example: Glycide *p*-bromophenyl ether (80 g.) in ethanol (400 ml.) and solution of ammonia (0·880) (400 ml.) was heated on the steam bath for 1½ hours. After allowing to cool the separated solids (secondary amine; *vide infra*) were collected and the mother liquors concentrated somewhat to remove ammonium hydroxide. After addition of ethanol to remove turbidity, concentrated hydrochloric acid in equal volume was added and the precipitated 3-amino-1-*p*-bromophenoxypropan-2-ol hydrochloride collected after standing overnight. Purification was achieved from ethyl acetate-methanol.

The foregoing solids, on crystallisation from aqueous ethanol, furnished di(*p*-bromophenoxypropanol) amine.

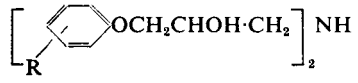
The primary and secondary amines obtained in this way are listed in Tables II and III.

TABLE II



R	M.pt. ° C.	Formula	Found C per cent.	Found H per cent.	Found N per cent.	Found Cl per cent.	Theory C per cent.	Theory H per cent.	Theory N per cent.	Theory Cl per cent.
o-Cl	225	$C_9H_{13}O_2NCl_2$	45·6	5·5	—	30·0	45·4	5·5	—	29·8
p-Br	*ca.* 185	$C_9H_{13}O_2NBrCl$	38·4	4·5	4·9	—	38·2	4·6	5·0	—
p-I	*ca.* 250 (*d*)	$C_9H_{13}O_2NClI$	33·0	4·0	4·3	—	32·8	4·0	4·3	—
o-OMe	173 to 175	$C_{10}H_{14}O_3NCl$	51·1	6·7	5·7	15·2	51·4	6·9	6·0	15·2
m-NO_2	212 to 213	$C_9H_{13}O_4N_2Cl$	43·7	5·1	11·2	14·2	43·4	5·3	11·3	14·3
o-NO_2	157 to 158	$C_9H_{13}O_4N_2Cl$			10·8	14·2			11·3	14·3
p-NO_2	125	$C_9H_{13}O_4N_2Cl$	43·6	5·4	11·6	14·1	43·4	5·3	11·3	14·3
p-Cl	*ca.* 182	$C_9H_{13}O_2NCl_2$	45·7	5·4	5·8		45·4	5·5	5·9	

TABLE III



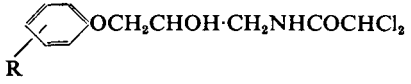
R	M.pt. ° C.	Formula	Found C per cent.	Found H per cent.	Found N per cent.	Theory C per cent.	Theory H per cent.	Theory N per cent.
p-NO_2	133 to 137	$C_{18}H_{21}O_8N_3$	52·5	5·1	10·3	53·0	5·2	10·3
o-OMe	114	$C_{20}H_{27}O_6N$	63·2	7·4	—	63·6	7·2	—
p-I	168 to 174	$C_{18}H_{21}O_4NI_2$	38·4	3·9	2·6	38·0	3·7	2·5
p-Br	127	$C_{18}H_{21}O_4Br_2N$	45·2	4·4	2·6	45·5	4·5	3·0
p-Cl	133	$C_{18}H_{21}O_4NCl_2$	56·2	5·5		55·9	5·5	3·6
o-Cl	92	$C_{18}H_{21}O_4NCl_2$	55·5	5·8		55·9	5·5	

Dichloroacetylation of the aryloxypropanolamine (hydrochlorides) was effected as follows. 3-Amino-1-*p*-chlorophenoxypropan-2-ol hydrochloride (5·95 g.) in ethanol (40 ml.) and anhydrous sodium acetate (2·5 g.) was treated with ethyl dichloroacetate (4 g.) under reflux for 5 hours. After allowing to cool, the mixture was precipitated with water and the product collected and purified from aqueous methanol.

The *dichloroacetyl* derivatives obtained in this way are listed in Table IV.

The 1-aryloxy-2-hydroxypropyl succinimides (IX) were prepared as indicated in the following example. Glycide *p*-nitrophenyl ether (5·83 g.)

TABLE IV

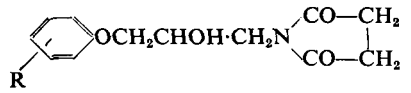


R	M. pt. ° C.	Formula	Found C per cent.	Found H per cent.	Found N per cent.	Found Cl per cent.	Theory C per cent.	Theory H per cent.	Theory N per cent.	Theory Cl per cent.
m-NO_2	134 to 135	$C_{11}H_{12}O_5N_2Cl_2$	40·9	3·7	8·9	21·5	40·9	3·8	8·7	22·0
o-Cl	102 to 104	$C_{11}H_{12}O_3NCl_3$	42·4	3·9	4·2		42·2	3·9	4·5	
o-Me	88	$C_{12}H_{15}O_3NCl_2$	49·8	5·0	4·6		49·3	5·2	4·8	
H	106	$C_{11}H_{13}O_3NCl_2$			4·9				5·0	
p-CN	123 to 125	$C_{12}H_{12}O_3N_2Cl_2$	(48·3)	4·1	9·0	23·0	47·5	4·0	9·2	23·4
o-NO_2	106 to 107	$C_{11}H_{12}O_5N_2Cl_2$	41·2	3·7	8·6	21·7	40·9	3·8	8·7	22·0
p-NO_2	110 to 111	$C_{11}H_{12}O_5N_2Cl_2$	40·8	3·8	9·0	22·4	40·9	3·8	8·7	22·0
p-Cl	115	$C_{11}H_{13}O_3NCl_3$	42·2	4·1	4·5	33·7	42·2	3·9	4·5	34·1

and succinimide (3·0 g.) in ethanol (25 ml.) was treated with 3 drops of pyridine and the mixture gently refluxed for 3 to 4 hours. After allowing to cool the crystalline succinimido-derative was collected and purified from ethyl acetate-light petroleum.

The *products* obtained in this way are listed in Table V.

TABLE V



R	M. pt. ° C.	Formula	Found C per cent.	Found H per cent.	Found N per cent.	Found Cl per cent.	Theory C per cent.	Theory H per cent.	Theory N per cent.	Theory Cl per cent.
m-NO_2	114 to 116	$C_{13}H_{14}O_6N_2$	53·3	5·1	9·5		53·1	4·8	9·5	
p-NHAc	166 to 167	$C_{15}H_{18}O_4N_2$	58·7	6·0	9·2		58·8	5·9	9·2	
H	130	$C_{13}H_{15}O_4N$	62·1	5·9	6·0		62·6	6·1	5·6	
o-NO_2	120	$C_{13}H_{14}O_6N_2$	52·9	4·7	10·1		53·1	4·8	9·5	
p-NO_2	132 to 133	$C_{13}H_{14}O_6N_2$	52·8	5·0	9·4		53·1	4·8	9·5	
p-Cl	115 to 116	$C_{13}H_{14}O_4NCl$	55·3	4·9	4·8	12·3	55·0	5·0	4·9	12·5
o-CH_3	99	$C_{14}H_{17}O_4N$	63·9	6·5	5·3		63·9	6·6	5·3	

Hydrolysis of the succinimides to the aryloxypropanolamine hydrochlorides was performed as indicated in the following example. 2-Hydroxy-1-*p*-nitrophenoxypropyl succinimide (IX; R = *p*-NO_2) (4·0 g.) in hot concentrated hydrochloric acid (20 ml.) was treated with ethanol until solution was complete. After heating under reflux for 6 hours the mixture was evaporated to dryness under reduced pressure. The solid residue was dissolved in a little water and extracted with ether to remove succinic acid. The aqueous liquors were then taken to dryness and the

residual 3-*amino*-2-*hydroxy*-1-*p*-*nitrophenoxypropylamine hydrochloride* purified from ethanol-ethyl acetate-ether.

Reaction of 2-hydroxy-1-*p*-nitrophenoxypropyl succinimide (XI; R = *p*-NO_2) (8·82 g.) in hot ethanol (60 ml.) with aqueous hydrazine hydrate (3 g. of 50 per cent.) at 70° C. for 2 hours led to the formation of *hydrazidosuccin*-(2-*hydroxy*-1-p-*nitrophenoxy*-3-*propyl*) *amide*, m.pt. 160° to 162°. Found: C, 48·0; H, 5·6. $C_{13}H_{18}O_6N_4$ requires C, 47·8; H, 5·6 per cent.

3-p-*Chlorophenoxy*-2-*hydroxypropyl urea* was prepared by treating 3-amino-1-*p*-chlorophenoxypropan-2-ol hydrochloride (3 g.) in water (30 ml.) with sodium cyanate (1·6 g.) in water (20 ml.) containing a trace of ethanol. After warming till solution was complete the mixture was left to stand overnight and the separated plates collected and purified from aqueous ethanol; m.pt. 132° C. Found: C, 49·0; H, 5·1; N, 11·5; Cl, 14·7. $C_{10}H_{13}O_3N_2Cl$ requires C, 49·1; H, 5·4; N, 11·5; Cl, 14·5 per cent. The following were similarly prepared: o-*Chlorophenoxy*-, m.pt. 113° to 115° C. Found: C, 49·3; H, 5·2; N, 11·2; Cl, 14·5 per cent. p-*Bromophenoxy*-, white plates, m.pt. 154° to 155° C. Found: C, 41·9; H, 4·6; N, 9·6. $C_{10}H_{13}O_3N_2Br$ requires C, 41·5; H, 4·5; N, 9·7 per cent p-*Nitrophenoxy*-2-*hydroxypropyl urea*, small shining plates, m.pt. 167° to 169° C. Found: C, 46·5; H, 5·0; N, 16·3. $C_{10}H_{13}O_5N_3$ requires C, 47·0; H, 5·1; N, 16·5 per cent.

p-*Methoxybenzylidene* 2-*hydroxy*-3-*nitrophenoxypropylamine*. 3-Amino-1-*p*-nitrophenoxypropan-2-ol hydrochloride (2 g.) dissolved in ethanol (20 ml.) was treated with anisaldehyde (1·2 g.) and anhydrous sodium acetate (700 mg.) and the mixture heated under reflux for 1 hour. After dilution the precipitated solids were collected and purified from aqueous ethanol. The *anil* formed pale yellow plates, m.pt. 135° C. Found: C, 61·4; H, 5·4; N, 8·1. $C_{17}H_{18}O_5N_2$ requires C, 61·8; H, 5·5; N, 8·5 per cent.

Preparation of p-*nitro*-2:3-*dihydroxypropyl aniline* (XII). (*a*) Glycide *p*-nitrophenyl ether (50 g.) was dissolved in ethanol (400 ml.), solution of ammonia (800 ml. of 0·880) added to the warm solution, and the mixture heated gently on the steam bath for 5 hours. After concentrating somewhat, the separated solids were collected and crystallised from water to give (XII), pale yellow plates (21 g.), m.pt. 126° to 128° C. Found: C, 50·9; H, 5·9; N, 13·1. Calc. for $C_9H_{12}O_4N_2$: C, 50·9; H, 5·7; N, 13·2 per cent. Caldwell and Schweiker[12] give m.pt. 127° to 128° C.

Acetylation with acetic anhydride for 1½ hours under reflux, followed by crystallisation from ethyl acetate-light petroleum, furnished the triacetyl-derivative, pale yellow prismatic needles, m.pt. 118° C. Found: C, 53·8; H, 6·0; N, 8·2. $C_{15}H_{18}O_7N_2$ requires C, 53·3; H, 5·4; N, 8·3 per cent.

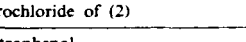
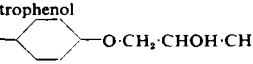
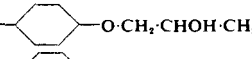
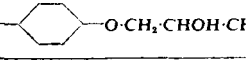
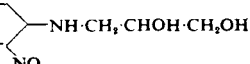
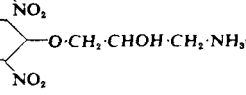
Treatment in ethanol solution with dry hydrogen chloride, followed by dilution with ether, gave bright yellow needles of the *hydrochloride*, m.pt. 125° to 127° C. Found: C, 43·8; H, 5·2; N, 11·0; Cl, 14·2. $C_9H_{13}O_4N_2Cl$ requires C, 43·4; H, 5·3; N, 11·3; Cl, 14·3 per cent.

Reaction in methanol (2·8 g. in 20 ml.) with formaldehyde (5 ml. of 36 per cent.) for 5 hours under reflux, followed by cooling, led to separation of the dioxolane (XIII) which was obtained from water in orange-yellow needles, m.pt. 142° to 144° C. Found: C, 53·6; H, 5·2; N, 12·2. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5 per cent.

(*b*) *p*-Nitroaniline (13·8 g.) was heated with glycidol (14·8 g.) at 170° C. for 3 hours, after which the product was precipitated with water. Purification from dilute ethanol furnished (XII) in very low yield, m.pt. 126° to 128° C., alone or in admixture with an authentic specimen.

TABLE VI

ULTRA-VIOLET ABSORPTION SPECTRA

Compound	max. mμ	$E^{1\%}_{1\,cm.}$	max. mμ	$E^{1\%}_{1\,cm.}$	max. mμ	$E^{1\%}_{1\,cm.}$
1. *p*-Nitroaniline	228	485	378	1140		
2. 	229	412	384	865		
3. Hydrochloride of (2)	230	310	385	730		
4. *p*-Nitrophenol	225	580	313	770		
5. 	224	367	304	503		
6. 	224	400	305	520		
7. 	225	362	305	561		
8. *o*-Nitroaniline	232	1415	275	367	403	400
9. 	232	1130	279	222	425	310
10. 	258	139	320	94·5	—	—

(Determined in *iso*propanol solution)

(*c*) 2-Hydroxy-3-*p*-nitrophenoxypropyl succinimide (IX; R = *p*-NO_2) (5·0 g.) in water (50 ml.) containing sodium hydroxide (1·4 g.) was heated under reflux for 2 hours. After standing overnight the separated yellow solids were collected and purified from aqueous methanol to give (XII); m.pt. 126° to 128° C., alone or in admixture with an authentic specimen.

(*d*) 2-Hydroxy-3-*p*-nitrophenoxypropyl succinimide (5·9 g.) was suspended in hot water and treated with anhydrous sodium carbonate (1·06 g.), when rapid solution occurred followed, after *ca.* 5 minutes, by separation of solids. Water (30 ml.) was then added and the mixture heated under reflux for 90 minutes. Precipitation with concentrated hydrochloric acid (2 ml.) followed by purification of the product from ethyl acetate-light petroleum, furnished 3-*amino*-1-p-*nitrophenoxypropan*-2-*ol half succinate* in almost white needle clusters, m.pt. 119° to 120° C. Found: C, 50·7; H, 5·7; N, 9·2. $C_{13}H_{16}O_7N_2$ requires C, 50·0; H, 5·2; N, 9·0 per cent. Further hydrolysis with alkali gave (XII), identified by m.pt. and mixed m.pt.

(*e*) 3-Amino-1-*p*-nitrophenoxypropan-2-ol hydrochloride dissolved in warm water, was treated with sodium hydroxide solution until alkaline and the mixture left overnight. The separated solids, after purification, yielded (XII), identified by m.pt. and mixed m.pt.

2-*Hydroxy*-3-p-*nitrophenoxypropylphthalimide* (VII).—A mixture of glycide *p*-nitrophenylether (19·5 g.) and phthalimide (14·7 g.) in ethanol (70 ml.) was treated with 3 drops of pyridine and the mixture heated under reflux until complete solution followed by separation of solids had occurred (*ca.* 1 hour). Ethanol (50 ml.) was then added and heating continued for a further 1½ hours. After allowing to cool the separated solids (32 g.) were collected and purified from ethanol. The *product* formed white, fluffy needles, m.pt. 176° C. Found: C, 59·7; H, 4·2; N, 7·6. $C_{17}H_{14}O_6N_2$ requires C, 59·6; H, 4·1; N, 8·2 per cent.

On treating the foregoing phthalimide (3.42 g.) in boiling ethanol (25 ml.) with 50 per cent. hydrazine hydrate (1 g.; *ca.* 1 mol.), rapid solution occurred followed by separation of (VIII) (88 per cent. yield) as a pale yellow microcrystalline solid, m.pt. 212° to 213° C. (decomp.). Found: C, 54·5; H, 4·8; N, 14·9. $C_{17}H_{18}O_6N_4$ requires C, 54·5; H, 4·9; N, 15·0 per cent. Hydrolysis of (VIII) by warming with ethanolic hydrochloric acid led to the separation of phthalyl hydrazide, which was removed. Concentration of the mother liquors, followed by dilution with ether, led to the separation of 3-amino-1-*p*-nitrophenoxypropan-2-ol hydrochloride, m.pt. 125° to 127° C. Found: C, 43·8; H, 5·1; N, 10·8; Calc. for $C_9H_{13}O_4N_2Cl$: C, 43·4; H, 5·3; N, 11·3; Cl, 14·3 per cent.

Hydrolysis of the phthalimide (VII) (6·84 g.) in water (25 ml.) with sodium hydroxide (2·4 g.) for 30 minutes on the steam bath led to the formation of *p*-nitro-2:3-dihydroxypropylaniline (XII), which separated in high yield on cooling. (VII) was recovered unchanged after heating under reflux for 8 hours with concentrated hydrochloric acid.

2-*hydroxy*-3-o-*toloxypropylphthalimide* was prepared as for the corresponding *p*-nitro-analogue (VII). It formed small white needles, m.pt. 118° C. Found: C, 69·8; H, 5·9; N, 5·1. $C_{18}H_{17}O_4N$, requires C, 69·4; H, 5·5; N, 4·5 per cent.

On treating this phthalimide (12·4 g.) in boiling ethanol (50 ml.) with 50 per cent. hydrazine hydrate (8 g.; *ca.* 2 mol.) and heating for a short while, the product (12·5 g.) separated from the hot solution and was purified by recrystallisation from ethanol, forming white fluffy needles, m.pt. 208° (decomp.). Found: C, 63·3; H, 6·5; N, 12·2. $C_{18}H_{21}O_4N_3$, requires C, 62·9; H, 6·2; N, 12·2 per cent.

Hydrolysis of this hydrazide (11 g.) by refluxing in ethanol (100 ml.), saturated with hydrochloric acid gas, yielded phthalyl hydrazide (5·1 g.), m.pt. 335° C., and 2-hydroxy-3-*o*-toloxypropylamine hydrochloride (6·35 g.), m.pt. (130°) to 252° C., identical with a specimen prepared by the method of Boyd[4].

Preparation of o-*nitro*-2:3-*dihydroxypropylaniline*.—Method (*a*) (as used for the *p*-nitro-analogue) furnished *o*-nitro-2:3-dihydroxypropylaniline, m.pt. 120° C. Found: C, 60·0; H, 5·7; N, 13·2. Calc. for $C_9H_{12}O_4N_2$: C, 50·9; H, 5·7; N, 13·2 per cent. Caldwell and Schweiker[12] give m.pt.

117° to 118° C. Methods (*b*) and (*c*) gave the same product, identified by m.pt. and mixed m.pt. The yield of *ca.* 50 per cent. obtained by method (*b*) was substantially higher than in the case of the corresponding *p*-nitro analogue.

1-*p-Nitrophenoxy*-2-*hydroxy*-3-*piperidinopropane*, prepared by heating glycide *p*-nitrophenyl ether (5·85 g.) in benzene (40 ml.) with piperidine (3·2 ml.) for 1 hour under reflux, separated from aqueous methanol in white nodules, m.pt. 80° to 82° C. Found: N, 10·2. Calc. for $C_{14}H_{20}O_4N_2$: N, 10·0 per cent. Ing and Ormerod[9] give a m.pt. of 79° to 80° C. to this compound.

2-*Hydroxy*-3-*methylamino*-1-p-*nitrophenoxypropane* (XIV; R = Me).—Glycide *p*-nitrophenyl ether was mixed with ethanolic methylamine (100 ml. of 33 per cent.) and the mixture heated in an open conical flask for 2 hours on the steam bath. The gummy residue, on solution in ethyl acetate and dilution with light petroleum (b.pt. 40° to 60° C.) deposited 2-*hydroxy*-3-*methylamino*-1-p-*nitrophenoxypropane* as yellow needles, m.pt. 96° C. Found: C, 52·9; H, 5·9; N, 12·1. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4 per cent.

3-*Ethylamino*-2-*hydroxy*-1-p-*nitrophenoxypropane* (XIV; R = Et) separated from ethyl acetate-light petroleum (b.pt. 60° to 80° C.) in white needles, m.pt. 120° C. Found: C, 55·4; H, 6·5; N, 11·5. $C_{11}H_{16}O_4N_2$ requires C, 55·0; H, 6·7; N, 11·7 per cent. The *hydrochloride*, after purification from ethanol-ethyl acetate, formed shining needles, m.pt. 165° to 167° C. Found: N, 10·0; Cl, 12·8. $C_{11}H_{16}O_4N_2$·HCl requires N, 10·1; Cl, 12·8 per cent.

3-*Butylamino*-2-*hydroxy*-1-p-*nitrophenoxypropane* (XIV; R = Bu) formed fluffy needles, m.pt. 99° to 100° C. Found: C, 58·8; H, 7·5; N, 10·0. $C_{13}H_{20}O_4N_2$ requires C, 58·2; H, 7·5; N, 10·4 per cent. The *hydrochloride*, after purification from methanol-ether, formed small, shining plates, m.pt. 155° to 156° C. Found: C, 51·7; H, 7·1; N, 9·0; Cl, 11·2. $C_{13}H_{21}O_4N_2Cl$ requires C, 51·2; H, 7·0; N, 9·2; Cl, 11·7 per cent.

N-2:3-*Dihydroxypropyl methyl*-p-*nitroaniline* (XV; R = Me).—(*a*) 1 G. of (XIV; R = Me), dissolved in the minimum quantity of hot ethanol, was treated with a few drops of sodium hydroxide solution. The deep orange mixture was warmed for a few minutes and then diluted with water, when separation of crystalline material occurred. Purification from ethyl acetate furnished N-2:3-*dihydroxypropyl methyl* p-*nitroaniline*, small bright yellow needles, m.pt. 145° to 147° C. Found: C, 53·3; H, 6·3; N, 12·4. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4 per cent.

(*b*) A mixture of *p*-nitromethyl aniline (10 g.) and glycidol (20 g.) was heated at 140° to 150° C. for 1 hour, when it was poured into water, diluted until turbid and then treated dropwise with ethanol until clear. After allowing to stand overnight the separated material was collected and crystallised from ethyl acetate (charcoal) to give (XV; R = Me), m.pt. 144° to 146° C., alone or in admixture with a sample prepared by method (*a*).

N-2:3-*Dihydroxypropyl ethyl* p-*nitroaniline* (XV; R = Et) was purified from chloroform-light petroleum (b.pt. 60° to 80° C.) to give small,

bright yellow crystals, m.pt. 94° C. Found: C, 54·8; H, 6·6; N, 11·2. $C_{11}H_{16}O_4N_2$ requires C, 55·0; H, 6·7; N, 11·7 per cent.

N-2:3-*Dihydroxypropyl*-n-*butyl* p-*nitroaniline* formed fluffy yellow needles, m.pt. 77° to 79° C. Found: C, 58·2; H, 7·7; N, 10·4. $C_{13}H_{20}O_4N_2$ requires C, 58·2; H, 7·5; N, 10·4 per cent.

Summary

1. The synthesis of 1-*p*-chloro- and 1-*p*-nitrophenoxy-3-dichloroacetamidopropan-2-ol is reported.

2. 3-Amino-1-*p*-nitrophenoxypropan-2-ol, required for the preparation of the latter compound, is shown to undergo a Smiles rearrangement on treatment with alkali, to give 2:3-dihydroxypropyl *p*-nitroaniline.

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