RESEARCH PAPERS

ARYLOXYPROPANE DERIVATIVES

PART III. SOME ARYLOXYPROPANOLUREAS

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AN attempt to prepare 2-hydroxy-3-*o*-toloxypropylurea (I; Ar = R; X = $NH{\cdot}CO{\cdot}NH_2$) by heating 2-hydroxy-3-*o*-toloxypropyl chloride (I; Ar = R; X = Cl) with 4 molar equivalents of urea at 180° to 190° for 1 hour[1] led to the formation of 5-*o*-toloxymethyloxazolid-2-one (II) in *ca.* 30 per cent yield. This was improved by using 1:2-epoxy-3-*o*-toloxypropane in place of the chloride and was raised to *ca.* 60 per cent by heating the epoxide with urethane at 195° for 1 hour in the presence of a catalytic quantity of potassium hydroxide. The oxazolidone (II) was additionally prepared[2] by heating the chloride (I; Ar = R; X = Cl) with potassium cyanate in aqueous ethanolic solution. Its structure followed from its formation from 2-hydroxy-3-*o*-toloxypropylamine (I; Ar = R; X = NH_2) and phosgene in benzene solution.

The required urea (I; Ar = R; X = $NH{\cdot}CO{\cdot}NH_2$) was finally obtained by heating the amine (·HCl) (I; Ar = R; X = NH_2) with potassium cyanate in aqueous solution. On reaction with ethyl sodiomalonate in boiling ethanol it passed into *N*(2-hydroxy-3-*o*-toloxypropyl)-barbituric acid. Reaction of the amine (·HCl) (I; Ar = R; X = NH_2) with potassium thiocyanate furnished 2-hydroxy-3-*o*-toloxypropylthiourea (I; Ar = R; X = $\cdot NH{\cdot}CS{\cdot}NH_2$).

When 3-*o*-toloxypropanediol (mephenesin) (I; Ar = R; X = OH) was heated with urea[3] at 190° for 5 hours the product consisted of unchanged material admixed with mephenesin carbonate, also prepared in nearly quantitative yield by condensing mephenesin with methyl or ethyl carbonate on the steam bath in the presence of sodium ethoxide as catalyst.

Fischer and Krämer[4] have described the condensation of 2-hydroxy-3-phenoxypropyl chloride with ethyl sodiomalonate to give a product hydrolysed to the lactone (III; Ar = Ph; R = H). We now find that this reaction proceeds more readily employing 1:2-epoxy-3-phenoxypropane in place of the propyl chloride, when 3-ethoxycarbonyl-2-oxo-5-phenoxymethyltetrahydrofuran (III; Ar = Ph; R = Et) is readily obtained in good yield. 1:2-Epoxy-3-*o*-toloxypropane likewise yields the *o*-toloxy analogue (III; Ar = *o*-tolyl; R = Et), directly converted into 5(2′-hydroxy-3′-*o*-toloxypropyl)-barbituric acid by reaction with urea. Ethyl sodioacetamidomalonate may also be employed in these condensations to give with 1:2-epoxy- or 1-chloro-2-hydroxy-3-*o*-toloxypropane an intermediate ester hydrolysed by hydrochloric acid to 3-amino-2-oxo-5-*o*-toloxymethyltetrahydrofuran (IV). Reaction of the last compound with

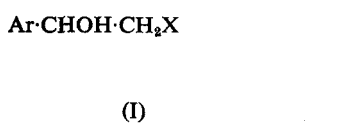
potassium cyanate gives 5(2′-hydroxy-3′-*o*-toloxypropyl) hydantoin (V).

By condensing *p*-ureidophenol with 2:3-epoxypropyl chloride in boiling ethanol-sodium ethoxide, Speckam[5] obtained a product formulated as 1:2-epoxy-3-(*p*-ureidophenoxy) propane (VI; Ar = R′). We now find that this material is actually 1:3-bis (*p*-ureidophenoxy)-2-hydroxypropane (R′·CHOH·R′), the authentic epoxide (VI; Ar = R′) being readily obtained by condensing *p*-ureidophenol with a large excess (6 moles) of 2:3-epoxypropyl chloride in aqueous alkaline solution. Decrease in the proportion of epoxy chloride employed results in the predominant formation of the bis-compound R′·CHOH·R′. The epoxypropane (VI; Ar = R′) was characterised by condensation with succinimide and phthalimide by methods previously described[6], and by reaction with piperidine and piperazine to give 2-hydroxy-1-piperidino-3-(*p*-ureidophenoxy)-propane (I; Ar = R′; X = NC_5H_{10}) and 1:4-bis (2-hydroxy-3-*p*-ureidophenoxypropyl)-piperazine (VII), respectively.

2-Hydroxy-3-*p*-ureidophenoxypropylurea (I; Ar = R′; X = ·NH·CO·NH_2) was prepared from 3-*p*-acetamido-1:2-epoxypropane (VI; Ar = R″). This was converted into N-(3-*p*-acetamidophenoxy-2-hydroxypropyl)-succinimide (I; Ar = R″; X = –$NC_4H_4O_2$) by reaction with succinimide in ethanolic solution containing a trace of pyridine as catalyst, from which 3-(*p*-aminophenoxy)-2-hydroxypropylamine (dihydrochloride) was obtained by hydrolysis with hydrochloric acid. Condensation with potassium cyanate in aqueous solution gave the urea (I; Ar = R′; X = ·NH·CO·NH_2). 3-*p*-Ureidophenoxypropane-1:2-diol (I; Ar = R′; X = OH)[7] was prepared (i) from the known 3-*p*-acetamidophenoxypropane-1:2-diol by acid hydrolysis, followed by condensation with potassium cyanate and (ii) from *p*-ureidophenol by reaction with 1:2-epoxypropan-3-ol. 1-*p*-Ureidophenoxy-4-oxahexane-2:6-diol (VIII) was similarly obtained by reaction between *p*-ureidophenol and 1-chloro-4-oxahexane-2:6-diol or 1:2-epoxy-4-oxahexan-6-ol (cf. ref. 8), or alternatively from *p*-acetamidophenol by the appropriate reaction sequence.

3-*o*-Ureidophenoxypropan-1:2-diol (I; Ar = R‴; X = OH), 2-hydroxy-3-*o*-ureidophenoxypropylurea (I; Ar = R‴; X = ·NH·CO·NH_2) and 1:3-bis (*o*-ureidophenoxy) propan-2-ol (R‴·CHOH·R‴) were similarly obtained from 3-*o*-acetamidophenoxy-1:2-epoxypropane.

Biological study of the foregoing compounds by Dr. A. David and his colleagues is in progress.



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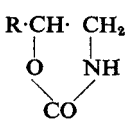

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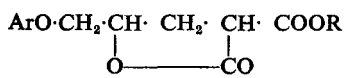

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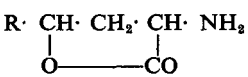

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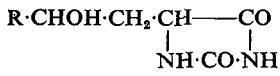

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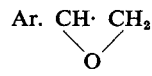

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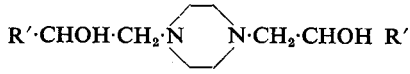

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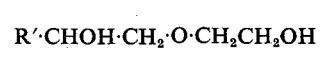

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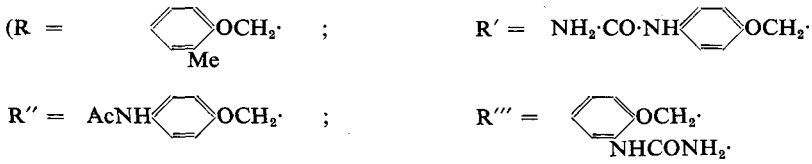

EXPERIMENTAL

5-o-*Toloxymethyl-oxazolid-2-one* (II)

(*a*) A mixture of 2-hydroxy-3-*o*-toloxypropyl chloride (20 g.) and urea (24 g.) was heated at 180° to 190° for 1 hour with occasional shaking. After cooling, the residue was suspended in water and extracted with chloroform. Concentration of the chloroform followed by dilution with light petroleum (b.p. 60° to 80°) yielded the product (6·5 g.), which was purified by crystallisation from ethyl acetate, forming colourless prisms, m.p. 128° to 129°. Found: C, 63·9; H, 6·1; N, 7·1. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3; N, 6·8 per cent.

(*b*) 1:2-Epoxy-3-*o*-toloxypropane (16·4 g.) and urea (7·2 g.) were heated at 175° to 180° and the product (II) (8·1 g.) isolated as in (*a*). The yield was not improved by using up to 4 moles of urea.

(*c*) To a solution of 1:2-epoxy-3-*o*-toloxypropane (16·4 g.) in ethanol (50 ml.) was added powdered sodium cyanate (7·8 g.) followed by concentrated hydrochloric acid (8·6 ml.). After heating under reflux for 4 hours, the mixture was diluted and the product (5·5 g.) isolated by extraction with chloroform.

(*d*) A mixture of 1:2-epoxy-3-*o*-toloxypropane (65·6 g.) and urethane (42·8 g.) was melted and potassium hydroxide (0·5 g.) in methanol (5 ml.) added as catalyst. The mixture was heated at 190° to 195° for one hour and the ethanol which distilled off was collected (23 ml.). The product (49 g.), isolated as in (*a*), had m.p. and mixed m.p. 127° to 128°. Pyridine was less satisfactory than potassium hydroxide as catalyst.

(*e*) A suspension of 2-hydroxy-3-*o*-toloxypropylamine hydrochloride (21·8 g.) in dry benzene (100 ml.) was treated with a solution of phosgene (20 g.) in dry benzene (250 ml.). The mixture was heated on the steam bath for 16 hours and the solvent removed at reduced pressure. The residue was dissolved in water and extracted with chloroform. Concentration of the chloroform extract followed by crystallisation from ethyl acetate-light petroleum (b.p. 60° to 80°) yielded the product (II) (7·5 g.), m.p. 126° to 128°, not depressed on admixture with a sample prepared by method (*a*).

Reaction of Mephenesin with Urea

A mixture of mephenesin (45·5 g.) and urea (30 g.) was heated at 180° to 190° for 5 hours, and then poured into water. The suspension was extracted with chloroform and the extract washed with water. The chloroform was removed and the residue distilled *in vacuo* to yield a mixture of unchanged mephenesin (12·4 g., m.p. 71°), mephenesin carbonate (8·5 g., m.p. 94° to 96°) and 5-*o*-toloxymethyloxazolid-2-one (16 g., m.p. 127° to 129°).

5-*Phenoxymethyloxazolid*-2-*one*, prepared from 1:2-epoxy-3-phenoxypropane and urea as for (II), had m.p. 125° to 127°, after crystallisation from a mixture of chloroform and light petroleum (b.p. 60° to 80°). Found: C, 62·2; H, 5·2; N, 7·0. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3 per cent.

5-o-*Chlorophenoxymethyloxazolid*-2-*one*, prepared by interaction of 2-hydroxy-3-*o*-chlorophenoxypropyl chloride and sodium cyanate in aqueous ethanol, separated from ethyl acetate in colourless prisms of m.p. 151°. Found: C, 53·1; H, 4·4; N, 5·8. $C_{10}H_{10}O_3NCl$ requires C, 52·7; H, 4·4; N, 6·2 per cent.

5-o-*Toloxymethyldioxol*-2-*one*. ("Mephenesin carbonate")

A mixture of mephenesin (182 g.) and ethyl carbonate (118 g.) was warmed until homogeneous and a solution of sodium (0·5 g.) in ethanol (10 ml.) added. The mixture was heated on the steam-bath for 30 minutes, ethanol being allowed to distil off freely. The residue solidified on cooling and was crystallised from ethanol-light petroleum (b.p. 60° to 80°) or from benzene. Yield 90 per cent of a product m.p. 96°. Found: C, 63·5; H, 5·9. Calculated for $C_{11}H_{12}O_4$; C, 63·4; H, 5·8 per cent.

5-p-*Chlorophenoxymethyldioxol*-2-*one* ("chlorphenesin carbonate"), prepared from chlorphenesin and ethyl carbonate, separated from ethanol in shining needles of m.p. 96° to 97°. Found: C, 52·8; H, 4·2; Cl, 15·8. $C_{10}H_9O_4Cl$ requires C, 52·5; H, 4·0; Cl, 15·5 per cent.

2-*Hydroxy*-3-o-*toloxypropyl urea* (I; Ar = R; X = $NH{\cdot}CO{\cdot}NH_2$)

To a solution of 2-hydroxy-3-*o*-toloxypropylamine hydrochloride (30 g.) in water (100 ml.) was added a solution of sodium cyanate (12 g.) in water (30 ml.) and the mixture warmed for a few minutes. The urea separated on cooling. It was crystallised from ethyl acetate forming small shining plates, m.p. 131° to 132°. Found: C, 59·2; H, 6·9; N, 12·6. $C_{11}H_{16}O_3N_2$ requires C, 58·9; H, 7·2; N, 12·5 per cent.

2-*Hydroxy*-3-o-*toloxypropyl thiourea* (I; Ar = R; X = NH_2) was prepared as above, but using potassium thiocyanate in place of sodium cyanate. It crystallised from ethanol-ether in fine white needles, m.p. 120° to 122°. Found: C, 54·6; H, 6·5; S, 12·8. $C_{11}H_{16}O_2N_2S$ requires C, 54·9; H, 6·7; S, 13·3 per cent.

N-(2-*Hydroxy*-3-o-*toloxy*)-*propyl barbituric acid*

A solution of 2-hydroxy-3-*o*-toloxypropylurea (28·5 g.) in absolute ethanol (120 ml.) was added to a solution of ethyl sodiomalonate prepared from ethyl malonate (20·4 g.), and sodium (2·93 g.) in absolute ethanol (150 ml.). The mixture was refluxed for 15 hours, cooled to 50° and water (50 ml.) added to dissolve the bulk of the solid. The solution was then acidified with concentrated hydrochloric acid (12 ml.) and filtered immediately. The product (26 g.) separated rapidly, it had m.pt. 170° to 172°. The m.p. was not raised by crystallisation from a large volume of water. Found: C, 57·3; H, 5·6; N, 9·9. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5; N, 9·6 per cent.

3-*Methoxycarbonyl*-2-*oxo*-5-*phenoxymethyltetrahydrofuran* (II, Ar = Ph; R = Me).

1:2-Epoxy-3-phenoxypropane (30 g.) was added in one portion to a warm solution of sodiomalonic ester, prepared from ethyl malonate (32 g.) and sodium (4·6 g.) in absolute methanol (100 ml.). The moderately exothermic reaction was completed by heating on the steam bath for 1 hour. Most of the methanol was then boiled off and the residue was treated with 50 per cent aqueous acetic acid (25 ml.), diluted with water and the oil extracted with chloroform. The chloroform was removed at reduced pressure. A portion of the residue was distilled *in vacuo* and had b.p. 190°/1·0 mm. Slight decomposition occurred. Found: C, 62·3; H, 5·5. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6 per cent.

5-(2′-*Hydroxy*-3′-o-*toloxy*)-*propyl barbituric acid*

1:2-Epoxy-3-*o*-toloxypropane (16·4 g.) was added to a solution of sodiomalonic ester, prepared from ethyl malonate (16 g.) and sodium (2·3 g.) in dry methanol (80 ml.). The mixture was refluxed for 1 hour and a solution of urea (6 g.) in dry methanol (50 ml.) was then added. Refluxing was continued for 10 hours. The solid which separated on cooling was collected, suspended in hot water (75 ml.) and acidified with concentrated hydrochloric acid (9 ml.). The product which separated (27·5 g.) was crystallised from water and then from ethanol and had m.p. 200°. Found: C, 57·7; H, 5·4; N, 9·9. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5; N, 9·6 per cent.

3-*Amino*-2-*oxo*-5-o-*toloxymethyltetrahydrofuran* (IV)

2-Hydroxy-3-*o*-toloxypropyl chloride (50 g.) was added to a solution of methyl sodio-acetamidomalonate, prepared from ethyl acetamidomalonate (54·3 g.) and sodium (5·8 g.) in anhydrous methanol (300 ml.), and the mixture heated under reflux for 5 hours. The precipitated sodium chloride was filtered off and washed with a little methanol. The combined filtrate and washings was concentrated and the residual oil hydrolysed by heating under reflux with concentrated hydrochloric acid (60 ml.) for 3 hours. The acid was removed at reduced pressure and the residue crystallised from methanol-ether. The crude crystalline solid was crystallised further from methanol-ethyl acetate yielding the product (9·8 g.) m.p.

228° to 230° (decomp.), which separated from methanol in small shining plates, m.p. 230° to 232° (decomp.).

Found: C, 56·0; H, 6·2; N, 5·3; Cl, 13·9. $C_{12}H_{16}O_3NCl$ requires C, 55·9; H, 6·3; N, 5·4; Cl, 13·8 per cent. Glycine methyl ester hydrochloride (14 g.) m.p. 176° to 178° (decomp.) was isolated from the mother liquors.

A similar result was obtained when 1:2-epoxy-3-*o*-toloxypropane was used in place of 2-hydroxy-3-*o*-toloxypropyl chloride in the reaction.

5-(2′-*Hydroxy*-3′-o-*toloxy*)-*propyl hydantoin* (V)

The preceding amine hydrochloride (4·4 g.) was dissolved in water (50 ml.) and treated with an aqueous solution of sodium cyanate (2 g.). The solid product was collected, washed with water and purified by crystallisation from ethyl acetate, separating in needles m.pt. 136° to 138°, solidifying rapidly and remelting at 210°. Found: C, 58·8; H, 6·0; N, 10·3. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6 per cent.

1:2-*Epoxy*-3-(p-*ureidophenoxy*)-*propane* (VI, Ar = R′)

To a solution of *p*-ureidophenol (30·4 g.) in water (420 ml.) containing sodium hydroxide (8 g.), 2:3-epoxypropyl chloride (epichlorohydrin) (110 g. = 6 mole equivs) was added in one portion with stirring. The mixture was stirred vigorously at room temperature for 6 hours. The solid was collected, washed with water and dried. Yield 41·5 g., m.p. 149° to 151°. Crystallisation from ethanol-light petroleum (b.p. 60° to 80°) raised the m.p. to 152° to 153°. Found: C, 58·2; H, 6·0; N, 13·2. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5 per cent.

1:3-*bis*-(p-*Ureidophenoxy*)-2-*hydroxypropane*

To a stirred solution of *p*-ureidophenol (30·4 g.) in water (250 ml.) containing potassium hydroxide (11·2 g.) was added 2:3-epoxy-propyl chloride (9·3 g.) and the mixture stirred at room-temperature for 8 hours. The solid was collected, washed well with water and purified by crystallisation from aqueous ethylene glycol. Yield 26 g., m.p. 234° to 235° (decomp.). Found: C, 55·9; H, 5·9; N, 14·7. $C_{17}H_{20}O_5N_4$ requires C, 56·6; H, 5·6; N, 15·6 per cent.

2-*Hydroxy*-1-*succinimido*-3-(p-*ureidophenoxy*)-*propane*

A mixture of 1:2-epoxy-3-(*p*-ureidophenoxy)-propane (10·4 g.) and succinimide (5 g.) was dissolved in hot ethanol (150 ml.), pyridine (5 drops) was added as catalyst and the mixture heated for 5 hours with concentration to *ca.* 100 ml. The product which separated on cooling was crystallised from water, forming white needles of m.p. 202° to 203°. Found: C, 54·5; H, 5·8. $C_{14}H_{17}O_5N_3$ requires C, 54·7; H, 5·6 per cent.

2-*Hydroxy*-1-*phthalimido*-3-(p-*ureidophenoxy*)-*propane*

A mixture of 1:2-epoxy-3-(*p*-ureidophenoxy)propane (5·2 g.) and phthalimide (3·7 g.) was dissolved in ethanol (40 ml.), pyridine (2 drops) was added as catalyst, and the solution heated for 10 hours. The product

which separated after slight concentration and cooling was crystallised from acetic acid and had m.p. 199° to 200°. Found: C, 60·3; H, 4·7; N, 11·8. $C_{18}H_{17}O_5N_3$ requires C, 60·8; H, 4·8; N, 11·8 per cent.

2-*Hydroxy*-1-*piperidino*-3-(p-*ureidophenoxy*)-*propane* (I, Ar = R′; X = $N{\cdot}C_5H_{10}$)

To a solution of 1:2-epoxy-3-(*p*-ureidophenoxy)-propane (10·4 g.) in ethanol (40 ml.) was added piperidine (4·3 g.). The solution was refluxed for 4 hours and then treated at once with a slight excess of hydrochloric acid gas. The hydrochloride (10·3 g.) was purified by crystallisation from methanol-ethyl acetate and had m.p. 198° to 199°. Found: C, 54·3; H, 7·5; N, 12·6; Cl, 10·7. $C_{15}H_{24}O_3N_3Cl$ requires C, 54·6; H, 7·3; N, 12·7; Cl, 10·8 per cent.

1:4-*bis*-(2-*Hydroxy*-3-p-*ureidophenoxy*)-*propyl piperazine* (VII)

A solution of 1:2-epoxy-3-(*p*-ureidophenoxy)-propane (8·2 g.) in ethanol (150 ml.) was treated with piperazine hexahydrate (3·9 g.) and the mixture heated on the steam bath for 1 hour. The product (9 g., m.p. 204° to 208°) was purified by dissolving in dilute hydrochloric acid and precipitating with dilute sodium carbonate solution. It then had m.p. 206° to 208°. Found: C, 56·4, 56·0; H, 7·1, 6·7; N, 16·7. $C_{24}H_{34}O_6N_6$; $\frac{1}{2}H_2O$, requires C, 56·3; H, 6·9; N, 16·4 per cent.

3-(p-*Aminophenoxy*)-2-*hydroxypropylamine dihydrochloride*

N-(3-*p*-Acetamidophenoxy-2-hydroxy)-propylsuccinimide[6] (20 g.) was heated under reflux with concentrated hydrochloric acid (50 ml.) for 6 hours. The mixture was evaporated to dryness at reduced pressure, the residue dissolved in water (50 ml.) and extracted with three portions of ethyl acetate to remove succinic acid. After concentration at reduced pressure again the solid residue (14·6 g.) was crystallised from aqueous ethanol and had m.p. 256° to 260° (decomp.). Found: N, 10·7; Cl, 27·2. $C_9H_{16}O_2N_2Cl_2$ requires N, 11·0; Cl, 27·8 per cent.

2-*Hydroxy*-3-(p-*ureidophenoxy*)-*propylurea* (I; Ar = R′; X = $NH{\cdot}CO{\cdot}NH_2$)

The foregoing dihydrochloride (2·55 g.) was dissolved in water (7 ml.) and treated with a solution of sodium cyanate (1·63 g.) in water (15 ml.). The product (2·5 g.) separated on standing and crystallised from water in nodules, m.p. 180° to 182°. Found: C, 48·9; H, 5·9; N, 21·4. $C_{11}H_{16}O_4N_4$ requires C, 49·2; H, 6·0; N, 20·9 per cent.

3-p-*Acetamidophenoxypropane*-1:2-*diol* was prepared by condensation of *p*-acetamidophenol with 2:3-dihydroxypropyl chloride (glycerol α-chlorohydrin) in aqueous alkaline solution or with glycidol in alcoholic solution using pyridine as catalyst. It crystallised from ethyl acetate containing a few drops of methanol and had m.p. 136° to 138°. Found: C, 58·4; H, 6·7; N, 6·2. Calculated for $C_{11}H_{15}O_4N$: C, 58·7; H, 6·7; N, 6·2 per cent.

3-(p-*Aminophenoxy*)-*propane*-1 : 2-*diol hydrochloride*

Hydrolysis of the foregoing acetamido-compound (5 g.) in concentrated hydrochloric acid (30 ml.) for 1 hour at reflux temperature yielded the amine hydrochloride, which separated from ethanol-ether in white needles, m.p. 166° to 168°. Found: C, 48·6; H, 6·5; N, 6·0; Cl, 15·8. Calculated for $C_9H_{14}O_3NCl$: C, 49·2; H, 6·4; N, 6·4; Cl, 16·1 per cent.

3-p-*Ureidophenoxypropane*-1 : 2-*diol* (I; Ar = R′; X = OH)[7]

A solution of the foregoing amine hydrochloride (20 g.) in water (100 ml.) was treated with a solution of sodium cyanate (7·1 g.) in water (20 ml.). The product which separated after a few hours standing was crystallised from ethanol-ether and had m.p. 156° to 157°. Found: C, 52·8; H, 6·2; N, 12·2. Calculated for $C_{10}H_{14}O_4N_2$: C, 53·1; H, 6·2; N, 12·4 per cent.

The same compound was obtained when *p*-ureidophenol (15·2 g.) dissolved in water (50 ml.) containing sodium hydroxide (4 g.) was treated with 2 : 3-dihydroxypropyl chloride (13·2 g.) and the solution stirred at room temperature for 2 hours. It was also formed by condensation of *p*-ureidophenol with glycidol in concentrated alcoholic solution in the presence of a basic catalyst.

1-p-*Acetamidophenoxy*-4-*oxahexan*-2 : 6-*diol*

(*a*) A mixture of *p*-acetamidophenol (20 g.) and 1 : 2-epoxy-4-oxahexan-6-ol[8] (15·6 g.) in the minimum of hot ethanol was treated with pyridine (3 drops) and the mixture heated on the steam bath for 3 hours with concentration.

The gummy residue crystallised on boiling with ethyl acetate containing a few drops of ethanol and had m.p. 116° to 117°. Found: N, 5·1. $C_{13}H_{19}O_5N$ requires N, 5·2 per cent.

(*b*) To a solution of *p*-acetamidophenol (15·1 g.) in water (85 ml.) containing sodium hydroxide (4 g.) was added 1-chloro-4-oxahexane-2 : 6-diol (15·6 g.) and the mixture heated with stirring for 1 hour. After concentration at reduced pressure the residue was purified as in (*a*).

1-p-*Aminophenoxy*-4-*oxahexane*-2 : 6-*diol*

The foregoing compound (8 g.) was hydrolysed by heating with concentrated hydrochloric acid (30 ml.) for 2 hours. The amine hydrochloride, isolated in the usual manner, was purified by crystallisation from ethanol-ether and had m.p. 151° to 152°. Found: C, 49·7; H, 6·9; N, 5·4. $C_{11}H_{18}O_4NCl$ requires C, 50·1; H, 6·9; N, 5·3 per cent.

1-p-*Ureidophenoxy*-4-*oxahexane*-2 : 6-*diol* (VIII)

To a solution of the foregoing hydrochloride (4·5 g.) in water (20 ml.) was added a solution of sodium cyanate (1·1 g.) in water (10 ml.). The product which separated on standing was crystallised from ethanol-ether and had m.p. 169° to 171°. Found: C, 53·3; H, 6·7; N, 10·0. $C_{12}H_{18}O_5N_2$ requires C, 53·3; H, 6·7; N, 10·4 per cent.

3-o-*Acetamidophenoxy-propane*-1:2-*diol* was prepared by condensation of *o*-acetamidophenol with 2:3-dihydroxypropyl chloride in aqueous alkaline solution by the standard method. The product was crystallised from ethyl acetate-ether, and had m.p. 146° to 147°. Found: C, 58·7; H, 6·8; N, 6·3. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7; N, 6·2 per cent.

3-o-*Aminophenoxypropane*-1:2-*diol* was prepared by hydrolysis of the corresponding acetamido-compound with concentrated hydrochloric acid. It crystallised from ethanol-ether in white needles, m.p. 170°. Found: C, 49·1; H, 6·3; N, 6·1. Calculated for $C_9H_{14}O_3NCl$; C, 49·2; H, 6·4; N, 6·4 per cent. Treatment of this compound with sodium cyanate in aqueous solution yielded 3-o-*ureidophenoxypropane*-1:2-*diol* of m.p. 95°, after crystallisation from ethanol-ether. Found: N, 12·1. Calculated for $C_{10}H_{14}O_4N_2$: N, 12·4 per cent.

2:3-*Epoxy*-1-(o-*acetamidophenoxy*)-*propane* was prepared by condensation of *o*-acetamidophenol with excess (5 mole equivs) of 2:3-epoxy-propyl chloride in aqueous alkaline solution. It crystallised from light petroleum (b.p. 80° to 100°) in white fluffy needles, m.p. 105°. Found: C, 64·0; H, 6·0; N, 7·0. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3; N, 6·8 per cent.

Condensation of this epoxide with succinimide in ethanol with pyridine as catalyst yielded 1-o-*acetamidophenoxy*-2-*hydroxy*-3-*succinimidopropane* which separated from ethyl acetate-light petroleum (b.p. 60° to 80°) in white needles, m.p. 112° to 114°. Found: C, 59·1; H, 5·8; N, 9·2. $C_{15}H_{18}O_5N_2$ requires C, 58·8; H, 5·9; N, 9·2 per cent. Hydrolysis of the foregoing succinimido-compound in the usual manner with concentrated hydrochloric acid yielded the dihydrochloride of 1-o-*aminophenoxy*-2-*hydroxy-propylamine*, which crystallised from ethyl acetate containing a little methanol, in white needles, m.p. 232° (decomp.). Found: C, 42·4; H, 6·1. $C_9H_{16}O_2N_2Cl_2$ requires C, 42·4; H, 6·4 per cent.

Treatment of this dihydrochloride in aqueous solution with sodium cyanate yielded 2-*hydroxy*-1-o-*ureidophenoxypropyl urea*, which had m.p. 174° after crystallisation from alcohol-ether. Found: C, 48·6; H, 6·0; N, 20·6. $C_{11}H_{16}O_4N_4$ requires C, 49·2; H, 6·0; N, 20·9 per cent.

1:3-bis-(o-*Acetamidophenoxy*)-2-*hydroxy propane*

Condensation of *o*-acetamidophenol (2 moles) with 2:3-epoxypropyl chloride (1 mole) in aqueous alkaline solution yielded the product which separated from aqueous ethanol as the monohydrate, m.p. 124° to 126°. Found: C, 60·2; H, 6·4; N, 7·8. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4; N, 7·4 per cent. The anhydrous compound was obtained on drying at 95° for some hours or by crystallisation from ethylene dichloride-light petroleum (b.p. 80° to 100°) and had m.p. 165° to 166°. Found: N, 7·9. Calculated for $C_{19}H_{22}O_5N_2$: N, 7·8 per cent.

Hydrolysis of the preceding compound with concentrated hydrochloric acid yielded 1:3-*bis*-(o-*aminophenoxy*)-2-*hydroxy propane dihydrochloride*, which separated from methanol-ether in white needles, m.p. 280° to 282° (decomp.). Found: C,51·7; H, 5·9; N, 7·8. $C_{15}H_{20}O_3N_2Cl_2$ requires C, 51·8; H, 5·8; N, 8·1 per cent.

Treatment of the dihydrochloride with sodium cyanate in aqueous solution yielded 1 : 3-*bis*-(p-*ureidophenoxy*)-2-*hydroxy propane* as a microcrystalline powder, m.p. 174° to 184° after repeated crystallisation from aqueous methanol. Found: C, 56·7; H, 5·7; N, 15·9. $C_{17}H_{20}O_5N_4$ requires C, 56·6; H, 5·6; N, 15·9 per cent.

Summary

1. Attempts to prepare an aryloxypropanolurea by condensing 3-aryloxy-2-hydroxypropyl chloride or 3-aryloxy-1 : 2-epoxypropane with urea led to the formation of the corresponding 5-aryloxymethyloxazolid-2-one. The required ureas were ultimately obtained in excellent yield by reaction between the 3-aryloxy-2-hydroxypropylamine and an alkali metal cyanate.

2. Some 3-ureidoaryloxypropane-1 : 2-diols and 2-hydroxy-3-ureidopropylamines were also prepared.

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