The Total Synthesis of (±)-Lycoramine. Part II [1,2]

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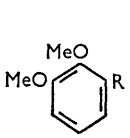
An alternative and improved synthetic pathway to lycoramine involving construction of the skeleton in the order ring A, ring B, ring C, ring D, is described. 2,3-Dimethoxybenzaldehyde (I) was converted into 2,3-dimethoxyphenylacetone (III), which was condensed with acrylonitrile, to give γ-acetyl-γ-(2,3-dimethoxyphenyl)pimelonitrile (IV). The corresponding ester (VII) was cyclised to 1-(2,3-dimethoxephenyl)-2,4-dioxocyclohexanepropionate (IX). Treatment of its monoacetal (X) with lithium aliminium hydride followed by oxalic acid yielded 4a-(2,3-dimethoxyphenyl)-7-oxoperhydrobenzo[*b*]pyran (XIV). This was converted into 1,2,3,4,4a,9b-hexahydro-6-hydroxy-9b-(3-iodopropyl)-3-oxodibenzofuran (XV) with hydriodic acid. 9-Acetoxy-1,2,8,9,10,11-hexahydro-6-methoxy-3*H*,7a*H*-benzo[*b*]naphtho[1,8-*cd*]furan-3-one (XXV), which was obtained in seven steps from (XV), was treated with hydrazoic acid to yield a mixture of isomeric lactams [(XXIX) and (XXX)] which were separated, and the required one (XXX) was *N*-methylated and treated with lithium aluminium hydride to furnish (±)-lycoramine, overall yield 0·67%.

In the preceding paper,[1] we reported a total synthesis of (±)-lycoramine from 3-ethoxy-2-hydroxybenzaldehyde. However, the yields from some of the reactions were low, and oxolycoraminone from natural sources had to be used to obtain enough of a key intermediate.

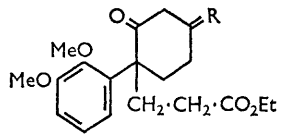
We therefore investigated an alternative method of synthesis and have now obtained lycoramine from 2,3-dimethoxybenzaldehyde in nineteen steps in a far better overall yield than that obtained in the twenty-three steps of the previous pathway.

2,3-Dimethoxybenzaldehyde (I), prepared from commercial 2-hydroxy-3-methoxybenzaldehyde by methylation, was treated with nitroethane in the presence of n-butylamine to give a satisfactory yield of 1-(2,3-dimethoxyphenyl)-2-nitropropene (II). This compound was then converted into (2,3-dimethoxyphenyl)acetone (III) by reduction with iron in acetic acid.[3] Michael condensation of (III) with acrylonitrile gave the pimelonitrile (IV) in good yield, and a little of the monocyanoethyl derivative (V). The structures of these compounds were established by their elemental analyses and n.m.r. spectra, which showed signals due to methyl ketones at τ 7·99 and 7·98, respectively. Saponification of the pimelonitrile (IV) with alkali afforded a nearly quantitative yield of the pimelic acid (VI) which was converted into the corresponding diethyl pimelate (VII) with absolute ethanol and toluene-*p*-sulphonic acid. Attempts to prepare the corresponding dimethyl ester directly from the phenylacetone (III) by the Michael condensation with methyl acrylate were not successful; only the mono-addition product (VIII) was obtained under a variety of reaction conditions. Cyclisation[4] of the ethyl pimelate (VII) with sodium ethoxide in ethanol gave ethyl 1-(2,3-dimethoxyphenyl)-2,4-dioxocyclohexanepropionate (IX) in a satisfactory yield. In the n.m.r. spectrum, the product (IX) showed the ethoxy-protons at τ 8·80 (3H, t) and 5·93 (2H, q) and the methylene protons between the two carbonyl groups at τ 6·61 and 6·28 (AB-type q, *J* 17 c./sec.).

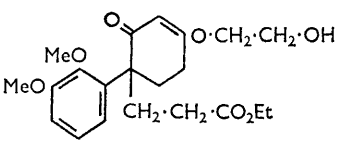
The 4 carbonyl group in (IX) was selectively acetalised in nearly quantitative yield with an excess of 2-ethyl-2-methyl-1,3-dioxolan in the presence of boron trifluoride. The structure of the product (X) was proved by its i.r. and n.m.r. spectra and by the fact that it resisted the action of sodium borohydride. However, the usual acetalisation of (IX) with ethylene glycol in the presence of boron trifluoride gave a mixture of (X) and the enol ether (XI) (64 and 25%, respectively).



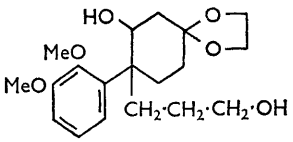
R
(I) CHO
(II) CH:CMe·NO$_2$
(III) CH$_2$·COMe
(IV) AcC(CH$_2$·CH$_2$·CN)$_2$
(V) AcCH·CH$_2$·CH$_2$·CN
(VI) AcC(CH$_2$·CH$_2$·CO$_2$H)$_2$
(VII) AcC(CH$_2$·CH$_2$·CO$_2$Et)$_2$
(VIII) AcCH·CH$_2$·CH$_2$·CO$_2$Me



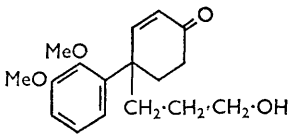
(IX) R = O
(X) R = O·CH$_2$·CH$_2$·O



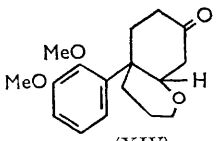
(XI)



(XII)



(XIII)



(XIV)

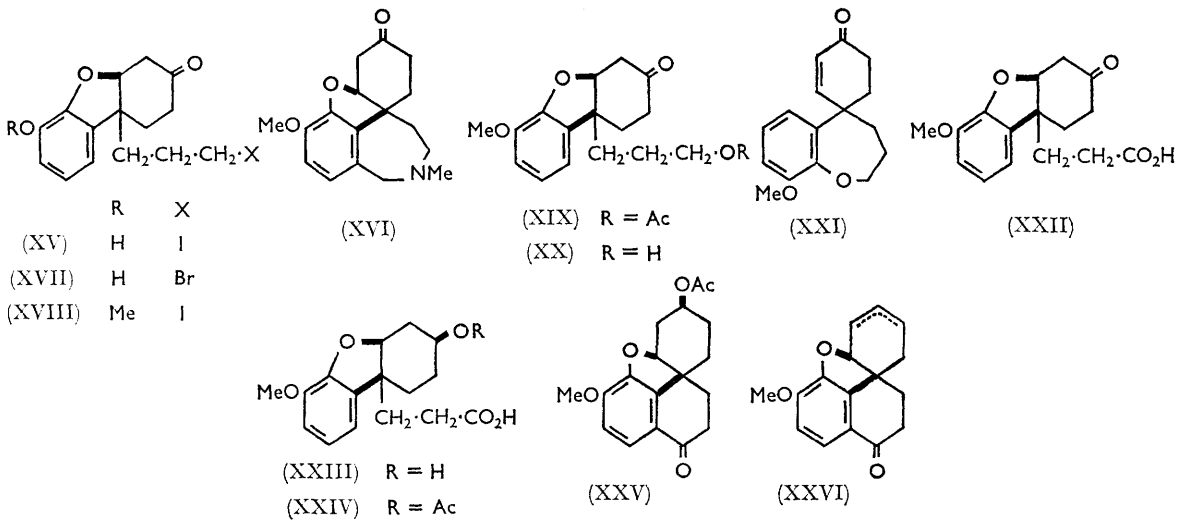
The monoacetal (X) was treated with lithium aluminium hydride in tetrahydrofuran to reduce the ketone and the ester groups. The i.r. spectrum of the product (XII) indicated complete disappearance of both carbonyl groups. When the product, without further purification, was treated with oxalic acid in boiling

[1] Part I, preceding paper.
[2] Preliminary communication, Y. Misaka, T. Mizutani, M. Sekido, and S. Uyeo, *Chem. Comm.*, 1967, 1258.
[3] H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, 1950, **15**, 8.
[4] P. Kloss, *Chem. Ber.*, 1964, **97**, 1723.

aqueous methanol, a crystalline compound, $C_{17}H_{22}O_4$, was obtained in a satisfactory yield. Its i.r. spectrum did not exhibit any absorptions corresponding to the hydroxy-group and αβ-unsaturated ketone anticipated from structure (XIII), but showed a normal carbonyl absorption. We therefore concluded that an intramolecular cyclisation of the hydroxy-group on the side-chain to the β-position of the αβ-unsaturated ketone in the intermediate (XIII) had taken place under the acidic conditions to furnish the perhydrobenzopyran (XIV). The structure of (XIV) was supported by its n.m.r. spectrum, which showed signals of a proton on the carbon of the cyclohexane ring bearing the ether oxygen atom [τ 5·15 (q, J_{AX} 3, J_{BX} 6 c./sec.)] and those of methylene protons geminal to the oxygen in the perhydropyran moiety [τ 6·60—5·70 (m)].

Treatment of (XIV) with constant-boiling hydriodic acid and acetic anhydride for 5 min. gave the phenolic hexahydrodibenzofuran (XV) which was purified by chromatography on Florisil. The spectral data were consistent with the proposed structure; $\nu_{max.}$ 3450 (OH) and 1715 (C=O) cm.$^{-1}$, τ 5·06 (t, hydrogen on the carbon bearing the ether oxygen of the dihydrofuran ring). Formation of the compound (XV) is apparently the results of reversal [(XIV) ⟶ (XIII) I for OH] of the reaction [(XIII) ⟶ (XIV)] accompanied by recyclisation of one of the hydroxy-functions, newly formed by hydrolysis of the methoxy-groups, to the β-position of the resulting αβ-unsaturated ketone in (XIII; I for OH and 2-OH for 2-OMe). That the fusion of the new furan ring to the cyclohexanone ring in (XV) is *cis* appears reasonable, since it represents a sterically stable configuration for the fused 5- and 6-membered ring system. In agreement with this assumption, the n.m.r. spectrum of (XV) showed a triplet (1H) at τ 5·06 (J_{AX+BX} 6 c./sec.) due to the equatorial hydrogen attached to the carbon bearing the ether oxygen of the dihydrofuran ring; this shows that the carbon–oxygen bond is axial and hence that the dihydrofuran ring is *cis*-fused. The n.m.r. spectrum of lycoraminone (XVI), which has been proved [5] to have a *cis*-junction similarly exhibited a triplet at τ 5·28 (J_{AX+BX} 6 c./sec.).

Methylation of the hydroxy-group in (XV) with methyl iodide and potassium carbonate in acetone gave the methoxy-iodide (XVIII). This iodide was also obtainable, but in poor yield, by treatment under similar conditions of the phenolic bromide (XVII), prepared by the action of hydrogen bromide on the perhydrobenzopyran (XIV). Treatment of the iodide (XVIII) with silver acetate in boiling acetonitrile gave the acetate (XIX), which when heated under reflux with an excess of ethanol in the presence of toluene-*p*-sulphonic acid formed the keto-alcohol (XX). An attempt to convert the iodide (XVIII) directly into (XX) failed. Treatment of (XVIII) with alkali furnished a crystalline compound (XXI) which exhibited no hydroxy-band in the i.r. spectrum but an αβ-unsaturated carbonyl band at 1675 cm.$^{-1}$.



	R	X
(XV)	H	I
(XVII)	H	Br
(XVIII)	Me	I

(XVI)

(XIX) R = Ac
(XX) R = H

(XXI)

(XXII)

(XXIII) R = H
(XXIV) R = Ac

(XXV)

(XXVI)

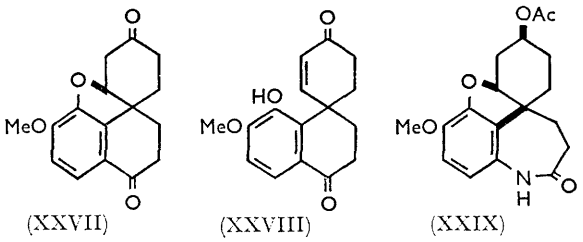
Chromic acid oxidation of (XX) in acetone containing sulphuric acid proceeded smoothly to afford the keto-acid (XXII), which was further treated with sodium borohydride to give the hydroxy-acid (XXIII) as the sole isolable product. That the newly formed hydroxy-group is *cis* to the oxide ring in (XXIII) seems reasonable, since a similar reduction of lycoraminone with the same reagent [1] gave lycoramine, which bears the hydroxy-group *cis* to the oxide ring.

The hydroxy-group in (XXIII) was acetylated with acetic anhydride and pyridine and the free carboxy-group of the resulting acetoxy-acid (XXIV) was converted into the acid chloride with phosphorus pentachloride in dry benzene. The acid chloride was then cyclised with stannic chloride in benzene to give a nearly quantitative yield of the acetoxynaphthalenone (XXV). When this cyclisation was carried out with polyphosphoric acid, an unsaturated compound was obtained to

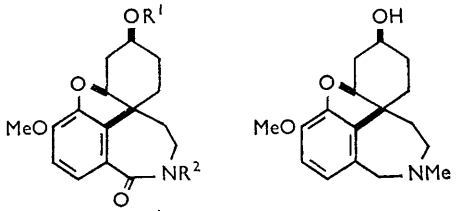
[5] D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806; D. J. Williams and D. Rogers, *Proc. Chem. Soc.*, 1964, 357.

which structure (XXVI) was assigned on the basis of following evidence. The compound had the molecular formula, $C_{16}H_{16}O_3$, which corresponded to the product of elimination of the elements of acetic acid from the desired acetoxy-naphthalenone (XXV). The i.r. spectrum exhibited an aryl ketonic absorption at 1670 cm.$^{-1}$ but no acetyl band in the carbonyl region. The n.m.r. spectrum showed a multiplet (2H, olefinic) at τ 4·35—3·60 and an aromatic AB-type quartet at τ 3·18 and 2·34 (J_{AB} 7 c./sec.). Direct cyclisation of (XXII) with polyphosphoric acid gave a mixture of the diketone (XXVII) and the phenolic compound (XXVIII) in nearly equal amounts, probably owing to equilibration in the acidic medium.

The acetoxy-naphthalenone (XXV) was submitted to the Schmidt reaction with sodium azide in trichloroacetic acid to afford a mixture of two isomeric lactams which were separated chromatographically on silica gel. The structures (XXIX) and (XXX) were assigned to



(XXVII) (XXVIII) (XXIX)



	R^1	R^2
(XXX)	Ac	H
(XXXI)	Ac	Me
(XXXIII)	H	Me

(XXXII)

these two compounds (m.p. 198—201 and 208—209°, respectively), since the former showed the lactam carbonyl absorption in the i.r. spectrum at a higher frequency than the latter. These spectral properties in related lactams have previously been established in our laboratory.[1,6] The desired acetoxy-lactam (XXX) possessing the homoisocarbostyril skeleton was *N*-methylated with methyl iodide and sodium hydride in toluene. The *N*-methyl derivative (XXXI) was identical with (±)-oxolycoramine acetate prepared from (±)-lycoramine [1] by permanganate oxidation followed by acetylation. Treatment of (XXXI) with lithium aluminium hydride afforded (±)-lycoramine (XXXII), identical in all respects with an authentic sample from natural sources. Thus (±)-lycoramine was unequivocally synthesised in an overall yield of 0·67% from 2,3-dimethoxybenzaldehyde.

[6] S. Uyeo, H. Irie, A. Yoshitake, and A. Ito, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 427; S. Minami, M. Tomita, H. Takamatsu, and S. Uyeo, *ibid.*, 1965, **13**, 1084; S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *ibid.*, 1966, **14**, 1033.

EXPERIMENTAL

For general experimental conditions see Part I.[1]

1-(2,3-Dimethoxyphenyl)-2-nitropropene (II).—2,3-Dimethoxybenzaldehyde (I) (16·6 g.) and nitroethane (9 g.) were heated under reflux with n-butylamine (0·5 ml.) in absolute ethanol (10 ml.) for 8 hr. Evaporation of the mixture under reduced pressure and crystallisation of the residue from ether gave the *2-nitropropene* (II) (17 g.) as yellow needles, m.p. 77—78·5° (Found: C, 59·4; H, 6·1. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9%), $\nu_{max.}$ 1655 (C=C) and 1515 and 1325 (NO_2) cm.$^{-1}$.

(2,3-Dimethoxyphenyl)acetone (III).—Hydrochloric acid (80 ml.) was added during 5 hr. to a stirred mixture of the 2-nitropropene (II) (120 g.), iron powder (215 g.), ferric chloride (0·5 g.), and water (450 ml.) at 80—85°. The mixture was heated under reflux for 2 hr., made alkaline with sodium hydroxide, and steam-distilled. The distillate was extracted with ether, and the extract was washed with saturated aqueous sodium chloride solution, dried, concentrated, and distilled under reduced pressure to give the *phenylacetone* (III) (57 g.) as an oil, b.p. 105—106°/0·15 mm. (Found: C, 68·0; H, 7·5. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%), $\nu_{max.}$ 1715 (CO) cm.$^{-1}$.

Condensation of the Phenylacetone (III) *with Acrylonitrile.*—A solution of acrylonitrile (11 g.) in t-butyl alcohol (10 ml.) was added dropwise with stirring to a solution of the phenylacetone (III) (19·4 g.) and potassium t-butoxide (1 g.) in t-butyl alcohol (30 ml.). Stirring was continued for 3 hr. at room temperature. After acidification with hydrochloric acid, the solution was extracted with chloroform. The extract was dried and evaporated to leave a gum which was chromatographed in chloroform on silica gel. Elution with chloroform gave *γ-acetyl-γ-(2,3-dimethoxyphenyl)pimelonitrile* (IV) (20 g.) as needles, m.p. 110—111° (from ether–ethanol) (Found: C, 68·4; H, 7·0. $C_{17}H_{20}N_2O_3$ requires C, 68·0; H, 6·7%). Further elution with chloroform gave *1-(2-cyanoethyl)-1-(2,3-dimethoxyphenyl)propan-2-one* (V) (400 mg.) as needles, m.p. 128—129·5° (from ethanol) (Found: C, 68·2; H, 6·7. $C_{14}H_{17}NO_3$ requires C, 68·0; H, 6·9%).

Condensation of the Phenylacetone (III) *with Methyl Acrylate.*—A solution of methyl acrylate (0·74 g.) in t-butyl alcohol (2 ml.) was added dropwise to a solution of the phenylacetone (III) (1·94 g.) and 40% methanolic Triton B (5 ml.) in t-butyl alcohol (3 ml.) under reflux. After a further 12 hr. under reflux, the solvent was distilled off and the residue was dissolved in chloroform. The chloroform solution was washed successively with dilute hydrochloric acid and aqueous sodium carbonate, and dried. Removal of the solvent and distillation of the residue gave *methyl γ-acetyl-γ-(2,3-dimethoxyphenyl)butyrate* (VIII) (1·9 g.) as an oil, b.p. 150°/1 mm. (Found: C, 64·1; H, 7·4. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2%), $\nu_{max.}$ 1725 (CO_2Me) and 1710 (CO) cm.$^{-1}$, τ 7·98 (3H, s, Ac), 6·35 (3H, s, OMe), and 6·12 (6H, s, 2OMe).

γ-Acetyl-γ-(2,3-dimethoxyphenyl)pimelic Acid (VI).—The

pimelonitrile (IV) (10 g.), sodium hydroxide (5 g.), and water (50 ml.) were heated under reflux for 10 hr. The mixture was cooled, washed with ether, acidified with hydrochloric acid, and extracted with ether, and the extract was dried and evaporated. The residue gave the *pimelic acid* (VI) (11·1 g.) as needles, m.p. 188—189·5° (from acetone–ether) (Found: C, 60·3; H, 6·5. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·6%).

Diethyl γ-Acetyl-γ-(2,3-dimethoxyphenyl)pimelate (VII).—The pimelic acid (VI) (34 g.), ethanol (30 ml.), and benzene (50 ml.) were boiled under reflux for 6 hr. in the presence of toluene-*p*-sulphonic acid (0·1 g.) with azeotropic removal of water. The mixture was concentrated, then diluted with benzene, and the benzene solution was washed with aqueous sodium carbonate and dried. Removal of the solvent and crystallisation of the residue from ethanol gave the *pimelate* (VII) (39 g.) as needles, m.p. 51—52° (Found: C, C, 63·9; H, 7·6. $C_{21}H_{30}O_7$ requires C, 63·9; H, 7·7%).

Ethyl 1-(2,3-*Dimethoxyphenyl*)-2,4-*dioxocyclohexanepropionate* (IX).—A solution of the pimelate (VII) (25 g.) in absolute ethanol (6 ml.) was added to a hot solution of sodium (1·85 g.) in absolute ethanol (18 ml.) and the solution was heated under reflux for 1 hr. The mixture was concentrated, diluted with water, washed with ether, acidified, and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness to leave a crystalline mass which gave the *diketone* (IX) (18·5 g.) as needles, m.p. 131—132° (from ethanol) (Found: C, 65·4; H, 7·2. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%), $\nu_{max.}$ 1730 (CO_2Et), and 1710 (CO) cm.$^{-1}$, τ 8·80 (3H, t, *J* 7 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), 6·61 and 6·28 (2H, ABq, *J* 17 c./sec., $CO{\cdot}CH_2{\cdot}CO$), 6·30 and 6·14 (each 3H, s, OMe), and 5·93 (2H, q, *J* 7 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$).

Ethyl-1-(2,3-*Dimethoxyphenyl*)-4-*ethylenedioxy*-2-*oxocyclohexanepropionate* (X).—A mixture of the diketone (IX) (1 g.), 2-ethyl-2-methyldioxolan (15 ml.), boron trifluoride–diethyl ether (a few drops), and dry benzene (5 ml.) was set aside overnight at room temperature. The mixture was poured into aqueous sodium carbonate and extracted with benzene and the extract was dried and evaporated. The residue gave the *ethylene acetal* (X) (1 g.) as plates, m.p. 113—116° (from ethanol) (Found: C, 64·0; H, 7·2. $C_{21}H_{28}O_7$ requires C, 64·3; H, 7·2%), $\nu_{max.}$ 1720 (CO) cm.$^{-1}$.

Reaction of the Diketone (IX) *with Ethylene Glycol*.—A mixture of the diketone (IX) (250 mg.), ethylene glycol (0·5 ml.), boron trifluoride–diethyl ether (3 drops), and dry tetrahydrofuran (3 ml.) was set aside overnight at room temperature. The mixture was poured into aqueous sodium carbonate and extracted with chloroform, and the chloroform layer was dried and evaporated to leave an oil which was chromatographed in chloroform on silica gel. Elution with chloroform gave the *acetal* (X) (180 mg.), as plates, m.p. and mixed m.p. 113—116° (from n-hexane–ether). Further elution with chloroform–ethanol (99 : 1) gave an oil which was distilled under reduced pressure to yield *ethyl* 1-(2,3-*dimethoxyphenyl*)-4-(β-*hydroxyethoxy*)-2-*oxocyclohex*-3-*enepropionate* (XI) (70 mg.) as an oil, b.p. 210°/0·1 mm. (Found: C, 63·7; H, 7·3. $C_{21}H_{28}O_7$ requires C, 64·3; H, 7·2%), $\nu_{max.}$ 3400 (OH), 1720 (CO_2Et), 1640 (αβ-unsaturated CO), and 1610 (C=C) cm.$^{-1}$, τ 8·77 (3H, t, *J* 7 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), 6·26 and 6·15 (each 3H, s, OMe), 6·07br (4H, s, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 5·89 (2H, q, 7 c./sec., $CO_2{\cdot}CH_2{\cdot}CH_3$), and 4·57 (1H, s, $-CH{=}C<$).

4a-(2,3-*Dimethoxyphenyl*)-7-*oxoperhydrobenzo*[b]*pyran* (XIV).—The acetal (X) (1·6 g.) was heated under reflux with lithium aluminium hydride (500 mg.) in tetrahydrofuran (40 ml.) for 5 hr. The mixture was treated with a slight excess of water, the precipitate was filtered off, and the filtrate was evaporated to dryness. The residue was taken up in methanol (20 ml.) and heated under reflux with 10% aqueous oxalic acid (10 ml.) for 1 hr. The mixture was concentrated and extracted with chloroform, and the extract was washed with aqueous sodium carbonate, dried, and evaporated to leave an oil which was chromatographed in chloroform on silica gel. Elution with chloroform gave the *perhydrobenzopyran* (XIV) (0·88 g.) as needles, m.p. 125° (from ethanol) (Found: C, 70·6; H, 7·9. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%), $\nu_{max.}$ 1710 cm.$^{-1}$ (CO), τ 6·11 and 6·10 (each 3H, s, OMe), 6·60—5·70 (2H, m, $CH_2{\cdot}CH_2{\cdot}O$), 5·15 (1H, q, angular H), and 3·25—2·90 (3H, m, aromatic H).

1,2,3,4,4a,9b-*Hexahydro*-6-*hydroxy*-9b-(3-*iodopropyl*)-*dibenzofuran*-3-*one* (XV).—A mixture of the perhydrobenzopyran (XIV) (300 mg.), acetic anhydride (1 ml.), constant-boiling hydriodic acid (15 ml.), and red phosphorus (50 mg.) was heated under reflux under nitrogen for 10 min. The mixture was diluted with water and extracted with chloroform, and the extract was washed with aqueous sodium hydrogen carbonate and aqueous sodium hydrogen sulphite and dried. Removal of the solvent left an oil which was chromatographed in chloroform on Florisil. Elution with chloroform gave the *phenolic iodide* (XV) (225 mg.), as needles, m.p. 140—141° (from ether–ethanol) (Found: C, 48·8; H, 4·6. $C_{15}H_{17}IO_3$ requires C, 48·5; H, 4·3%), $\nu_{max.}$ 3450 (OH) and 1715 (CO) cm.$^{-1}$, τ 7·20 (2H, symmetrical heptet, J_{AB} 17 c./sec., $O{\cdot}CH{\cdot}CH_2{\cdot}CO$), 6·83 (2H, m, $CH_2{\cdot}CH_2{\cdot}I$), 5·06 (1H, t, $J_{AX} + J_{BX}$ 6 c./sec., $O{\cdot}CH{\cdot}CH_2{\cdot}CO$), and 3·50—3·00 (3H, m, aromatic H).

9b-(3-*Bromopropyl*)-1,2,3,4,4a,9b-*hexahydro*-6-*hydroxydibenzofuran*-3-*one* (XVII).—A solution of the perhydrobenzopyran (XIV) (240 mg.) in acetic acid (3 ml.) and constant-boiling hydrobromic acid (5 ml.) was heated under reflux for 1 hr. The mixture was diluted with water and extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to leave an oil which was chromatographed in chloroform on Florisil. Elution with chloroform gave the *phenolic bromide* (XVII) (50 mg.) as prisms, m.p. 118—119° (from ether) (Found: C, 55·4; H, 5·1. $C_{15}H_{17}BrO_3$ requires C, 55·4; H, 5·3%).

1,2,3,4,4a,9b-*Hexahydro*-9b-(3-*iodopropyl*)-6-*methoxydibenzofuran*-3-*one* (XVIII).—(*a*) A solution of the phenolic iodide (XV) (200 mg.) and methyl iodide (3 ml.) in acetone (15 ml.) was heated under reflux for 3 hr. in the presence of potassium carbonate (50 mg.). The mixture was evaporated and the residue taken up in water and extracted with chloroform. The extract was washed with 5% aqueous sodium hydroxide, dried, and evaporated. The residue gave the *iodide* (XVIII) (200 mg.) as needles, m.p. 100—102° (from methanol) (Found: C, 50·1; H, 4·9. $C_{16}H_{18}IO_3$ requires C, 50·0; H, 4·7%), $\nu_{max.}$ 1715 (CO) cm.$^{-1}$.

(*b*) Treatment of the phenolic bromide (XVII) in the same way as described in (*a*) gave the same *product* (XVIII).

9b-(3-*Acetoxypropyl*)-1,2,3,4,4a,9b-*hexahydro*-6-*methoxydibenzofuran*-3-*one* (XIX).—The iodide (XVIII) (450 mg.) in acetonitrile (30 ml.) was heated under reflux with silver acetate (850 mg.) for 5 hr. The mixture was filtered, diluted with water, and extracted with ether, and the extract was dried and evaporated. The resulting crystalline mass

yielded the *acetate* (XIX) (300 mg.) as needles, m.p. 86—87° (from methanol) (Found: C, 67·9; H, 7·3. $C_{18}H_{22}O_5$ requires C, 67·9; H, 7·0%), $\nu_{max.}$ 1725 (CO) cm.$^{-1}$.

1,2,3,4,4a,9b-*Hexahydro*-9b-(3-*hydroxypropyl*)-6-*methoxydibenzofuran*-3-*one* (XX).—A solution of the acetate (XIX) (200 mg.) in absolute ethanol (50 ml.) was heated under reflux for 3 hr. in the presence of toluene-*p*-sulphonic acid (50 mg.). After concentration of the solution to about half its volume, absolute ethanol (25 ml.) was added and the whole was heated under reflux for a further 3 hr. After removal of the ethanol, water was added and the product was extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, dried, evaporated, and distilled under reduced pressure to give the *hydroxy-compound* (XX) (155 mg.) as an oil, b.p. 160—163°/0·09 mm. (Found: C, 69·3; H, 7·6. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%), $\nu_{max.}$ 3350 (OH) and 1715 (CO) cm.$^{-1}$.

2,3,4,5-*Tetrahydro*-9-*methoxyspiro*-[1-*benzoxepin*-5,1′-*cyclohex*-2-*en*]-4′-*one* (XXI).—The iodide (XVIII) (100 mg.) in 10% aqueous sodium hydroxide (10 ml.) and ethanol (10 ml.) was heated under reflux for 2 hr. After removal of the ethanol, the solution was extracted with chloroform and the extract was dried and evaporated to leave an oil which was chromatographed in chloroform on silica gel. Elution with chloroform gave the *benzoxepin* (XXI) (58 mg.) as needles, m.p. 103—104° (from methanol) (Found: C, 74·2; H, 6·9. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%), $\nu_{max.}$ 1675 cm.$^{-1}$ (αβ-unsaturated CO), τ 6·15 (3H, s, OMe), 6·38 and 5·63 (each 1H, m, O·CH_2), and 3·38 and 3·11 (2H, q, *J* 10 c./sec., CH:CH).

1,2,3,4,4a,9b-*Hexahydro*-6-*methoxy*-3-*oxodibenzofuran*-9b-*propionic Acid* (XXII).—A solution of chromium trioxide (200 mg.) in 10% sulphuric acid (4 ml.) was added gradually at 0—2° to the alcohol (XX) (400 mg.) in acetone (30 ml.) until a permanent orange colour was observed. The mixture was stirred at the same temperature for a further 1·5 hr., methanol was added, and the mixture was diluted with water and extracted with chloroform. The extract was extracted with aqueous sodium hydrogen carbonate and the alkaline extract was acidified and extracted with chloroform. The organic layer, after drying and evaporation, gave the *propionic acid* (XXII) (300 mg.) as needles, m.p. 140·5—141·5° (from ether–methanol) (Found: C, 66·4; H, 6·5. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·3%), $\nu_{max.}$ 1720sh (CO) and 1705 (CO_2H) cm.$^{-1}$.

1,2,3,4,4a,9b-*Hexahydro*-3-*hydroxy*-6-*methoxydibenzofuran*-9b-*propionic Acid* (XXIII).—Sodium borohydride (200 mg.) in water (2 ml.) was added to a solution of the keto-acid (XXII) (100 mg.) in tetrahydrofuran (20 ml.). The mixture was stirred for 8 hr. at room temperature, acidified with dilute hydrochloric acid, and evaporated under reduced pressure to leave an oil which was taken up in chloroform. The chloroform solution was dried, and evaporated and the resulting viscous oil (XXIII) (80 mg.) was converted into its crystalline *dicyclohexylamine salt*, which formed needles, m.p. 134—136° (from ethanol) (Found: C, 71·1; H, 8·7. $C_{16}H_{20}O_5$,$C_{12}H_{23}N$ requires C, 71·0; H, 9·1%).

3-*Acetoxy*-1,2,3,4,4a,9b-*hexahydrodibenzofuran*-9b-*propionic Acid* (XXIV).—The hydroxy-acid (XXIII) (100 mg.) in pyridine (3 ml.) was kept overnight with acetic anhydride (1 ml.) at room temperature and worked up in the usual way. Chromatography of the crude product in chloroform on silica gel and elution with chloroform gave the *acetoxy-acid* (XXIV) (100 mg.) as an oil, $\nu_{max.}$ 1725 (OAc) and 1710 (CO_2H) cm.$^{-1}$, τ 8·06 (3H, s, OAc), 6·13 (3H, s, OMe), and 5·60—5·10 (2H, m, OC*H*·CH_2·C*H*·OAc).

9-*Acetoxy*-1,2,8,9,10,11-*hexahydro*-6-*methoxy*-3H,7aH-*benzo*[b]*naphtho*[1,8-cd]*furan*-3-*one* (XXV).—The acetoxy-acid (XXIV) (86 mg.) in dry benzene (20 ml.), stirred and cooled in ice, was chlorinated with phosphorus pentachloride (200 mg.). Stirring was continued for 1 hr. and then stannic chloride (300 mg.) in dry benzene (5 ml.) was added. The mixture was stirred for a further 30 min. at 0°, ice and hydrochloric acid (2 ml.) were added, and the benzene layer was separated, washed with water and with aqueous sodium hydrogen carbonate, dried, and evaporated to dryness under reduced pressure. The residue was chromatographed in chloroform on silica gel and eluted with chloroform to yield the *acetoxy-naphthalenone* (XXV) (78 mg.) as needles, m.p. 125—126·5° (from methanol) (Found: C, 68·4; H, 6·3. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%), $\nu_{max.}$ 1725 (OAc) and 1670 (aryl CO) cm.$^{-1}$, τ 7·95 (3H, s, OAc), 6·02 (3H, s, OMe), and 5·63—5·42 (1H, m, >C*H*·OAc).

Cyclisation of the Acetoxy-acid (XXIV) *with Polyphosphoric Acid*.—A mixture of the acetoxy-acid (XXIV) (80 mg.) and polyphosphoric acid (5 g.) was heated on a water-bath for 2 hr. and then cooled. Ice–water and chloroform were added and the organic layer was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to leave an oil which was chromatographed in chloroform on silica gel. Elution with chloroform gave the *naphthalenone* (XXVI) (44 mg.) as needles, m.p. 108—109° (from methanol) (Found: C, 74·6; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%), $\nu_{max.}$ 1670 (aryl CO) cm.$^{-1}$, τ 6·10 (3H, s, OMe), 5·08—4·80 (1H, m, O·C*H*·CH<), 4·35—3·60 (2H, m, >CH:CH<), and 3·18 and 2·34 (2H, ABq, *J* 7 c./sec., aromatic *ortho*-protons).

Cyclisation of the Keto-acid (XXII) *with Polyphosphoric Acid*.—A mixture of the keto-acid (XXII) (80 mg.) and polyphosphoric acid (5 g.) was heated on a water-bath for 2 hr. It was then diluted with ice–water and chloroform and the organic layer was extracted with aqueous sodium hydroxide. The alkali-washed chloroform solution was dried and evaporated to give 1,2,8,9,10,11-*hexahydro*-6-*methoxy*-3H,7aH-*benzo*[b]*naphtho*[1,8-cd]*furan*-4,9-*dione* (XXVII) (30 mg.) as prisms, m.p. 197—199° (from methanol) (Found: C, 70·2; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%), $\nu_{max.}$ 1720 (CO), 1670 (aryl CO), and 1615 (C=C) cm.$^{-1}$. The initial alkaline extract was acidified with hydrochloric acid and extracted with chloroform. The extract was dried and evaporated to give 1′,2′,3′,4′-*tetrahydro*-8-*hydroxy*-7-*methoxyspiro*[*cyclohex*-2-*ene*-1,1′-*naphthalene*]-4,4′-*dione* (XXVIII) (35 mg.) as prisms, m.p. 190—193° (from methanol) (Found: C, 70·2; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%), $\nu_{max.}$ 3450 (OH), 1665 (αβ-unsaturated CO), and 1605 (C=C) cm.$^{-1}$.

Schmidt Reaction with the Acetoxy-naphthalenone (XXV).—Sodium azide (60 mg.) was added during 30 min. to a stirred solution of the acetoxy-naphthalenone (XXV) (150 mg.) in trichloroacetic acid (5 g.) at 60°. Stirring was continued for 2 hr. at the same temperature, and the mixture was diluted with ice–water, made alkaline with aqueous ammonia, and extracted with chloroform. The extract was dried and evaporated to leave a viscous oil which was chromatographed in chloroform on silica gel. From the first fraction eluted with chloroform unchanged starting material (XXV) (40 mg.) was recovered. The second fraction eluted with chloroform gave 5-*acetoxy*-4a,5,7,8,9,10-

hexahydro-5-methoxy-6H-*benzofuro*[3a,3,2-ef][1]*benzazepin*-11(12H)-*one* (XXIX) (38 mg.) as needles, m.p. 198—201° (from methanol) (Found: C, 65·0; H, 6·3. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4%), $\nu_{max.}$ 3350 (NH), 1725 (OAc), and 1665 (lactam CO) cm.$^{-1}$. Further elution with chloroform-methanol (99 : 1) gave 5-*acetoxy*-4a,5,7,8,9,10-*hexahydro-5-methoxy*-6H-*benzofuro*[3a,3,2-ef][2]*benzazepin*-12(11H)-*one* (XXX) (43 mg.) as needles, m.p. 208—209° (from methanol) (Found: C, 65·3; H, 6·5. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4%), $\nu_{max.}$ 3350 (NH), 1725 (OAc), and 1660 (lactam CO) cm.$^{-1}$.

N-*Methylation of the Acetoxy-lactam* (XXX).—A solution of the acetoxy-lactam (XXX) (40 mg.) in dry toluene (40 ml.) was evaporated to about half its volume with azeotropic removal of a trace of water, and treated with sodium hydride (50% dispersion in oil; 100 mg.) under reflux for 12 hr. Methyl iodide (5 ml.) was then added and the mixture was heated under reflux for a further 8 hr. The excess of sodium hydride was destroyed with dilute acetic acid and the organic layer was separated, washed with aqueous sodium hydrogen sulphite and aqueous sodium carbonate, and dried. Removal of the solvent left a viscous oil which was chromatographed in chloroform on silica gel. Elution with chloroform gave (±)-oxolycoramine acetate (XXXI) (26 mg.) as prisms, m.p. 229—231° (from methanol), identical (mixed m.p. and i.r., n.m.r., and mass spectra) with an authentic sample.

(±)-*Lycoramine* (XXXII).—(±)-Oxolycoramine acetate (XXXI) (50 mg.) was heated under reflux with lithium aluminium hydride (50 mg.) in tetrahydrofuran (20 ml.) for 5 hr. The excess of reagent was destroyed with a slight excess of water and the resulting precipitate was filtered off. The filtrate was evaporated under reduced pressure and the residue was chromatographed in benzene on alumina. Elution with benzene gave (±)-lycoramine (35 mg.) as needles, m.p. 98—99° (from ether–acetone), identical with an authentic sample.[1]

(±)-*Oxolycoramine* (XXXIII) *from* (±)-*Lycoramine* (XXXII).—A solution of potassium permanganate (0·5 g.) in water (50 ml.) was gradually added to a solution of (±)-lycoramine [1] (XXXII) (0·5 g.) in water (30 ml.) below 5°. The precipitate was filtered off, dried at room temperature, and extracted with boiling chloroform. Evaporation of the extract and crystallisation of the residue from ethanol gave (±)-oxolycoramine (XXXIII) as needles, m.p. 245—247°, i.r. spectum (chloroform) identical with that of (−)-oxolycoramine (Found: C, 67·1; H, 7·0. Calc. for $C_{17}H_{21}NO_4$: C, 67·3; H, 7·0%).

(±)-*Oxolycoramine Acetate* (XXXI) *from* (±)-*Oxolycoramine* (XXXIII).—(±)-Oxolycoramine (XXXIII) (100 mg.), sodium acetate (60 mg.), and acetic anhydride (2 ml.) were heated on a water-bath for 2 hr. The mixture was diluted with water and extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was recrystallised (methanol) to give (±)-*oxolycoramine acetate* (XXXI) (100 mg.) as prisms, m.p. 229—231° (Found: C, 65·8; H, 6·8. $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7%), $\nu_{max.}$ 1720 (OAc), 1730 (lactam CO), and 1615 (phenyl) cm.$^{-1}$.

[8/991 *Received, July 12th,* 1968]