The Total Synthesis of (±)-Lycoramine. Part I.

By **Naohiko Hazama, Hiroshi Irie, Tamio Mizutani, Tetsuro Shingu, Masao Takada, Shojiro Uyeo,*** and **Akira Yoshitake,** Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

A stepwise synthesis of (±)-lycoramine, an alkaloid of the Amaryllidaceae, has been achieved by initial construction of rings A and B followed by formation of ring C, and finally establishment of ring D. The Dieckmann cyclisation of dimethyl γ-cyano-γ-(3-ethoxy-2-methoxyphenyl)pimelate (VIII), obtained from 3-ethoxy-2-hydroxybenzaldehyde (III) in five steps, gave methyl 5-cyano-5-(3-ethoxy-2-methoxyphenyl)-2-oxocyclohexanecarboxylate (IX) which was converted into 4-acetoxy-7′-ethoxy-1′,2′-dihydro-8′-methoxyspiro[cyclohexane-1,1′-naphthalen]-4′(3′*H*)-one (XXII) by a sequence of reactions including the Wittig and the Friedel-Crafts. The Schmidt reaction on this compound gave two isomeric lactams (XXV) and (XXVI), the latter of which was *N*-methylated, deacetylated, and oxidised to furnish 7-ethoxy-2,3,4,5-tetrahydro-6-methoxy-2-methyl-1*H*-spiro[2-benzazepine-5,1′-cylcohexane]-1,4′-dione (XXX) which could also be derived from natural lycoramine. By use of this relay substance as a key intermediate, (±)-lycoramine was synthesised.

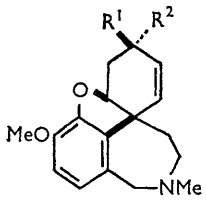
Barton and Kirby [1] have reported a synthesis of galanthamine (I), an alkaloid of the Amaryllidaceae, by a sequence of reactions along the lines of the biogenetic pathway, including a phenol oxidative coupling reaction. This represents the first synthesis of lycoramine (II), which is also an alkaloid of the Amaryllidaceae, isolated earlier by Kondo, Tomimura, and Ishiwata [2] from *Lycoris radiata* Herb., since galanthamine can readily be converted into this alkaloid by

[1] D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806.

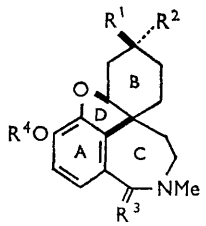
[2] (*a*) H. Kondo, K. Tomimura, and S. Ishiwata, *J. Pharm. Soc. Japan*, 1932, **52**, 433; (*b*) H. Kondo and S. Ishiwata, *Ber.*, 1937, **70**, 2427.

[3] (*a*) S. Uyeo and S. Kobayashi, *Pharm. Bull.* (*Japan*), 1953, **1**, 139; (*b*) S. Uyeo and J. Koizumi, *ibid.*, p. 202; S. Kobayashi, T. Shingu, and S. Uyeo, *Chem. and Ind.*, 1956, 177; S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, 1957, 638; J. Koizumi, S. Kobayashi, and S. Uyeo, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 696; S. Minami and S. Uyeo, *ibid.*, p. 1012.

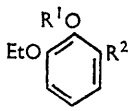
catalytic hydrogenation of its double bond.[3a] In continuation of our studies on the structures of these alkaloids [3] and also as a part of our work [4] on the synthesis of heterocyclic compounds containing a seven-membered nitrogenous ring, our investigation has been directed for several years to the total synthesis of lycoramine (II), which was shown to have such a ring system, by routes which would provide a conclusive chemical proof for its structure. This paper describes our initial total synthesis of this alkaloid.



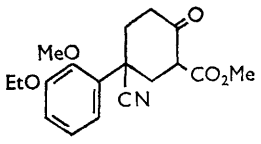
(I) R^1 = OH, R^2 = H
(XXXIX) R^1R^2 = O



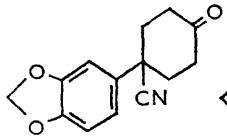
(II) R^1 = OH, R^2 = H, R^3 = H_2, R^4 = Me
(XXXI) R^1R^2 = O, R^3 = O, R^4 = Me
(XXXIII) R^1R^2 = O, R^3 = O, R^4 = H
(XXXIV) R^1R^2 = O, R^3 = O, R^4 = Et
(XXXVI) R^1R^2 = O, R^3 = H_2, R^4 = Me
(XL) R^1 = OH, R^2 = H, R^3 = O, R^4 = Me



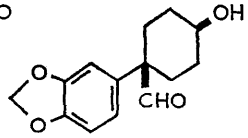
	R^1	R^2
(III)	H	CHO
(IV)	Me	CHO
(V)	Me	CH_2OH
(VI)	Me	CH_2Cl
(VII)	Me	CH_2·CN
(VIII)	Me	$C(CH_2·CH_2·CO_2Me)_2$ | CN



(IX)



(XI)



(XII)

As in our synthesis of dihydrocrinine,[4a] our approach was directed toward the construction of rings A and B of lycoramine before formation of the seven-membered nitrogenous ring C and finally construction of the dihydrofuran ring D.

3-Ethoxy-2-hydroxybenzaldehyde (III), which was at the time more readily available to us than its 3-methoxy-analogue, was selected as starting material. It was converted into 3-ethoxy-2-methoxybenzaldehyde (IV) by methylation and submitted to the crossed Cannizzaro reaction in the presence of formaldehyde to form in good yield the benzyl alcohol (V), which was then converted into the corresponding benzyl cyanide (VII) by way of the benzyl chloride (VI). Michael condensation of the cyanide (VII) with methyl acrylate in the presence of Triton B afforded the oily methyl pimelate (VIII), which on Dieckmann cyclisation yielded the keto-ester (IX). When the keto-ester (IX) was treated with acid, saponification of the ester group and decarboxylation occurred and the keto-nitrile (X) was obtained. The structure of (X) was confirmed by its i.r. spectrum: $\nu_{max.}$ 2220 (CN) and 1715 (CO) cm.$^{-1}$. Since 4-hydroxy-1-(3,4-methylenedioxyphenyl)cyclohexanecarbaldehyde (XII) [4a] is obtainable in good yield from lithium aluminium hydride reduction of the keto-nitrile (XI), the new keto-nitrile (X) was submitted to the same reaction. This reaction gave, however, a mixture of the hydroxy-aldehyde (XIII), the hydroxy-nitrile (XIV), and the hydroxy-amine (XV), and the yield of the desired hydroxy-aldehyde (XIII) did not exceed 30% under a variety of reaction conditions. An attempt to convert the keto-nitrile (X) into the keto-aldehyde (XIII; =O for OH) by the Stephen reaction [5] gave only unchanged starting material, and the reduction of the hydroxy-nitrile (XIV) with di-isobutylaluminium hydride [6] was unsuccessful; no change in the nitrile group was observed, presumably owing to steric hindrance. The poor yield of the hydroxy-aldehyde (XIII) from the keto-nitrile (X) is the chief disadvantage of this synthesis of lycoramine; a better synthesis is described in the following paper.

The hydroxy-aldehyde (XIII) was treated with acetic anhydride in pyridine. The resulting acetoxy-aldehyde (XVI) was condensed with triethyl phosphonoacetate by a modified Wittig reaction [7] to give the acetoxy-acrylate (XVII). The structure of this was supported by elemental analysis and i.r. spectrum: $\nu_{max.}$ 1736 (OAc), 1719 (αβ-unsaturated ester), and 1640 (C=C) cm.$^{-1}$. Hydrogenation of this acrylate (XVII) over Adams catalyst gave, after slow absorption of hydrogen (1 equiv.), the acetoxy-propionate (XVIII). This dihydro-compound, without further purification, was saponified in alkali to afford the hydroxy-propionic acid (XIX), which was acetylated with acetic anhydride in pyridine. The resulting acetoxy-propionic acid (XX) was cyclised by way of its acid chloride (XXI) in the presence of stannic chloride in benzene to furnish fair yields of the acetoxy-naphthalenone (XXII), which was purified by column chromatography on silica gel.

During the preparation of (XXII), we have occasionally noticed the formation of small amounts of a con-

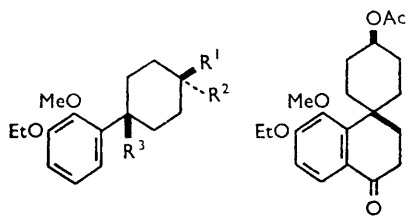
[4] (*a*) S. Uyeo, H. Irie, A. Yoshitake, and A. Ito, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 427; H. Irie, S. Uyeo, and A. Yoshitake, *J. Chem. Soc.* (*C*), 1968, 1802; (*b*) S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 1033; S. Minami, M. Tomita, H. Takamatsu, and S. Uyeo, *ibid.*, 1965, **13**, 1084.

[5] H. Stephen, *J. Chem. Soc.*, 1925, **127**, 1874.

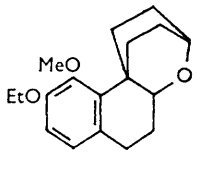
[6] L. I. Zakharkin and I. M. Khorlina, *Doklady Akad. Nauk S.S.S.R.*, 1957, **116**, 422.

[7] W. S. Wadsworth, jun., and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.

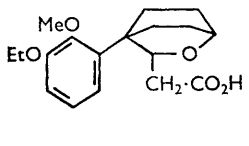
taminant which had the correct analysis for $C_{18}H_{22}O_4$ and was assigned the structure (XXIII), based on its spectral properties. The i.r. spectrum did not show any hydroxy- or acetyl-absorption, but did exhibit an aryl ketone band at 1668 cm.$^{-1}$. The n.m.r. spectrum showed signals at τ 2·16 and 3·11 (2H, AB-type quartet) corresponding to aromatic protons, and at τ 5·66 (1H, t) and 6·80 (1H, m) assigned to the protons on the carbons bearing the ether-type oxygen. Such a compound (XXIII) may be formed from a small amount of the acetoxy-acrylate (XVII) which survived hydrogenation of the double bond which underwent an intramolecular Michael-type addition under the alkaline saponification



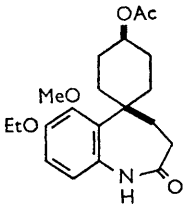
(XXII)



(XXIII)



(XXIV)



(XXV)

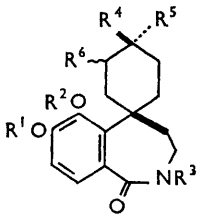
	R^1	R^2	R^3
(X)	O		CN
(XIII)	OH	H	CHO
(XIV)	OH	H	CN
(XV)	OH	H	$CH_2{\cdot}NH_2$
(XVI)	OAc	H	CHO
(XVII)	OAc	H	$CH{=}CH{\cdot}CO_2Et$
(XVIII)	OAc	H	$CH_2{\cdot}CH_2{\cdot}CO_2Et$
(XIX)	OH	H	$CH_2{\cdot}CH_2{\cdot}CO_2H$
(XX)	OAc	H	$CH_2{\cdot}CH_2{\cdot}CO_2H$
(XXI)	OAc	H	$CH_2{\cdot}CH_2{\cdot}COCl$

conditions to form an ether (XXIV) which was then transformed by the Friedel-Crafts reaction to the compound (XXIII). Such an ether formation took place in the case of 4-hydroxy-1-(3,4-methylenedioxyphenyl)cyclohexaneacrylic acid.[4a]

The acetoxy-naphthalenone (XXII) was subjected to the Schmidt reaction in trichloroacetic acid to give a mixture of isomeric lactams which, after chromatography on silica gel, yielded (XXV) and (XXVI) (3 : 2). The structure of the desired compound (XXVI) was established by the spectral data of the corresponding amino-compound obtained by reduction with lithium aluminium hydride. This amine exhibited no hypsochromic shift in the u.v. spectrum in acid in contrast to the aniline-type compound derived from (XXV) by similar reduction. The i.r. spectral data [4] so far accumulated on analogous compounds in our laboratory agreed well with those of (XXV) and (XXVI), which exhibited lactam bands at 1670 and 1650 cm.$^{-1}$ respectively.

The desired acetoxy-lactam (XXVI), possessing the homoisocarbostyril skeleton, is oily, and its homogeneity was confirmed by conversion into the crystalline hydroxy-lactam (XXVII) by alkaline saponification. The acetoxy-lactam (XXVI) was then converted into its *N*-methyl derivative (XXVIII) by treatment with sodium hydride followed by methyl iodide in boiling toluene. This *N*-methyl-acetoxy-lactam (XXVIII), without further purification, was deacetylated to form the *N*-methyl-hydroxy-lactam (XXIX), which was oxidized with chromic acid in acetic acid to give the *N*-methyl-keto-lactam (XXX). Spectral properties and the elemental analysis confirmed the structure of this product.

Although this compound possesses the ABC ring system comparable to lycoramine, the amount of the material obtained after the many steps required was so small that it would not have been possible to proceed if we had not found that the dihydrofuran ring of natural oxolycoraminone (XXXI), in contrast to that of lycoraminone (XXXVI), is cleaved smoothly by catalytic hydrogenolysis in alkali. The resulting phenolic keto-lactam (XXXII) no longer has the asymmetric centre because of the plane of symmetry and hence is optically inactive. This compound (XXXII) differs from the synthetically obtained *N*-methyl-keto-lactam



	R^1	R^2	R^3	R^4	R^5	R^6
(XXVI)	Et	Me	H	OAc	H	H
(XXVII)	Et	Me	H	OH	H	H
(XXVIII)	Et	Me	Me	OAc	H	H
(XXIX)	Et	Me	Me	OH	H	H
(XXX)	Et	Me	Me	O		H
(XXXII)	Me	H	Me	O		H
(XXXV)	Et	H	Me	O		H
(XXXVII)	Et	Me	Me	O		Br
(XXXVIII)	Et	Me	Me	O		Double bond $\alpha\beta$- to keto-carbonyl

(XXX) with respect to the alkyl ether moiety in ring A; the former possesses a hydroxy- and a methoxy-group at positions 6 and 7, while the latter has a methoxy- and an ethoxy-group at positions 6 and 7, respectively.

However, by the use of the ethyl analogue (XXXIV) of oxolycoraminone, the synthetic compound (XXX) was derived from natural sources.

The ethyl analogue (XXXIV) was prepared by demethylation of oxolycoraminone (XXXI) with boron tribromide followed by ethylation of the resulting demethyloxolycoraminone (XXXIII) with ethyl iodide in the presence of potassium carbonate in acetone. Hydrogenolysis of this over palladium–carbon in the presence of sodium ethoxide gave the phenolic keto-lactam (XXXV) used in the preparation of (XXXII). In the n.m.r. spectrum of (XXXV), the proton signal on the carbon of the cyclohexanone ring bearing the oxygen of the dihydrofuran ring observed in the spectrum of (XXXIV) had disappeared, indicating that the cleavage of the dihydrofuran ring of (XXXIV) had occurred. Methylation of the phenolic keto-lactam (XXXV) gave, as expected, a compound identical with the synthetic product (XXX).

An ample supply of the key intermediate (XXX) enabled us to proceed on the indicated pathway to (±)-lycoramine (II). Bromination of (XXX) in chloroform gave the monobromide (XXXVII), which was treated with lithium carbonate and lithium chloride in dimethylformamide to furnish the αβ-unsaturated ketone (XXXVIII) which, without isolation, was then dealkylated with boron tribromide in methylene chloride to give (±)-demethyloxolycoraminone (XXXIII) in 5% overall yield based on (XXX). The racemic (XXXIII) was spectrographically identical with a sample of natural demethyloxolycoraminone (XXXIII) but differed in optical properties and m.p.

Methylation of the phenolic function of (±)-(XXXIII) with methyl iodide and potassium carbonate in acetone regenerated (±)-oxolycoraminone (XXXI), the spectral data of which were identical with those of natural oxolycoraminone (XXXI). Lithium aluminium hydride reduction of (±)-oxolycoraminone (XXXI) in tetrahydrofuran gave (±)-lycoramine (II), with i.r. (chloroform) and n.m.r. spectra identical with those of natural lycoramine, but with different optical rotation and m.p.

Further correlation of synthetic (±)-lycoramine (II) with that from natural sources was obtained by hydrogenation of (±)-narwedine (XXXIX), prepared from galanthamine (I) by the reported method,[1,8] to give (±)-lycoraminone (XXXVI), which was treated with lithium aluminium hydride to furnish (±)-lycoramine (II), identical with our final product.

EXPERIMENTAL

Ultraviolet absorptions were recorded for solutions in ethanol and i.r. spectra for solutions in chloroform. N.m.r. spectra were obtained with a Varian A-60 spectromer for solutions in deuteriochloroform with tetramethylsilane as internal reference. Mass spectra were determined with a Hitachi RMU-6D mass spectromer with a direct heated-inlet system.

3-Ethoxy-2-methoxybenzyl Alcohol (V).—A solution of 3-ethoxy-2-methoxybenzaldehyde (IV)[9] (32 g.) and 37% formalin (24 ml.) in methanol (20 ml.) was added dropwise to a stirred solution of potassium hydroxide (36 g.) in methanol (45 ml.) at 55—57°. The mixture was stirred for 4 hr. at this temperature and then heated under reflux for 1 hr. After dilution with water, the mixture was extracted with benzene. The extract was washed with dilute hydrochloric acid and with water, dried, and evaporated. Distillation of the residue under reduced pressure gave the *benzyl alcohol* (V) (24·6 g.) as an oil, b.p. 145—147°/10 mm.; *p*-nitrobenzoate, m.p. 80—81° (from ethanol) (Found: C, 61·4; H, 5·0. $C_{17}H_{17}NO_6$ requires C, 61·6; H, 5·2%).

3-Ethoxy-2-methoxybenzyl Cyanide (VII).—Thionyl chloride (65 ml.) in dry benzene (75 ml.) was added to a stirred solution of the benzyl alcohol (V) (43 g.) in dry benzene (55 ml.). The mixture was heated under reflux for 3 hr. and then evaporated to dryness under reduced pressure, and the resulting chloride (VI) was taken up in ethanol (150 ml.). This solution was added to a stirred solution of potassium cyanide (45 g.) in water (140 ml.) and the mixture was heated under reflux for 8 hr. It was then evaporated under reduced pressure to *ca.* half volume, diluted with water, and extracted with benzene. The extract was washed with water and dried. Removal of the solvent and distillation of the residue under reduced pressure gave the *cyanide* (VII) (30·2 g.), b.p. 115—125/° 0·7 mm., which gave leaflets, m.p. 46° (from n-hexane–benzene) (Found: C, 68·8; H, 6·9. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·9%), $\nu_{max.}$ 2240 (CN) cm.$^{-1}$.

Dimethyl γ-Cyano-γ-(3-ethoxy-2-methoxyphenyl)pimelate (VIII).—A solution of 40% methanolic Triton B (19 ml.) in t-butyl alcohol (28 ml.) was added rapidly to a stirred boiling solution of the benzyl cyanide (VII) (24 g.), and methyl acrylate (58 ml.) in t-butyl alcohol (60 ml.). The mixture was heated under reflux for 4 hr., the solvent was distilled off, and the residue was dissolved in chloroform. The chloroform solution was washed with dilute hydrochloric acid and water, dried, and evaporated. Distillation of the residue under reduced pressure gave the *pimelate* (VIII) (24 g.) as a viscous oil, b.p. 200—205°/ 0·7 mm. (Found: C, 63·1; H, 6·8. $C_{19}H_{25}NO_6$ requires C, 62·8; H, 6·9%), $\nu_{max.}$ 2240 (CN) and 1730 (CO_2Me) cm.$^{-1}$.

Methyl 5-Cyano-5-(3-ethoxy-2-methoxyphenyl)-2-oxocyclohexanecarboxylate (IX).—The pimelate (VIII) (15 g.), and sodium hydride (6 g.; 50% dispersion in oil) were heated under reflux for 5 hr. in dry toluene (500 ml.). The mixture was acidified with dilute acetic acid and the organic layer was separated, washed with aqueous sodium carbonate and with water, dried, and evaporated. The residue was washed with n-hexane and gave the β-*keto-ester* (IX) (12 g.), m.p. 132° (from methanol) (Found: C, 64·8; H, 6·2. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4%), $\nu_{max.}$ 3150 (enolic OH), 2222 (CN), 1720sh (CO_2Me), 1661 (enolic C=C), and 1620 (phenyl) cm.$^{-1}$.

1-(3-Ethoxy-2-methoxyphenyl)-4-oxocyclohexanecarbonitrile (X).—The β-keto-ester (IX) (7 g.) was heated on a water-bath with acetic acid (140 ml.) and 10% sulphuric acid (70 ml.) for 5 hr. The mixture was extracted with benzene, and the extract was washed with water and with aqueous sodium carbonate, dried, and evaporated to dryness. The residue gave the *keto-nitrile* (X) (4·5 g.) as flakes, m.p.

[8] (*a*) H. M. Fales, L. D. Giuffrida, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1956, **78**, 4145; (*b*) J. Koizumi, S. Kobayashi, and S. Uyeo, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 696.

[9] W. Davies, *J. Chem. Soc.*, 1923, **123**, 1575.

125° (from methanol) (Found: C, 70·0; H, 7·0. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0%), $\nu_{max.}$ 2220 (CN) and 1715 (CO) cm.$^{-1}$.

Action of Lithium Aluminium Hydride on the Keto-nitrile (X).—The keto-nitrile (X) (2·0 g.) was heated under reflux with lithium aluminium hydride (250 mg.) in tetrahydrofuran (100 ml.) for 5 hr. The excess of the reagent was decomposed with water, the precipitate was filtered off, and the filtrate was evaporated to dryness to leave a residue which was taken up in chloroform. The chloroform solution was extracted with ice-cold dilute hydrochloric acid. The chloroform layer was dried and evaporated to give 1-(3-*ethoxy*-2-*methoxyphenyl*)-4-*hydroxycyclohexanecarbo-nitrile* (XIV) (1·2 g.) as prisms, m.p. 131° (from n-hexane–acetone) (Found: C, 69·9; H, 7·6; N, 5·2. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·7; N, 5·1%), $\nu_{max.}$ 3310 (OH) and 2237 (CN) cm.$^{-1}$. The acidic aqueous layer was basified with aqueous ammonia and extracted with chloroform. The extract was evaporated and the residue was heated with concentrated sulphuric acid (1 drop) in 50% acetic acid (15 ml.) on a water-bath for 30 min. The mixture was extracted with chloroform, and the organic layer was washed with water, dried, and evaporated to give 1-(3-*ethoxy*-2-*methoxyphenyl*)-4-*hydroxycyclohexanecarbaldehyde* (XIII) (0·69 g.), as needles, m.p. 112° (from ether) (Found: C, 68·9; H, 7·8. $C_{16}H_{22}O_4$ requires C, 69·0; H, 8·0%), $\nu_{max.}$ 3290 (OH), 2720 (CH), and 1715 (CO) cm.$^{-1}$. Basification of the aqueous layer with aqueous ammonia was followed by extraction with chloroform. The extract was dried and evaporated to give 4-aminomethyl-4-(3-ethoxy-2-methoxy-phenyl)cyclohexanol (XV) (0·08 g.) as an oil, *picrate* (yellow needles), m.p. 186° (Found: C, 50·5; H, 6·0. $C_{16}H_{25}NO_3,C_6H_3N_3O_7,H_2O$ requires C, 50·2; H, 5·7%).

4-*Acetoxy*-1-(3-*ethoxy*-2-*methoxyphenyl*)*cyclohexanecarb-aldehyde* (XVI).—The hydroxy-aldehyde (XIII) (2·7 g.) was kept overnight with acetic anhydride (3 ml.) and pyridine (9 ml.) at room temperature and worked up in the usual way. Crystallisation from methanol gave the *acetate* (XVI) (2·6 g.) as needles, m.p. 77—78° (Found: C, 67·7; H, 7·6. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·6%), $\nu_{max.}$ 2710 (CH) and 1730 (CHO and Ac) cm.$^{-1}$.

Ethyl 4-*Acetoxy*-1-(3-*ethoxy*-2-*methoxyphenyl*)*cyclohexane-acrylate* (XVII).—Triethyl phosphonoacetate (250 mg.) was added to a suspension of sodium hydride (60 mg.; 50% dispersion in oil) in dry benzene (5 ml.) below 25°. The mixture was stirred for 30 min. and then added dropwise, at 20—25°, to the acetoxy-aldehyde (XVI) (220 mg.) in dry benzene (10 ml.). Stirring was continued at room temperature for 2 hr., water was added to the mixture, and the organic layer was separated, dried, and evaporated to give the *acrylate* (XVII) (240 mg.) as prisms, m.p. 105° (from methanol) (Found: C, 67·5; H, 7·9. $C_{22}H_{30}O_6$ requires C, 67·7; H, 7·7%), $\lambda_{max.}$ 277 mμ (log ε 3·20), $\nu_{max.}$ 1736 (Ac), 1714 (αβ-unsaturated ester), and 1640 (C=C) cm.$^{-1}$.

Ethyl 4-*Acetoxy*-1-(3-*ethoxy*-2-*methoxyphenyl*)*cyclohexane-propionate* (XVIII).—The acrylate (XVII) (380 mg.) was hydrogenated in ethanol (50 ml.) over Adams catalyst (50 mg.). After the calculated volume of hydrogen had been consumed, the solution was filtered from the catalyst. Evaporation of the filtrate gave the propionate (XVIII) (360 mg.) as an amorphous solid which did not crystallise.

1-(3-*Ethoxy*-2-*methoxyphenyl*)-4-*hydroxycyclohexanepro-pionic Acid* (XIX).—The crude propionate (XVIII) (260 mg.) was heated under reflux with 5% aqueous potassium hydroxide (5 ml.) in ethanol (20 ml.) for 3 hr. The mixture was concentrated, diluted with water, washed with ether, acidified, and extracted with ether. The extract was washed with water, dried, and evaporated to leave a residue which gave the *propionic acid* (XIX) (200 mg.) as prisms, m.p. 136—137° (from ethanol) (Found: C, 66·8; H, 8·3. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·1%), $\nu_{max.}$ 3500—3000 (OH) and 1710 (CO_2H) cm.$^{-1}$.

4-*Acetoxy*-1-(3-*ethoxy*-2-*methoxyphenyl*)*cyclohexanepro-pionic Acid* (XX).—The hydroxy-propionic acid (XIX) (170 mg.) was treated with acetic anhydride (1 ml.) in pyridine (3 ml.) at room temperature over-night. Work-up in the usual way gave the acetoxy-propionic acid (XX) (170 mg.), which could not be crystallised.

4-*Acetoxy*-7′-*ethoxy*-1′,2′-*dihydro*-8′-*methoxyspiro*[*cyclo-hexane*-1,1′-*naphthalen*]-4′(3′H)-*one* (XXII).—Phosphorus pentachloride (320 mg.) was added to a solution of the acetoxy-propionic acid (XX) (170 mg.) in dry benzene (10 ml.) at 0°. The mixture was stirred for 1 hr., stannic chloride (540 mg.) was added, and stirring was continued for 1 hr. at 0°. Ice and dilute hydrochloric acid were then added and the organic layer was separated, washed with dilute hydrochloric acid, water, and aqueous sodium carbonate, and dried. Removal of the solvent left an oil which was chromatographed on silica gel. Elution with chloroform gave the *spiro*[*cyclohexanenaphthalene*] (XXII) (130 mg.), as prisms, m.p. 133—134° (from n-hexane–benzene) (Found: C, 69·3; H, 7·7. $C_{22}H_{26}O_5$ requires C, 69·3; H, 7·6%), $\lambda_{max.}$ 233 and 280 mμ (log ε 4·39 and 4·20), $\nu_{max.}$ 1732 (Ac) and 1683 (aryl CO) cm.$^{-1}$.

9-*Ethoxy*-2,3,4a,5,6,10b-*hexahydro*-10-*methoxy*-1H-3,10b-*ethanonaphtho*[2,1-b]*pyran*-6-*one* (XXIII).—The mother-liquors from the compound (XXII) obtained in several experiments were combined and chromatographed in chloroform on silica gel. The initial chloroform eluate gave the *naphthopyran* (XXIII) in small yield. It gave leaflets, m.p. 110° (from methanol) (Found: C, 71·7; H, 7·6. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%), $\nu_{max.}$ 1668 (aryl CO) cm.$^{-1}$.

Schmidt Reaction on the Acetoxy-ketone (XXII).—Sodium azide (560 mg.) was added in portions during 30 min. to a stirred solution of the acetoxy-ketone (XXII) (1·7 g.) in trichloroacetic acid (26 g.) at 60° and stirring was continued at this temperature for 2·5 hr. Ice–water was added to the mixture, and the whole was 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. The initial fraction eluted with chloroform gave 4′-acetoxy-7-ethoxy-1,3,4,5-tetrahydro-6-methoxy-2*H*-spiro-[1-benzazepine-5,1′-cyclo-hexan]-2-one (XXV) (870 mg.) as an oil, $\nu_{max.}$ 3380 (NH), 1725 (Ac), and 1670 (lactam CO) cm.$^{-1}$. This compound (5 mg.) was reduced with lithium aluminium hydride (10 mg.) to the amine, $\lambda_{max.}$ 249 and 306 mμ, shifted to 220 and 283 mμ on addition of hydrochloric acid. Further elution with chloroform gave 4′-acetoxy-7-ethoxy-2,3,4,5-tetra-hydro-6-methoxy-1*H*-spiro-[2-benzazepine-5,1′-cyclo-hexan]-1-one (XXVI) (530 mg.) as an oil, $\nu_{max.}$ 3430 (NH), 1720 (Ac), and 1650 (lactam CO) cm.$^{-1}$. A portion (5 mg.) of this compound was reduced with lithium aluminium hydride (10 mg.) to the amine, $\lambda_{max.}$ 253 and 283 mμ, unchanged on addition of hydrochloric acid.

7-*Ethoxy*-2,3,4,5-*tetrahydro*-4′-*hydroxy*-6-*methoxy*-1H-*spiro*-[2-*benzazepine*-5,1′-*cyclohexan*]-1-*one* (XXVII).—The acetoxy-lactam (XXVI) (75 mg.) was heated under reflux

with 5% aqueous potassium hydroxide (5 ml.) in ethanol (16 ml.) for 2 hr. The mixture was concentrated, diluted with water, and extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue gave the *hydroxy-lactam* (XXVII) (65 mg.), as needles, m.p. 230° (from methanol) (Found: C, 67·4; H, 7·7. $C_{18}H_{25}NO_4$ requires C, 67·7; H, 7·9%), $\nu_{max.}$ 3430 (NH), 3300 (OH), and 1648 (lactam CO) cm.$^{-1}$.

4′-Acetoxy-7-ethoxy-2,3,4,5-tetrahydro-6-methoxy-2-methyl-1H-spiro-[2-benzazepine-5,1′-cyclohexan]-1-one (XXVIII).—A solution of the acetoxy-lactam (XXVI) (400 mg.) in dry toluene (100 ml.) was evaporated to *ca.* half volume with azeotropic removal of a trace of water. Sodium hydride (150 mg.; 50% dispersion in oil) was added to the solution and the whole was heated under reflux for 10 hr. Methyl iodide (2 ml.) was then added and the mixture was heated under reflux for a further 10 hr. After addition of acetic acid and water, the organic layer was separated, washed with aqueous sodium disulphite and aqueous sodium carbonate, and dried. Removal of the solvent left an oil which was chromatographed in chloroform on silica gel. Elution with chloroform gave the *N*-methyl-acetoxy-lactam (XXVIII) as a viscous oil (350 mg.), $\nu_{max.}$ 1720 (Ac) and 1630 (lactam CO) cm.$^{-1}$.

7-Ethoxy-2,3,4,5-tetrahydro-4′-hydroxy-6-methoxy-2-methyl-1H-spiro-[2-benzazepine-5,1′-cyclohexan]-1-one (XXIX).—The *N*-methyl-acetoxy-lactam (XXVIII) (300 mg.) was heated under reflux with 5% aqueous potassium hydroxide (10 ml.) and ethanol (10 ml.) for 1 hr. After removal of the ethanol, the solution was extracted with chloroform and the extract was dried and evaporated to leave the *N*-methyl-hydroxy-lactam (XXIX) as an oil (288 mg.), $\nu_{max.}$ 3400 (OH) and 1630 (lactam CO) cm.$^{-1}$.

7-Ethoxy-2,3,4,5-tetrahydro-6-methoxy-2-methyl-1H-spiro-[2-benzazepine-5,1′-cyclohexane]-1,4′-dione (XXX).—Chromium trioxide (130 mg.) in water (0·5 ml.) and acetic acid (5 ml.) was added to the *N*-methyl-hydroxy-lactam (XXIX) (250 mg.) in acetic acid (5 ml.) and the mixture was kept overnight at room temperature. Methanol was then added and the mixture was concentrated under reduced pressure to a small volume. The concentrate was diluted with water and extracted with chloroform. The extract was washed with water and aqueous sodium carbonate, dried, and evaporated to leave a residue which gave the *N-methyl-keto-lactam* (XXX) (190 mg.) as needles, m.p. 143—145° (from ether) (Found: C, 68·7; H, 7·6. $C_{19}H_{25}NO_4$ requires C, 68·8; H, 7·6%), $\nu_{max.}$ 1713 (CO) and 1630 (lactam CO) cm.$^{-1}$, τ 8·50 (3H, t, J 7 c./sec., O·CH$_2$·C*H*$_3$), 6·88 (3H, s, NMe), 6·28 (3H, s, OMe), 5·68 (2H, q, J 7 c./sec., O·C*H*$_2$·CH$_3$), and 2·49 and 3·10 (2H, AB-type q, J 8·5 c./sec., aromatic protons).

Demethyloxolycoraminone (XXXIII).—Boron tribromide (3 ml.) was added to a solution of oxolycoraminone (XXXI) (1·5 g.) in methylene chloride (300 ml.) below 5°. The mixture was set aside overnight at 5°, water was added, and the organic layer was separated and extracted with 5% aqueous sodium hydroxide. The extract was acidified and extracted with chloroform. This extract was washed with water, dried, and evaporated to leave a semi-solid which was chromatographed in chloroform on Florisil. Elution with chloroform–ethanol (98 : 2) gave the *demethylation product* (XXXIII) (1·1 g.) as colourless needles, m.p. 240—242° (from acetone), $[\alpha]_D$ −281·6° (*c* 0·16 in chloroform) (Found: C, 66·7; H, 5·9. $C_{16}H_{17}NO_4$ requires C, 66·9; H, 6·0%), $\nu_{max.}$ 3200 (OH), 1715 (CO), and 1615 (lactam CO) cm.$^{-1}$. The optical rotations of oxolycoramine (XL), and oxolycoraminone (XXXI) derived from natural (−)-lycoramine (II) were erroneously described as dextrorotatory in the previous paper.[2b] Our re-examination gave the following values: lycoraminone (XXXVI), $[\alpha]_D$ −241·1° (*c* 0·99 in chloroform); oxolycoramine, $[\alpha]_D$ −95·5° (*c* 0·98 in chloroform); oxolycoraminone, $[\alpha]_D$ −276·6° (*c* 1·00 in chloroform).

Ethylation of Demethyloxolycoraminone (XXXIII).—Demethyloxolycoraminone (XXXIII) (100 mg.) was heated under reflux with ethyl iodide (3 ml.) and potassium carbonate (200 mg.) in acetone (15 ml.) for 4 hr. After concentration of the mixture water was added and the whole was extracted with chloroform. The chloroform layer was washed with 5% aqueous sodium hydroxide, dried, and evaporated to dryness to leave a solid which gave the *ethyl ether* (XXXIV) (100 mg.) as needles, m.p. 205—207° (from methanol), $[\alpha]_D$ −247·1° (*c* 0·95 in chloroform) (Found: C, 68·8; H, 6·9. $C_{18}H_{21}NO_4$ requires C, 68·6; H, 6·7%), $\nu_{max.}$ 1715 (CO), 1625 (lactam CO), and 1615 (phenyl) cm.$^{-1}$.

Catalytic Hydrogenolysis of Oxolycoraminone (XXXI).—A solution of oxolycoraminone (XXXI) (80 mg.) in absolute ethanol (10 ml.) was submitted to hydrogenolysis in hydrogen over 10% palladium–carbon (500 mg.) in the presence of potassium t-butoxide (50 mg.). After removal of the catalyst and the solvent, the residue was dissolved in water and washed with ether. Acidification of the aqueous layer was followed by extraction with chloroform. The extract was washed with water, dried, and evaporated to leave a semi-solid which was chromatographed in chloroform on silica gel. Elution with chloroform gave 2,3,4,5-tetrahydro-6-hydroxy-7-methoxy-2-methyl-1*H*-spiro-[2-benzazepine-5,1′-cyclohexane]-1,4′-dione (XXXII) (40 mg.) as fine crystals, m.p. 196—198° (from acetone) [Found: *M*, 303 (mass spectrum). Calc. for $C_{17}H_{21}NO_4$: *M*, 303], $\nu_{max.}$ 3400 (OH), 1705 (CO), and 1625 (lactam CO) cm.$^{-1}$.

Catalytic Hydrogenolysis of the Ethyl Analogue (XXXIV) *of Oxolycoraminone*.—A solution of the ethyl analogue (XXXIV) (610 mg.) of oxolycoraminone in absolute ethanol (35 ml.) was shaken in hydrogen over 10% palladium–carbon (1 g.) in the presence of sodium ethoxide (300 mg.). Work-up gave *7-ethoxy-2,3,4,5-tetrahydro-6-hydroxy-2-methyl-1H-spiro-[2-benzazepin-5,1′-cyclohexane]-1,4′-dione* (XXXV) (330 mg.) as fine crystals, m.p. 183—186° (from acetone) (Found: C, 68·4; H, 7·4. $C_{18}H_{23}NO_4$ requires C, 68·1; H, 7·3%), $\nu_{max.}$ 3400 (OH), 1705 (CO), and 1625 (lactam CO) cm.$^{-1}$.

Methylation of the Phenolic Keto-lactam (XXXV).—The phenolic keto-lactam (XXXV) (300 mg.) was heated under reflux with methyl iodide (5 ml.) in acetone (20 ml.) for 4 hr. in the presence of potassium carbonate (400 mg.). The mixture was evaporated to dryness to leave a residue to which water was added, and the insoluble product was extracted with chloroform. The extract was washed with 5% aqueous sodium hydroxide, dried, and evaporated. The residue gave the methoxy-keto-lactam (295 mg.) as needles, m.p. 143—145° (from ether), identical in mixed m.p. and i.r. and n.m.r. spectra with the *N*-methyl-keto-lactam (XXX) described above.

(±)-*Demethyloxolycoraminone* (XXXIII).—Bromine (160 mg.) in chloroform (5 ml.) was added with stirring to a cold mixture of the keto-lactam (XXX) (300 mg.) and calcium carbonate (200 mg.) in chloroform (20 ml.). After the colour of the mixture had been discharged, stirring was

continued for 15 min. Water was added and the organic layer was separated, washed with water, and dried. Removal of the solvent left a viscous oil (370 mg.). This crude bromide (XXXVII) (370 mg.) was dissolved in dimethylformamide (55 ml.) and the solution was heated under reflux under nitrogen with lithium carbonate (130 mg.) and lithium chloride (700 mg.) for 5 hr. The mixture was acidified with dilute hydrochloric acid, diluted with water, and extracted with benzene. The extract was washed with aqueous sodium carbonate and water and dried, and the benzene was distilled off to leave an oil which was chromatographed in chloroform on silica gel. The chloroform eluate (XXXVIII) (100 mg.) which showed $\nu_{max.}$ 1670 cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone) was dissolved in methylene chloride (100 ml.) and treated with boron tribromide (1 ml.) while being stirred and cooled in ice. The mixture was set aside overnight at 5°, water was added, and the organic layer was washed with water, dried, and evaporated to leave an oil which was chromatographed in chloroform on Florisil. Elution with chloroform–ethanol (98 : 2) and crystallisation from acetone gave the (±)-demethyloxolycoraminone (XXXIII) (15 mg.) as needles, m.p. 229—231° [Found: *M*, 287 (mass spectrum). Calc. for $C_{16}H_{17}NO_4$: *M*, 287], identical in i.r. (chloroform) and mass spectra of this compound with natural demethyloxolycoraminone (XXXIII).

(±)-*Oxolycoraminone* (XXXI).—A solution of (±)-demethyloxolycoraminone (XXXIII) (30 mg.) and methyl iodide (2 ml.) in acetone (10 ml.) was heated under reflux with potassium carbonate (100 mg.) for 4 hr. After evaporation of the mixture, water was added and the whole was extracted with chloroform. The extract was washed with 5% aqueous sodium hydroxide, dried, and evaporated to dryness to leave a solid which gave (±)-oxolycoraminone (XXXI) as prisms, m.p. 185—190° (from ethanol) [Found: *M*, 301 (mass spectrum). Calc. for $C_{17}H_{19}NO_4$: *M*, 301], i.r. (chloroform) and mass spectra identical with those of natural oxolycoraminone (XXXI).

(±)-*Lycoramine* (II).—(±)-Oxolycoraminone (XXXI) (20 mg.) was heated under reflux with lithium aluminium hydride (20 mg.) in tetrahydrofuran (10 ml.) for 5 hr. The excess of reagent was decomposed with a slight excess of water, the precipitate was filtered off, and the filtrate was evaporated to dryness to leave a residue which was chromatographed in benzene on alumina. Elution with benzene and crystallisation from acetone–ether gave (±)-lycoramine (II) (15 mg.) as needles, m.p. 98—99°, identical in mixed m.p. and i.r. spectrum with an authentic sample of (±)-lycoramine prepared as described below.

(±)-*Lycoraminone* (XXXVI).—(±)-Narwedine (XXXIX) (1·6 g.) in ethanol (100 ml.) was hydrogenated over 10% palladium–carbon (0·5 g.). When the calculated volume of hydrogen had been consumed, the mixture was filtered and evaporated to leave a semi-solid which was chromatographed in chloroform on silica gel. Elution with chloroform and crystallisation from acetone–ether gave (±)-lycoraminone (XXXVI) (1·4 g.) as fine crystals, m.p. 99—100°, i.r. spectrum (chloroform) identical with that of natural lycoraminone (XXXVI).

(±)-*Lycoramine* (II).—(±)-Lycoraminone (XXXVI) (300 mg.) was heated under reflux with lithium aluminium hydride (100 mg.) in tetrahydrofuran (50 ml.) for 3 hr. The mixture was treated with a slight excess of water, the precipitate was filtered off, and the solvent was removed. The residue was chromatographed in benzene on alumina. The benzene eluate was crystallised from acetone–ether to yield (±)-lycoramine (II) (250 mg.) as needles, m.p. 98—99° [Found: *M*, 289 (mass spectrum). Calc. for $C_{17}H_{23}NO_3$: *M*, 289], i.r. (chloroform) and mass spectra were identical with those of (−)-lycoramine (II).

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