# Synthesis of δ-Lycorane derived from the Alkaloid Caranine

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δ-Lycorane (IV), one of the four possible stereoisomers of the skeleton of the Amaryllidaceae alkaloids including lycorine and caranine, was synthesised from methyl 1,2,*t*-4a,*t*-9a-tetrahydro-6,7-methylenedioxy-9-oxofluorene-*r*-1-carboxylate (V). Treatment of its hydrogenation product with base gave the epimeric methyl 1,2,3,4,*c*-4a,*c*-9a-hexahydro-6,7-methylenedioxy-9-oxofluorene-*r*-carboxylate (VII), from which 1,2,3,4,*c*-4a,*c*-9a-hexahydro-*r*-1-hydroxymethyl-6,7-methylenedioxyfluoren-9-one (IX) was prepared. The Schmidt reaction with the fluorenone afforded 1,2,3,4,*c*-4a,5,6,*c*-10b-octahydro-*r*-4-hydroxymethyl-8,9-methylenedioxyphenanthiridin-6-one (X), which was converted into 1,2,3,4,*c*-4a,5,6,*c*-10b-octahydro-8,9-methylenedioxy-6-oxophenanthiridin-*r*-4-ylacetonitrile (XIII). Hydrolysis of the nitrile followed by cyclisation gave 2,3,*r*-3a,*t*-11c-tetrahydro-9,10-methylenedioxy-7*H*-pyrrolo[3,2,1-*de*]phenanthiridine-5(4*H*),7(*t*-11b*H*)-dione (XV), furnishing δ-lycorane on reduction with lithium aluminium hydride.

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Of the four stereoisomeric α-, β-, γ-, and δ-lycoranes (I)—(IV), all of which can be obtained from the Amaryllidaceae alkaloids lycorine or caranine by degradative transformations,[1] the α-, β-, and γ-isomers have already been elaborated by several groups of workers;[2,3] δ-lycorane (IV) has not hitherto been synthesised and we now report its synthesis.

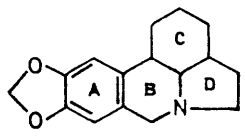
Hydrogenation of the 1,2,*t*-4a,*t*-9a-tetrahydrofluorenone-*r*-1-carboxylate (V)[3] in tetrahydrofuran over palladium–charcoal gave the hexahydro-compound (VI). Treatment of the hexahydro-compound (VI) with sodium methoxide in methanol furnished a mixture consisting of the 1,2,3,4,*c*-4a,*c*-9a-hexahydrofluorenone-*r*-1-carboxylate (VII), the corresponding acid (VIII), and the starting 1,2,3,4,*t*-4a,*t*-9a-hexahydro-*r*-1-carboxylate (VI). The acid (VIII) was esterified with diazomethane to give the carboxylate (VII). The ratio of the C-1-isomers (VII) : (VI) was *ca.* 85 : 15, epimerisation having taken place predominantly as expected. Reduction of (VII) with lithium aluminium hydride followed by oxidation with manganese dioxide in tetrahydrofuran gave the 1,2,3,4,*c*-4a,*c*-9a-hexahydro-*r*-1-hydroxymethylfluorenone (IX), which was subjected to the Schmidt reaction with sodium azide in trichloroacetic acid to yield the lactam (X) as its trichloroacetate (XI) in 70% yield. The structure of the lactam was confirmed by the u.v. spectra of the product of its reduction with lithium aluminium hydride, in neutral and acidic media. After removal of the trichloroacetyl group in (XI) by hydrolysis with potassium carbonate in ethanol, the lactam (X) was converted into the tosylate (XII), which was treated with potassium cyanide in dimethyl sulphoxide to give the cyanomethyl-lactam (XIII), in an almost quantitative overall yield. Hydrolysis of (XIII) with concentrated hydrochloric acid in acetic acid gave the homo-acid (XIV), which was cyclised in acetic anhydride, giving the imide (XV) in 30% yield. The i.r. spectrum of the imide exhibited no bands due to NH or OH, but a strong band at 1760 $cm^{-1}$ and a medium band at 1655 $cm^{-1}$ due to imide carbonyl groups confirming the structure. Reduction of the imide with lithium aluminium hydride in tetrahydrofuran furnished a mixture from which δ-lycorane was isolated, by making use of the solubility of its hydrochloride in chloroform. The i.r.

[1] K. Takeda, K. Kotera, S. Mizukami, and M. Kobayashi, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 483; K. Kotera, *Tetrahedron*, 1961, **12**, 240, 248.

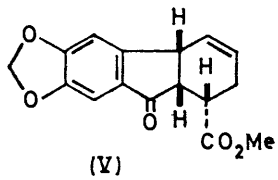
[2] R. K. Hill, J. A. Joule, and L. J. Loeffler, *J. Amer. Chem. Soc.*, 1962, **84**, 4951; N. Ueda, T. Tokuyama, and T. Sakan, *Bull. Chem. Soc. Japan*, 1966, **39**, 2012.

[3] H. Irie, Y. Nishitani, M. Sugita, and S. Uyeo, *Chem. Comm.*, 1970, 1313.

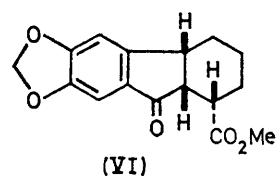
spectrum of the synthetic (±)-δ-lycorane was identical with that of an authentic sample of (+)-δ-lycorane.



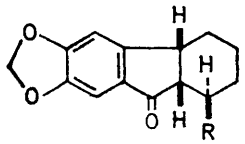
(I) BC = *trans* CD = *cis*
(II) BC = *trans* CD = *trans*
(III) BC = *cis* CD = *cis*
(IV) BC = *cis* CD = *trans*



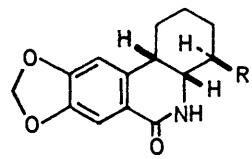
(V)



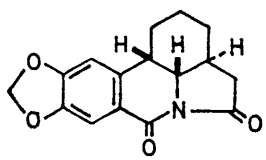
(VI)



(VII) R = $CO_2Me$
(VIII) R = $CO_2H$
(IX) R = $CH_2OH$



(X) R = $CH_2OH$
(XI) R = $CH_2O{\cdot}OC{\cdot}CCl_3$
(XII) R = $CH_2{\cdot}OTs$
(XIII) R = $CH_2{\cdot}CN$
(XIV) R = $CH_2CO_2H$



(XV)

EXPERIMENTAL

*Hydrogenation of Methyl* 1,2,t-4a,t-9a-*Tetrahydro*-6,7-*methylenedioxy*-9-*oxofluorene*-r-1-*carboxylate* (V).—The fluorenone (V) (2·85 g) was hydrogenated in tetrahydrofuran (80 ml) over 10% palladium–charcoal (2 g). After uptake of the theoretical amount of hydrogen, the mixture was worked up in the usual manner to yield *methyl* 1,2,3,4,t-4a,t-9a-*hexahydro*-6,7-*methylenedioxy*-9-*oxofluorene*-r-1-*carboxylate* (VI) (2·8 g), which crystallised from ethyl acetate–ether as needles, m.p. 142—144° (Found: C, 66·4; H, 5·9. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%), $\nu_{max.}$ (Nujol) 1724 and 1686 (CO) $cm^{-1}$.

*Methyl* 1,2,3,4,c-4a,c-9a-*Hexahydro*-6,7-*methylenedioxy*-9-*oxofluorene*-r-1-*carboxylate* (VII).—The 1,2,3,4,*t*-4a,*t*-9a-hexahydrofluorenone-*r*-1-carboxylate (VI) (1 g) was heated under nitrogen under reflux for 4 h in methanolic sodium methoxide [from sodium (1 g) and methanol (50 ml)]. After removal of the solvent under reduced pressure, water was added with ice-cooling and the residue was extracted with ether. The extract was washed with water, dried, and concentrated to dryness. Fractional crystallisation of the residue from ethyl acetate–ether gave the hexahydro-oxofluorenecarboxylate (VII) (200 mg), m.p. 122—124° (Found: C, 66·7; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%), $\nu_{max.}$ (Nujol) 1730 and 1692 (CO) $cm^{-1}$. The mother liquor from the foregoing crystallisation was concentrated to dryness; the residue was chromatographed in chloroform on silicic acid. The first fraction eluted with chloroform gave an additional crop of (VII) (100 mg). Further elution with the same solvent gave unchanged starting material (VI) (160 mg). The aqueous layer was acidified with hydrochloric acid and extracted with ether. The organic layer was washed with water and dried. Removal of the solvent left a residue which was crystallised from ethyl acetate to give the 1,2,3,4filtra,*c*-9a-hexahydro-oxofluorene-*r*-1-carboxylic acid (VIII) (430 mg), m.p. 174—177, as fine needles. The acid was treated with ethereal diazomethane to give the methyl ester (VII).

1,2,3,4,c-4a,c-9a-*Hexahydro*-r-1-*hydroxymethyl*-6,7-*methylenedioxyfluoren*-9-*one* (IX).—The ester (VII) (0·5 g) was treated with lithium aluminium hydride (0·2 g) in tetrahydrofuran (40 ml) for 2 h at room temperature, and after the excess of the reagent had been decomposed with a few drops of water with ice–salt cooling, the resulting precipitate was filtered off and washed with tetrahydrofuran. The washings were combined with the filtrate and the whole was dried ($MgSO_4$) and filtered. To the filtrate, manganese dioxide (5 g) was added and the mixture was stirred for 2·5 h at room temperature. The reagent was filtered off and the filtrate was concentrated to dryness. The residue (0·35 g) was chromatographed in chloroform over silicic acid. Elution with chloroform gave the *hexahydrohydroxymethylfluorenone* (IX) (0·2 g) as prisms, m.p. 109—112° (from ethyl acetate–ether) (Found: C, 69·1; H, 6·4. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·3%), $\nu_{max.}$ (Nujol) 3430 (OH) and 1682 (CO) $cm^{-1}$.

*Schmidt Reaction of the Hexahydrohydroxymethylfluorenone* (IX).—Sodium azide (260 mg) was added with stirring to a solution of compound (IX) (260 mg) in trichloroacetic acid (5 g) in four portions during 12 h at 60°. Stirring was continued for 2 days and the mixture was neutralised with aqueous ammonia and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness to give an oil (330 mg), which was chromatographed in chloroform on silicic acid. The first fraction eluted with chloroform gave an oil which showed two spots on t.l.c. (silica gel) and was not investigated further. The second fraction eluted with the same solvent gave 1,2,3,4,c-4a,5,6,c-10b-*octahydro*-8,9-*methylenedioxy*-6-*oxophenanthridin*-r-4-*ylmethyl trichloroacetate* (XI) as fine needles (230 mg), m.p. 239—242° (from ethanol–chloroform) (Found: C, 48·6; H, 4·0; N, 2·9. $C_{17}H_{16}Cl_3NO_5$ requires C, 48·5; H, 3·8; N, 3·3%), $\nu_{max.}$ (KBr) 3200, 3050 (NH), 1760, and 1667 (CO) $cm^{-1}$. Saponification of the trichloroacetate (XI) (70 mg) with potassium carbonate (140 mg) in ethanol (15 ml) and water (1 ml) by heating under reflux for 1 h gave, after work-up in the usual manner, 1,2,3,4,c-4a,5,6,c-10b-*octahydro*-r-4-*hydroxymethyl*-8,9-*methylenedioxyphenanthiridin*-6-*one* (X) (45 mg), m.p. 250—253° (Found: C, 65·0; H, 6·2; N, 5·1. $C_{15}H_{17}NO_4$ requires C, 65·4; H, 6·2; N, 5·1%), $\nu_{max.}$ (KBr) 3350, 3160, 3050 (OH and NH), and 1665 (CO) $cm^{-1}$.

*Tosylation of the Lactam* (X).—A solution of the lactam (X) (20 mg) and tosyl chloride (35 mg) in anhydrous pyridine (1 ml) was kept at room temperature overnight, diluted with water, and acidified with hydrochloric acid. The mixture was extracted with chloroform and the organic layer was washed with water, dried, and evaporated to dryness to

give the *tosylate* (35 mg) (XII) (Found: C, 61·3; H, 5·4; N, 3·4. $C_{22}H_{23}NO_6S$ requires C, 61·5; H, 5·4; N, 3·3%), $\nu_{max.}$ (KBr) 3150, 3040 (NH), and 1662 (CO) $cm^{-1}$.

1,2,3,4,c-4a,5,6,c-10b-*Octahydro*-8,9-*methylenedioxy*-6-*oxophenanthridin*-r-4-*ylacetonitrile* (XIII).—The tosylate (XII) (600 mg) and potassium cyanide (500 mg) in dimethyl sulphoxide (20 ml) were heated with stirring at 50° overnight. The mixture was diluted with water and the deposited crystals were collected by filtration and crystallised from ethanol–tetrahydrofuran to give the *nitrile* (XIII) (400 mg), m.p. 254—258° (Found: C, 67·6; H, 5·8; N, 9·9. $C_{16}H_{16}N_2O_3$ requires C, 67·6; H, 5·7; N, 9·9%), $\nu_{max.}$ (KBr) 3150, 3050 (NH), 2235 (CN), and 1670 (CO) $cm^{-1}$.

1,2,3,4,c-4a,5,6,c-10b-*Octahydro*-8,9-*methylenedioxy*-6-*oxophenanthiridin*-r-4-*ylacetic Acid* (XIV).—The nitrile (XIII) (890 mg) was heated in acetic acid (30 ml) and concentrated hydrochloric acid (30 ml) on a water-bath for 2 h. Evaporation of the mixture under reduced pressure left a solid mass which was taken up in aqueous 5% sodium carbonate. Insoluble materials were filtered off and the filtrate was washed with chloroform and ethyl acetate, successively. The aqueous layer was acidified with concentrated hydrochloric acid, and kept overnight. The precipitate which formed was collected and crystallised from ethanol–tetrahydrofuran to give the *homo-acid* (XIV) (800 mg), m.p. 265—270° (decomp.) after sintering at 240—242° (Found: C, 63·2; H, 5·6; N, 4·6. $C_{16}H_{17}NO_5$ requires C, 63·4; H, 5·7; N, 4·6%), $\nu_{max.}$ 3180 (NH), 2670—2300 ($CO_2H$), 1960, and 1638 (CO) $cm^{-1}$.

2,3,r-3a,t-11,c-*Tetrahydro*-9,10-*methylenedioxy*-1H-*pyrrolo*-[3,2,1-de]*phenanthridine*-5(4H),7(t-11bH)-*dione* (XV).—The homo-acid (XIV) (600 mg) was heated in acetic anhydride (30 ml) on a water-bath for 3 h and concentrated to dryness to leave an oil which was chromatographed in chloroform on silicic acid. Elution with chloroform gave an oil which was not investigated further. Further elution with the same solvent gave the imide (210 mg), which crystallised from benzene as prisms, m.p. 103—107°, *M* (mass spectrum), 285, $\nu_{max.}$ (KBr) 1760s and 1655m (CO) $cm^{-1}$.

δ-*Lycorane* (IV).—The imide (XV) (100 mg) and lithium aluminium hydride (100 mg) were heated in tetrahydrofuran (25 ml) on a water-bath for 3 h. Work-up in the usual manner gave a residue (60 mg), which was taken up in chloroform. The chloroform solution was washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and concentrated to dryness. The residue was again taken up in benzene and shaken with dilute hydrochloric acid. The acidic layer was made basic with potassium carbonate and extracted with benzene, and the organic layer was evaporated to give δ-lycorane (8 mg), needles, m.p. 112—115° (from benzene–hexane), *M* (mass spectrum), 257. The i.r. spectrum (in carbon disulphide) was identical with that of δ-lycorane provided by Dr. Kotera, Shionogi Research Lab. The acid washings of the chloroform solution were made basic with potassium carbonate and extracted with chloroform to give a mixture (28 mg) which was not investigated further.

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