Synthesis of the Amaryllidaceae Alkaloids Clivonine and Clividine

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(±)-Clivonine (I) and (±)-clividine (II), lactone alkaloids isolated from Amaryllidaceae plants, have been synthesised from *c*-2-methoxycarbonyl-*t*-6-(3,4-methylenedioxyphenyl)cyclohex-4-ene-*r*-carboxylic acid (III). Curtius rearrangement of (III) followed by treatment with methanol gave methyl *c*-6-(*N*-methoxycarbonylamino)-*t*-5-(3,4-methylenedioxyphenyl)cyclohex-3-ene-*r*-carboxylate (VI), which was converted into methyl *c*-6-(*N*-methoxycarbonylamino)-*t*-5-(3,4-methylenedioxyphenyl)cyclohex-3-enyl-*r*-acetate (IX) by an Arndt–Eistert reaction. Compound (IX) was, after hydrolysis, cyclised to 1-methoxycarbonyl-*r*-7-(3,4-methylenedioxyphenyl)-2,3,*t*-3a,4,7,*t*-7a-hexahydro-2-oxindole (XI). Chloromethylation followed by acetylation of (XI) gave *r*-7-(6-acetoxymethyl-3,4-methylenedioxyphenyl)-1-methoxycarbonyl-2,3,*t*-3a,4,7,*t*-7a-hexahydro-2-oxindole (XII). Lithium aluminium hydride reduction of (XII) furnished the corresponding amino-alcohol, which gave (±)-tetrahydroclividine (XV) and (±)-tetrahydroclivonine (XVI) in 1 : 1 ratio upon oxidation with osmium tetraoxide. Oxidation of (XV) and (XVI) with manganese dioxide yielded (±)-clividine and (±)-clivonine, respectively.

CLIVONINE (I) [1] and clividine (II) [2] are the lactone alkaloids from *Clivia miniata* Regel (Amaryllidaceae) and classified as lycorenine type alkaloids.[3] We report a synthesis of these alkaloids in racemic modification [4] as a continuation of our synthetic work of Amaryllidaceae alkaloids.[5]

The half-ester (III) obtained from the anhydride (IV), the structure of which has been confirmed by its transformation to α-lycorane, was subjected to the Curtius rearrangement as indicated previously.[6] Treatment of the resulted isocyanate (V) with methanol gave the urethane (VI), which was smoothly converted into the acid (VII) by hydrolysis. The acid was subjected to the Arndt–Eistert reaction. Treatment of the acid (VII) with thionyl chloride followed by diazomethane gave the diazoketone (VIII). The diazoketone was transformed to the homoester (IX) by treatment with silver oxide in dry methanol in 50% yield. However, the yield was not always reproducible. After we completed the synthesis of these alkaloids, we started work on the total synthesis of lycorine.[7] During the course of the synthesis, we found that silver benzoate and triethylamine [8] as catalyst for the Wolff rearrangement gave much better results than silver oxide in the sense of giving reproducible yields. We obtained the homoester (IX) in 75% yield by application of this catalyst. Hydrolysis of the homoester (IX) with hydrochloric acid in acetic acid gave the corresponding acid (X). Treatment of the acid with acetic anhydride furnished smoothly the imide (XI) which showed two carbonyl bands at 1 780 and 1 730 cm^{-1} in its i.r. spectrum, confirming the structure.

The introduction of one carbon unit into the aromatic ring of the imide (XI) was performed by chloromethylation with chloromethyl methyl ether in acetic acid in the presence of zinc chloride. The resulted chloromethyl compound was, without further purification, treated with silver acetate in acetic acid and acetic anhydride to give the imide-acetate (XII) in 58% yield from the imide (XI). The position of the newly introduced one carbon unit was indicated by two n.m.r. singlets (δ 6.81 and 6.68) assigned to two aromatic *para*-protons.

Lithium aluminium hydride reduction of the imide-acetate (XII) in tetrahydrofuran gave two oily products separable on alumina column chromatography. The minor product (15.5% yield) showed the molecular ion peak at *m/e* 287 in the mass spectrum and the n.m.r. spectrum was consistent with the structure of the required amino-alcohol (XIII). The major product (55.5% yield) showed the molecular ion peak at *m/e* 305 in the mass spectrum and the n.m.r. spectrum revealed two singlets due to two aromatic protons, an AB-type quartet assigned to the methylene protons of the benzyl alcohol moiety, and a broad singlet at δ 4.45 corresponding to three protons assigned to two hydroxy and a secondary amino group (confirmed by deuterium oxide treatment). These data suggested that the compound was the amino-diol (XIV) derived from cleavage of the five-membered imide ring of the imide-acetate (XII). When the imide-acetate was reduced with the same reagent in ether, the required amino-alcohol (XIII) was obtained in 65% yield.

Oxidation of the amino-alcohol (XIII) with osmium tetraoxide in pyridine and ether followed by treatment with sodium sulphite gave a mixture of the diastereoisomeric triols, (±)-tetrahydroclividine (XV) and (±)-tetrahydroclivonine (XVI) in 1 : 1 ratio as expected from molecular models. Of these triols, (±)-tetrahydroclividine (XV), m.p. 230—232°, was nicely crystallised from acetone. Column chromatographic separation of the mother liquor on alumina gave (±)-tetrahydroclivonine (XVI), m.p. 180—183°. Treatment of (XV) and (XVI) with dilute sulphuric acid gave (±)-deoxyclividine (XVII) and (±)-deoxyclivonine (XVIII), respectively. Oxidation of (XV) and (XVI) with manganese dioxide in chloroform furnished (±)-clividine (II) and (±)-clivonine (I) in 10% yield, respectively. The i.r. and n.m.r. spectra of (I) were superimposable upon those of naturally occurring clivonine,† thus

† We thank Professor W. C. Wildman, Iowa State University, for a generous sample of clivonine.

furnishing a total synthesis of clivonine (I). Compound (II) is proposed to be (±)-clividine, because it has a virtually identical mass spectrum to that of clivonine, although no direct comparison of (II) with clividine has been carried out.

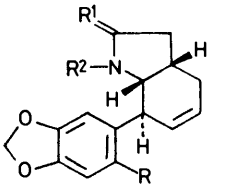
EXPERIMENTAL

M.p.s were determined with a Yanagimoto microscope hot-stage apparatus. I.r. spectra were recorded by a Hitachi model 215 grating spectrophotometer. N.m.r. spectra were obtained with Varian A-60 and HA-100 spectrometers (tetramethylsilane as internal standard). Mass spectra were determined with a Hitachi RMU-6D spectrometer with a direct, heated inlet system.

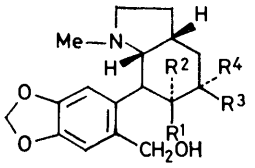
Methyl c-6-(N-*Methoxycarbonylamino*)-t-5-(3,4-*methylenedioxyphenyl*)*cyclohex*-3-*ene*-r-*carboxylate* (VI).—A solution of the half-ester (III) (30 g) and thionyl chloride (30 ml) in benzene (100 ml) was heated under reflux for 1 h and concentrated under reduced pressure to dryness to leave an oily residue which was taken up in acetone (150 ml). The solution was added dropwise to a stirred solution of sodium azide (60 g) in water (180 ml) with cooling for 1 h. After additional stirring for 1.5 h, the solution was diluted with water and extracted with benzene (3 × 100 ml). The extract was washed with brine, dried, and filtered. The filtrate was heated under reflux for 2 h and concentrated to 50 ml. Methanol (100 ml) was added to the solution and the whole was refluxed for 1 h. Removal of the solvent gave the *urethane* (VI) (25 g), m.p. 131—132° (Found: C, 61.1; H, 5.7; N, 4.3. $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.8; N, 4.2%), $\nu_{max.}$(KBr) 3 350 (NH), 1 733, and 1 690 cm^{-1} (CO), $\delta(CDCl_3)$ 6.75 (3 H, m, aromatic H), 5.90 (2 H, s, methylenedioxy), and 3.64 and 3.60 (3 H, each, s, OMe).

c-6-(N-*Methoxycarbonylamino*)-t-5-(3,4-*methylenedioxyphenyl*)*cyclohex*-3-*ene*-r-*carboxylic Acid* (VII).—Hydrolysis of the urethane-ester (VI) (35 g) with 10% hydrochloric acid (600 ml) in acetic acid (600 ml) gave the *acid* (VII) (32 g), m.p. 168—172° (Found: C, 60.0; H, 5.3; N, 4.5. $C_{16}H_{17}NO_6$ requires C, 60.2; H, 5.4; N, 4.4%), $\nu_{max.}$(KBr) 3 350 (NH), 1 720, and 1 705 cm^{-1} (CO).

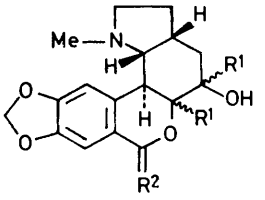
Methyl c-6-(N-*Methoxycarbonylamino*)-t-5-(3,4-*methylenedioxyphenyl*)*cyclohex*-3-*enyl*-r-*acetate* (IX).—A solution of the acid (VII) (8 g), thionyl chloride (8 ml) in benzene (240 ml), and pyridine (0.3 ml) was stirred at room temperature



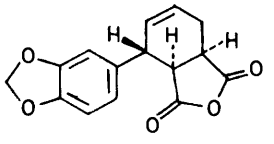
(XI) $R^1 = O$; $R^2 = CO_2Me$; $R^3 = H$
(XII) $R^1 = O$; $R^2 = CO_2Me$; $R^3 = CH_2OAc$
(XIII) $R^1 = H_2$; $R^2 = Me$; $R^3 = CH_2OH$



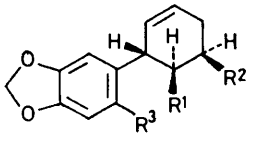
(XV) $R^1 = R^3 = OH$; $R^2 = R^4 = H$
(XVI) $R^1 = R^3 = H$; $R^2 = R^4 = OH$



(I) $R^1 = —H$; $R^2 = O$
(II) $R^1 = ---H$; $R^2 = O$
(XVII) $R^1 = ---H$; $R^2 = H_2$
(XVIII) $R^1 = —H$; $R^2 = H_2$



(IV)



(III) $R^1 = CO_2H$; $R^2 = CO_2Me$; $R^3 = H$
(V) $R^1 = N=C=O$; $R^2 = CO_2Me$; $R^3 = H$
(VI) $R^1 = NHCO_2Me$; $R^2 = CO_2Me$; $R^3 = H$
(VII) $R^1 = NHCO_2Me$; $R^2 = CO_2H$; $R^3 = H$
(VIII) $R^1 = NHCO_2Me$; $R^2 = COCHN_2$; $R^3 = H$
(IX) $R^1 = NHCO_2Me$; $R^2 = CH_2CO_2Me$; $R^3 = H$
(X) $R^1 = NHCO_2Me$; $R^2 = CH_2CO_2H$; $R^3 = H$
(XIV) $R^1 = NHMe$; $R^2 = CH_2CH_2OH$; $R^3 = CH_2OH$

overnight and concentrated to dryness under reduced pressure to give a residue which was dissolved in benzene (160 ml). To this solution was added a solution of diazomethane in ether [prepared from nitrosomethylurea (20 g)] and the whole was stirred at room temperature for 1 h, and concentrated to dryness under reduced pressure to give a residue which was taken up in methanol (240 ml). Triethylamine (40 ml) and silver benzoate (2.5 g) were added in portions. The whole was stirred at 40° for 4 h and filtered and concentrated. The residue was taken up in chloroform and the chloroform solution was washed with aqueous sodium carbonate, dilute hydrochloric acid, and water and dried. Removal of the solvent gave a residue (6.9 g) which crystallised from methanol to yield the *homo-ester* (IX) (4.5 g), m.p. 142—144° (Found: C, 62.0; H, 6.0; N, 3.9. $C_{18}H_{21}NO_6$ requires C, 62.2; H, 6.1; N, 4.0%), $\nu_{max.}$(KBr) 3 320 (NH), 1 730 and 1 683 cm^{-1} (CO), $\delta(CDCl_3)$ 6.76 (3 H, m, aromatic H), 5.95 (2 H, s, methylenedioxy), 5.50—6.15 (2 H, m, olefinic), and 3.70 and 3.60 (3 H each, s, OMe). The mother liquor, after being concentrated, was chromatographed on silica gel in chloroform. Elution with chloroform gave an additional crop of the homo-ester. The homo-ester (IX) was easily hydrolysed with 10% hydrochloric acid in acetic acid to give the corresponding *acid* (X), m.p. 146—149° (from methanol–ether) (Found: C, 61.1; H, 5.8; N, 4.1. $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.8; N, 4.2%), $\nu_{max.}$(KBr) 3 320 (NH), 1 705, and 1 685 cm^{-1} (CO).

1-*Methoxycarbonyl*-r-7-(3,4-*methylenedioxyphenyl*)-2,3,t-3a,4,7,t-7a-*hexahydro*-2-*oxindole* (XI).—A solution of the foregoing acid (X) (10 g) in acetic anhydride (50 ml) was refluxed for 2 h, and concentrated to dryness under reduced pressure to leave the oxindole (6.8 g) which crystallised from ether, m.p. 98—99° (Found: C, 64.5; H, 5.3; N, 4.5. $C_{17}H_{17}NO_5$ requires C, 64.8; H, 5.4; N, 4.4%), $\nu_{max.}$($CHCl_3$) 1 780 and 1 730 cm^{-1} (CO), $\delta(CDCl_3)$ 6.70 (3 H, m, aromatic H), 5.92 (2 H, s, methylenedioxy), 5.80 (2 H, m, olefinic), and 3.50 (3 H, s, OMe).

r-7-(6-*Acetoxymethyl*-3,4-*methylenedioxyphenyl*)-1-*methoxycarbonyl*-2,3,t-3a,4,7,t-7a-*hexahydro*-2-*oxindole* (XII).—A solution of the imide (XI) (3.4 g), chloromethyl methyl ether (2 g), and zinc chloride (3 g) in acetic acid (20 ml) was stirred at room temperature overnight, diluted with water, and extracted with methylene chloride. The extract was washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and concentrated to dryness to leave a residue. A suspended solution of the residue and silver acetate (5 g) in acetic acid (10 ml) and acetic anhydride (10 ml) was stirred at room temperature for 5 h and filtered. The filtrate was concentrated to dryness under reduced pressure to leave an oily residue which was chromatographed on silica gel with chloroform. Elution with chloroform gave the *imide-acetate* (XII) (2.4 g) which crystallised from benzene, m.p. 75—77° (Found: C, 67.0; H, 5.8; N, 2.9. $C_{20}H_{21}NO_7,C_6H_6$ requires C, 67.1; H, 5.9; N, 3.0%), *m/e* 387 (M^+), $\nu_{max.}$(KBr) 1 785 and 1 718 cm^{-1} (CO), $\delta(CDCl_3)$ 6.81 and 6.68 (1 H, each s, aromatic H), 5.95 (2 H, s, methylenedioxy), 5.70 (2 H, m, olefinic), 5.02 (2 H, s, CH_2OAc), 3.45 (3 H, s, OMe), and 2.05 (3 H, s, COMe).

Lithium Aluminium Hydride Reduction of the Imide-acetate (XII) *in Tetrahydrofuran*.—A solution of the imide-acetate (XII) (480 mg) and lithium aluminium hydride (450 mg) in tetrahydrofuran (50 ml) was heated under nitrogen for 3 h. The usual work-up gave an oily residue which was chromatographed on alumina in benzene. Elution with benzene gave the *amino-alcohol* (XIII) (55 mg) as an oil (Found: M^+, 287. $C_{17}H_{21}NO_3$ requires M^+, 287), $\nu_{max.}$($CHCl_3$) 3 300—2 900 cm^{-1} (OH), $\delta(CDCl_3)$ 6.80 and 6.70 (1 H each, s, aromatic H), 5.95 (2 H, s, methylenedioxy), 5.80 (2 H, m, olefinic), 4.75 and 4.20 (1 H each, d, *J* 11.5 Hz, CH_2OH), and 1.38 (3 H, s, NMe), which was characterised as its *picrate*, m.p. 188—189° (Found: C, 53.8; H, 4.8; N, 10.9. $C_{17}H_{21}NO_3,C_6H_3N_3O_7$ requires C, 53.5; H, 4.7; N, 10.9%). Elution with chloroform gave the *amino-diol* (XIV) (250 mg) as an oil (Found: M^+, 305. $C_{17}H_{23}NO_4$ requires M^+, 305), $\nu_{max.}$($CHCl_3$) 3 400br cm^{-1} (NH and OH), $\delta(CDCl_3)$ 6.83 and 6.73 (1 H each, s, aromatic H), 5.93 (2 H, s, methylenedioxy), 5.55 (2 H, m, olefinic), 4.45br (3 H, s, NH and 2 × OH), 4.75 and 4.40 (1 H each, d, *J* 12 Hz, CH_2OH), and 2.15 (3 H, s, NMe).

(±)-*Tetrahydroclividine* (XV) *and* (±)-*Tetrahydroclivonine* (XVI).—Osmium tetraoxide (1 g) was added to a solution of the amino-alcohol (XIII) (920 mg) in ether (20 ml) and pyridine (1 ml) and the whole was allowed to stand at room temperature for 2 days. After removal of the solvent under reduced pressure, the resulted residue was heated under reflux with sodium sulphite (5 g) in 50% aqueous ethanol (60 ml) for 4 h. After removal of a precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure to leave a residue which was taken up in chloroform. The chloroform solution was washed with aqueous sodium carbonate and water, and dried. Removal of the solvent gave a residue which crystallised from acetone to give (±)-tetrahydroclividine (XV) (230 mg), m.p. 230—232° (Found: C, 63.4; H, 7.3; N, 4.2. $C_{17}H_{23}NO_5$ requires C, 63.5; H, 7.2; N, 4.4%), $\nu_{max.}$(KBr) 3 300 and 3 000—2 500 cm^{-1} (OH). The mother liquor was chromatographed on alumina with chloroform. Elution with 3% ethanol in chloroform gave (±)-tetrahydroclivonine (XVI) (210 mg) which crystallised from acetone as prisms, m.p. 180—183° (Found: C, 62.7; H, 7.4; N, 4.3%; M^+, 321. $C_{17}H_{23}NO_5,1/4H_2O$ requires C, 62.6; H, 7.3; N, 4.3%; M^+, 321), $\nu_{max.}$(KBr) 3 460, 3 300, and 3 000 cm^{-1} (OH), $\delta(CDCl_3)$ 6.85 and 6.82 (1 H each, s, aromatic H), 5.95 (2 H, s, methylenedioxy), 4.75 and 4.15 (1 H each, d, *J* 11.5 Hz, CH_2OH), and 1.85 (3 H, s, NMe).

(±)-*Deoxyclividine* (XVII) *and* (±)-*Deoxyclivonine* (XVIII).—(±)-Tetrahydroclividine (XV) (60 mg) was heated in 3% sulphuric acid (15 ml) on a water-bath for 3 h. After cooling, the solution was basified with aqueous sodium hydroxide and extracted with chloroform. The extract was washed with water, dried, and concentrated to give (±)-deoxyclividine (XVII) (25 mg) which crystallised from acetone, m.p. 155—158° (Found: C, 67.0; H, 7.0; N, 4.6. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%), $\nu_{max.}$(KBr) 3 400 cm^{-1} (OH), $\delta(CDCl_3)$ 7.05 and 6.45 (1 H each, s, aromatic H), 5.90 (2 H, s, methylenedioxy), 4.80 (2 H, s, CH_2O), and 2.25 (3 H, s, NMe). The same treatment of (±)-tetrahydroclivonine (XVI) (15 mg) gave (±)-deoxyclivonine (XVIII) (8 mg) which crystallised from acetone as prisms, m.p. 133—134° (Found: C, 67.6; H, 6.9; N, 4.6. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%), $\nu_{max.}$(KBr) 3 450 cm^{-1} (OH), $\delta(CDCl_3)$ 7.97 and 6.40 (1 H each, s, aromatic H), 5.90 (2 H, s, methylenedioxy), 4.77 (2 H, s, CH_2O), and 2.50 (3 H, s, NMe).

(±)-*Clividine* (II) *and* (±)-*Clivonine* (I).—A suspended solution of (±)-tetrahydroclivonine (XVI) (135 mg) and manganese dioxide (1.5 g) in chloroform (16 ml) was stirred at room temperature overnight. The usual work-up gave a basic residue which was chromatographed on neutral

alumina in benzene. Elution with benzene–chloroform (6 : 1) gave (±)-clivonine (I) (10 mg), m.p. 223—225° (from ethyl acetate), with identical i.r. ($CHCl_3$) and n.m.r. spectra with those of naturally occurring chivonine. The same oxidation of (±)-tetrahydroclividine (XV) gave (±)-clividine (II), m.p. 170—172° (Found: C, 64.6; H, 6.2; N, 4.4. $C_{17}H_{19}NO_5$ requires C, 64.3; H, 6.0; N, 4.4%), $\nu_{max.}$(KBr) 3 350 (OH) and 1 705 cm^{-1} (CO), δ($CDCl_3$) 7.50 and 6.95 (1 H each, s, aromatic H), 6.04 (2 H, s, methylenedioxy), 4.58 (1 H, t, *J* 3 Hz, CHOCO), 3.98 (1 H, dd, *J* 8.5 and 3.0 Hz, C*H*OH), and 2.16 (3 H, s, NMe).

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