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Studies on Orchidaceae Alkaloids

XXXIII.* Two New Alkaloids, *N-cis-* and *N-trans*-Cinnamoylnorcuskhygrine from *Dendrobium chrysanthum* Wall.

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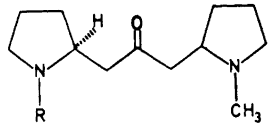
Dedicated to Professor *František Šorm* on his 60th birthday

Two new alkaloids, *cis-* and *trans*-dendrochrysine (I and II), have been isolated from *Dendrobium chrysanthum* Wall. Their structures have been determined by physical methods and confirmed by the synthesis of racemic II. The absolute configuration at the *N*-cinnamoylpyrrolidinyl group has been established by comparing the CD curve of I with those of *N-cis*-cinnamoyl-L-prolinol (VIII) and *N-cis*-cinnamoyl-L-2-methylpyrrolidine (X).

The occurrence of hygrine in *Dendrobium chrysanthum* Wall. has been reported earlier.[2] Two further alkaloids, *cis-* and *trans*-dendrochrysine (I and II), have now been isolated from this species. The alkaloids I and II have the same empirical formula, $C_{21}H_{28}N_2O_2$, as shown by high resolution mass spectrometry. From the IR, UV, and NMR spectra it is evident that I contains a *cis*-cinnamoylamide and II a *trans*-cinnamoylamide grouping.[3] The occurrence in both I and II of a keto group, an *N*-methyl group and two tertiary nitrogen atoms is also indicated. The base peak (*m/e* 84) in the mass spectra of I and II indicates the presence of an *N*-methylpyrrolidin-2-yl group,



I: R = *cis*-cinnamoyl

II: R = *trans*-cinnamoyl

Fig. 1.

* For number XXXII of this series, see Ref. 1.

and the peaks at *m/e* 140 and 126 show the position of the keto group. On the basis of the evidence presented above, the structures of I and II shown in Fig. 1 have been deduced.

The structures of I and II were confirmed by the synthesis of racemic II. An equimolar mixture of *N*-methylpyrrolidin-2-one and *N*-benzylpyrrolidin-2-one was reduced with sodium dihydro-bis(2-methoxyethoxy)aluminate, and the resulting mixture of the corresponding carbinolamines was condensed with 3-oxopentanedioic acid at pH 8 in aqueous solution (*cf.* the synthesis of cuskhygrine[4]). The condensation product was decarboxylated (pH 2) giving *N*-benzyl-norcuskhygrine (III). Hydrogenation of III in glacial acetic acid (PtO_2, 70°, 3.5 atm.) followed by reaction with *trans*-cinnamoyl chloride produced, according to TLC and MS, two isomers of *N-trans*-cinnamoyl-dihydronorcuskhygrine (V). Upon oxidation with chromic acid, the two isomers of V gave the same *N-trans*-cinnamoyl-norcuskhygrine which was indistinguishable from II (UV, IR, NMR, MS, and TLC).

Hydrogenation of *cis*- and *trans*-dendrochrysine (I and II) gave the same dihydroderivative (VI), showing that the alkaloids have the same absolute configuration. The absolute configuration at the *N*-cinnamoylpyrrolidinyl group has been established by comparing the CD curve of I with those of *N-cis*-cinnamoyl-L-prolinol (VIII) and *N-cis*-cinnamoyl-L-2-methylpyrrolidine (X). It follows from the similarity of the CD curves (Fig. 2) that these compounds

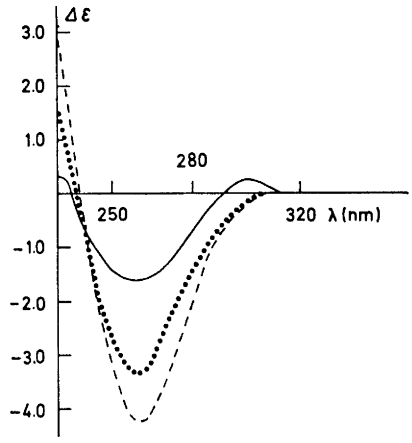


Fig. 2. CD curves of *cis*-dendrochrysine (I, —), *N-cis*-cinnamoyl-L-prolinol (VIII, ···), and *N-cis*-cinnamoyl-L-2-methylpyrrolidine (X, - - -). Methanol was used as solvent.

have the same absolute configuration, and hence that I and II possess the absolute configuration depicted in Fig. 1. Since compounds containing the $N-CH-CH_2-C=O$ system are easily isomerised in alkaline solution, the isolation procedure used would produce the thermodynamically most stable configuration at the *N*-methylpyrrolidinyl group (*cf.* Ref. 1). The absolute configuration at this centre remains to be determined.

In the synthesis of VIII and X, L-prolinol[5] and L-2-methylpyrrolidine were reacted with phenylpropiolyl chloride[6] and the amides (VII and IX) formed were hydrogenated over a palladium catalyst poisoned with quinoline.[7]

EXPERIMENTAL

All melting points are corrected. Mass spectra were measured on an LKB 9000 spectrometer (ionization energy 70 eV) and on an Atlas SM 1 spectrograph, the optical rotations on a Perkin-Elmer 141 polarimeter, and the circular dichroism spectra on a Cary 60 spectropolarimeter. The IR spectra were recorded on a Perkin-Elmer 257 instrument, the UV spectra on a Beckmann DK 2 instrument, and the NMR spectra on a Varian A-60A spectrometer.

Isolation of the alkaloids. Fresh plants of *Dendrobium chrysanthum* Wall. (10 kg) were extracted with methanol (40 l). The extract was concentrated to 1 l, acidified with hydrochloric acid and washed with carbon tetrachloride (5 × 0.4 l). The aqueous solution was made alkaline with sodium hydroxide and extracted with chloroform (5 × 0.4 l). The combined chloroform solutions were dried (Na_2SO_4) and concentrated, leaving the crude alkaloid mixture (13 g). The alkaloids were separated by preparative thin layer chromatography on neutral alumina. The plates were developed twice with chloroform. From 180 mg of the crude alkaloid mixture were isolated 30 mg of I, 30 mg of II, and 60 mg of hygrine.

Characterization of I. The base was obtained as a viscous oil, $[\alpha]_D^{22}$ −19°(*c* 1.92, chloroform). CD curve, see Fig. 2. IR spectrum: σ_{max} (CCl_4) 1719 (s), 1647 (s), 1620 (s) cm^{-1}. UV spectrum, nm (log ε): λ_{max} (ethanol) 253 (4.06), 210 (4.24). NMR spectrum ($CDCl_3$) τ: 2.4 − 2.9. (m, 5 H), 3.37 (d, 1 H, J = 12.5 Hz) and 3.98 (d, 1 H, J = 12.5 Hz) AB spectrum, 7.71 (s, 3 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 340 (3), 140 (12), 131 (25), 126 (5), 103 (13), 97 (10), 84 (100), 83 (11), 82 (8), 77 (8), 70 (7), 42 (11).

Characterization of II. The base was obtained as a viscous oil, $[\alpha]_D^{22}$ −11° (*c* 0.81, chloroform). (Found: Mol weight 340.211. Calc. for $C_{21}H_{28}N_2O_2$: 340.215. ^{12}C = 12.0000.) IR spectrum: σ_{max} (CCl_4) 1713 (s), 1655 (s), 1611 (s) cm^{-1}. UV spectrum, nm (log ε): λ_{max} (ethanol) 281 (4.31), 224 (4.05), 218 (4.14). NMR spectrum ($CDCl_3$) τ: 2.33 (d, 1 H, J = 16 Hz) and 3.27 (d, 1 H, J = 16 Hz) AB spectrum, 2.5 − 2.9 (m, 5 H), 7.72 (s, 3 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 340 (3), 140 (16), 131 (34), 126 (8), 103 (16), 97 (15), 84 (100), 83 (16), 82 (13), 77 (9), 70 (9), 42 (13).

N-*Benzyl-norcuskhygrine* (*III*). To a solution of *N*-methylpyrrolidin-2-one (17.5 g) and *N*-benzylpyrrolidin-2-one (31.0 g) in dry ether (500 ml), sodium dihydro-bis(2-methoxyethoxy)aluminate (56.5 g of a 70 % solution in benzene) was added with stirring at room temperature. After refluxing for 30 min, the reaction mixture was cooled to room temperature and a solution of 3-oxopentanedioic acid (25.0 g) and sodium hydroxide (6.85 g) in water (1500 ml) was added with cooling. The pH was adjusted to 8 with sodium dihydrogen phosphate (65.0 g, containing 2 mol of water of crystallisation) and the mixture was diluted with water to 4 l and left at room temperature for 60 h. The reaction mixture was acidified (pH 2) and heated until the evolution of carbon dioxide ceased, cooled and washed with chloroform (6 × 50 ml). The reaction mixture was made alkaline (pH 13) and extracted with chloroform (20 × 100 ml). The combined chloroform solutions were dried and the solvent evaporated, leaving a dark brown oil (46.4 g). After distillation (0.02 torr, bath temperature 145 − 155°), III (9.0 g) was obtained as a pale yellow oil. IR spectrum: σ_{max} ($CHCl_3$) 1710 (s). NMR spectrum ($CDCl_3$) τ: 2.55 − 2.95 (m, 5 H), 6.13 (d, 1 H, J = 13.0 Hz) and 6.76 (d, 1 H, J = 13.0 Hz) AB spectrum, 7.80 (s, 3 H), 6.76 − 8.90 (18 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 300 (1), 216 (3), 209 (13), 160 (39), 159 (21), 91 (65), 84 (100), 42 (11).

Dihydronorcuskhygrine (*IV*). A solution of III (1.93 g) in glacial acetic acid (200 ml) was hydrogenated over Adams catalyst (100 mg) at 70° and 3.5 atm. After 5 h the catalyst was filtered off and the solution concentrated, diluted with water and washed with ether. The aqueous solution was made alkaline (pH 13, volume 100 ml) and extracted with ether (4 × 50 ml) followed by chloroform (3 × 50 ml). The combined chloroform solutions were dried (Na_2SO_4) and the solvent evaporated leaving IV (0.41 g) as an oil. NMR spectrum ($CDCl_3$) τ: 5.42 (s, 1 H) 5.7 − 6.4 (m, 1 H), 6.45 − 7.60 (6 H), 7.63 (s, 3 H), 7.70 − 9.10 (13 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 212 (3), 110 (3), 98 (4), 85 (6), 84 (100), 83 (5), 82 (3), 70 (19), 44 (4), 43 (3), 42 (6), 41 (3).

N-trans-*Cinnamoyl-dihydronorcuskhygrine* (*V*). To a solution of IV (0.24 g) in sodium hydroxide (1 M, 10 ml), *trans*-cinnamoyl chloride (0.19 g) dissolved in tetrahydrofuran (30 ml) was added dropwise under stirring at room temperature. The reaction mixture

was then extracted with chloroform (4 × 15 ml), the combined chloroform solutions dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on neutral alumina (3 × 15 cm) using chloroform as eluent. The second fraction consisted of two products (0.13 g, 1:1), which were separated by preparative thin layer chromatography using the same system as above. The plates were developed eight times. The mass spectra of the two components are indistinguishable which indicates that they are isomers. IR spectrum (on the mixture): σ_{max} (CCl_4) 3350 (m), 1650 (s), 1605 (s) cm^{-1}. Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 342 (3), 211 (3), 142 (4), 131 (13), 128 (3), 124 (3), 103 (6), 98 (3), 85 (6), 84 (100), 77 (3), 70 (5), 42 (5).

Oxidation of V. The two isomers of V were oxidised separately with Jones' reagent [8] (0°, 3 h), giving the same compound indistinguishable from II (IR, MS, TLC).

Hydrogenation of I and II. Solutions of I (8 mg) and II (13 mg) in methanol (5 ml) were hydrogenated over palladium supported on carbon (10 %, 20 mg) at room temperature and atmospheric pressure. After 20 min the catalyst was filtered off and the solvent evaporated to give the dihydro derivative VI, $[\alpha]_{578}^{24}$ −13° (*c* 0.70, chloroform). IR spectrum: σ_{max} (CCl_4) 1714 (s), 1642 (s) cm^{-1}. Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 342 (3), 140 (15), 126 (10), 105 (3), 98 (5), 91 (6), 85 (6), 84 (100), 83 (7), 82 (4), 70 (21), 42 (5).

L-*Prolinol*, $[\alpha]_D^{22}$ +2.6° (*c* 0.75, methanol) (lit. [9] $[\alpha]_D$ + ≃ 1°), was synthesized according to the procedure of Gassman and Fentiman.[5]

N-*Phenylpropiolyl*-L-*prolinol* (*VII*). To a solution of L-prolinol (0.47 g) in ether (15 ml), phenylpropiolyl chloride [6] (0.38 g) dissolved in ether (5 ml) was added dropwise under stirring over a period of 15 min. After the addition, the stirring was continued for 30 min at room temperature. The reaction mixture was washed successively with hydrochloric acid (4 M, 20 ml) and sodium hydroxide (2 M, 15 ml), dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed on neutral alumina (2.5 × 15 cm) using chloroform as eluent. The first fraction contained, according to its IR spectrum, the phenylpropiolyl ester of VII. After evaporation of the solvent, the second fraction gave VII (0.23 g) as a viscous oil, $[\alpha]_D^{23}$ −61° (*c* 0.32, methanol). IR spectrum: σ_{max} ($CHCl_3$) 3380 (m), 2220 (m), 1608 (s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 2.12 − 2.60 (m, 5 H), 5.69 (m, 1 H), 5.74 (s, 1 H), 6.00 − 6.50 (m, 4 H), 7.58 − 8.35 (m, 4 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 229 (2), 198 (31), 129 (100), 102 (4), 101 (5), 85 (13), 83 (19), 77 (4), 75 (7), 70 (4), 51 (5).

N- cis-*Cinnamoyl*-L-*prolinol* (*VIII*). A solution of VII (230 mg) in methanol (9 ml) was hydrogenated over 5 % palladium supported on barium sulphate (60 mg) poisoned with quinoline [7] (60 mg) at room temperature and atmospheric pressure. When one molar equivalent of hydrogen had been consumed (18 min) the catalyst was filtered off and the solvent evaporated. The residue was chromatographed on neutral alumina (2.5 × 15 cm) using chloroform as eluent, giving VIII (150 mg) as an oil, $[\alpha]_D^{25}$ −52.5° (*c* 0.55, methanol). CD curve of VIII, see Fig. 2. UV spectrum, nm (log ε): λ_{max} (methanol) 253 (4.08). IR spectrum: σ_{max} ($CHCl_3$) 3350 (m), 1640 (m), 1605 (s), 1595 (s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 2.30 − 2.70 (m, 5 H), 3.20 (d, 1 H, J = 12.5 Hz) and 3.82 (d, 1 H, J = 12.5 Hz) AB spectrum, 5.69 (s, 1 H), 5.72 (m, 1 H), 6.10 − 7.13 (m, 4 H), 7.85 − 8.55 (m, 4 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 231 (2), 200 (22), 132 (11), 131 (100), 103 (30), 77 (20), 70 (28), 51 (7).

N-*p*-Toluenesulphonyl-L-prolinol-*p*-toluenesulphonate, m.p. 99°, $[\alpha]_D^{23}$ −119° (*c* 0.62, methanol) and *N*-*p*-toluenesulphonyl-L-2-methylpyrrolidine, m.p. 70 − 71°, $[\alpha]_D^{23}$ −69° (*c* 0.45, ethanol), were prepared according to Karrer and Ehrhardt [10] who reported m.p. 104 − 105°, $[\alpha]_D^{16}$ −129.5° and m.p. 68 − 69°, $[\alpha]_D^{18}$ −61.1° (ethanol), respectively.

L-*2-Methylpyrrolidine*. A mixture of *N*-*p*-toluenesulphonyl-L-2-methylpyrrolidine [10] (20 g), phenol (1.9 g), hydrobromic acid (48 %, 20 ml) and propionic acid (3 ml) was refluxed for 2 h under nitrogen (*cf.* the preparation of dihydroisoindole [11]). The reaction mixture was cooled to room temperature, washed with ether (4 × 25 ml), made alkaline (pH 13) with sodium hydroxide pellets and extracted with ether (8 × 25 ml). The combined ether solutions were dried (Na_2SO_4) and concentrated. From the residue, L-2-methylpyrrolidine, $[\alpha]_{578}^{25}$ −13° (*c* 0.45, water) was isolated by preparative GLC (column: 5 % SE-52 on Chromosorb AW DMCS, 60 − 80 mesh; 3 mm × 2.0 m; retention time 3 min at 80°, gas flow rate 80 ml/min). Karrer and Ehrhardt [10] have reported $[\alpha]_D^{22}$ −11.97° (water) for L-2-methylpyrrolidine.

N-*Phenylpropiolyl*-L-*2-methylpyrrolidine* (*IX*). L-2-Methylpyrrolidine (0.20 g) in ether (5 ml) and sodium hydroxide (1 M, 15 ml) was reacted with phenylpropiolyl chloride [6] (0.80 g) at room temperature. After stirring for 1 h, IX (0.23 g) was isolated as a viscous oil, $[\alpha]_D^{24}$ −38° (*c* 1.29, methanol). IR spectrum: σ_{max} ($CHCl_3$) 2220 (m), 1612 (s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 2.18 – 2.70 (m, 5 H), 5.43 – 5.87 (m, 1 H), 6.03 – 6.55 (m, 2 H), 7.68 – 8.35 (m, 4 H), 8.62 and 8.73 (2 d, 1:1, 3 H, $J = 6$ Hz). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 213 (18), 198 (17), 130 (10), 129 (100), 116 (5), 102 (8), 101 (5), 77 (2), 75 (6), 51 (5).

N-cis-*Cinnamoyl*-L-*2-methylpyrrolidine* (*X*). IX (0.20 g) was hydrogenated in the same way as described for VIII. The reaction mixture was concentrated and chromatographed on neutral alumina (1 × 15 cm) using ether as eluent, giving X as an oil, $[\alpha]_D^{25}$ −21° (*c* 1.12, methanol). CD curve of X, see Fig. 2. UV spectrum, nm (log ε): λ_{max} (methanol) 252.5 (4.11). IR spectrum: σ_{max} ($CHCl_3$) 1640 (m), 1608 (s), 1600 (s) cm^{-1}. NMR spectrum ($CDCl_3$) τ: 2.30 – 2.80 (m, 5 H), 3.30 (d, 1 H, $J = 12.5$ Hz) and 3.84 (d, 1 H, $J = 12.5$ Hz) AB spectrum, 5.50 – 7.20 (m, 3 H), 7.83 – 8.64 (m, 4 H), 8.65 – 9.05 (m, 3 H). Pertinent mass spectral peaks *m/e* (rel. intensity): M^+ 215 (31), 132 (13), 131 (100), 103 (35), 84 (29), 77 (23), 70 (22).

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