ALKALOIDS OF *Glaucium fimbrilligerum*

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From the epigeal part and roots of *Glaucium fimbrilligerum* 22 alkaloids have been isolated, of which three have proved to be new — d-isocorytuberine, dehydrocorydine, and corydine N-oxide.

We have studied the epigeal part and roots of the plant *Glaucium fimbrilligerum* [1, 3] collected in the flowering stage on the slopes of the Fergana range. Chloroform extraction of the epigeal part of the plant yielded 0.54% of total alkaloids (0.43% of ether fraction and 0.11% of chloroform fraction).

The combined ether-soluble material was separated into phenolic and nonphenolic fractions. From the total nonphenolic alkaloids we isolated dihydrosanguinarine [4], sanguinarine, chelerythrine, chelidonine, corydine, protopine, allocryptopine, and base (I), and from the phenolic fraction isocorypalmine [5], isocorydine, corydine, glaufidine [1], N-methyllindcarpine [3], isoboldine, scoulerine [6], N-methylcoclaurine [7], reticuline [8], norcorydine, norisocorydine, and the new bases (II) and (III).

From the combined chloroform-soluble alkaloids we isolated corydine, glaufidine, glaunine, and glaunidine [2]. All the known alkaloids isolated were identified on the basis of spectral characteristics and a direct comparison with authentic samples, and the norcorydine and norisocorydine on the basis of spectral characteristics and conversion by Craig methylation [9] into corydine and isocorydine, respectively.

Alkaloid (I) proved to be a new, optically inactive, base. Its UV spectrum showed maxima at 220, 310, and 340 nm (log ε 4.33, 4.27, 4.10). In the NMR spectra there are signals from a N-methyl group (2.96 ppm) and three methoxy groups (3.65, 3.89, 3.93 ppm), and from four aromatic protons appearing in the form of two singlets at 6.32 and 6.97 ppm and two doublets at 7.10 and 7.34 ppm (J = 8 Hz). The spectral characteristics permit base (I) to be assigned to the dehydroaporphine alkaloids ($\Delta^{6a,7}$) with four oxygen-containing substituents in positions 1, 2, 10, and 11. The Adams hydrogenation of (I) led to corydine. Consequently, (I) is dehydrocorydine.

Base (II) is amorphous, $[\alpha]_D$ +181° (c 0.5, methanol). Hydrochloride, mp 220-221°C (from ethanol). UV spectrum, λ_{max}: 225, 275, 313 nm (log ε 4.39), 3.87, 3.67). Mass spectrum: 327 (M^+), 312, 310, 296, 284, 270, 269, 163.5 (M^{++}).

The NMR spectrum shows signals at 2.51 ppm ($N\text{-}CH_3$), 3.62 ppm (OCH_3), and 3.84 ppm (OCH_3), while in the aromatic region there are a one-proton singlet at 6.61 ppm and one-proton doublets at 6.75 and 6.93 ppm (J = 8 Hz), and also multiplets of methylene and methine protons in the 2.10-3.70 ppm region. What has been said permits (II) to be assigned to the aporphine alkaloids of the corydine type containing two methoxy and two hydroxy groups [10].

The methylation of (II) with diazomethane yielded corydine, which shows the presence of one hydroxy group at C_1 in (II).

A comparison of the characteristics given above with those for racemic isocorytuberine obtained synthetically [11] permitted the assumption that base (II) was d-isocorytuberine, isolated from a plant for the first time.

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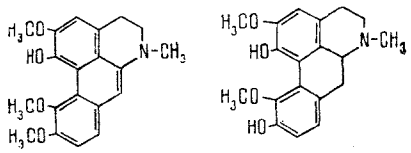

I II

Optically active base (III) has three maxima in the UV spectrum at 225, 270, and 313 nm (log ε 4.43, 3.89, 3.70). Its mass spectrum contains the peaks of ions with m/e 357 (M^+), 341, 340, 339, 326, 324, 298, 283, and 267, and the NMR spectrum contains signals at 3.43 ppm ($N-CH_3$), 3.67 ppm (OCH_3), and 3.85 ppm (2 OCH_3). In the aromatic region there are a one-proton singlet at 6.67 ppm, one-proton doublets at 6.84 and 7.10 ppm (J = 8 Hz) from orthoaromatic protons, and multiplets at 2.0-4.0 ppm.

The presence in the mass spectrum of the M − 16, M − 17, and M − 18 ions, the low intensity of the molecular ion, and the appearance of the signal of a $N-CH_3$ group in the weak-field of the NMR spectrum permitted the assumption that the base was a N-oxide. When (III) was reduced with zinc in sulfuric acid at room temperature, corydine was obtained.

Thus, base (III) is corydine N-oxide, not previously described in the literature.

Chloroform extraction of the roots of *C. fimbrilligerum* gave 0.82% of combined alkaloids (0.64% ethereal fraction and 0.18% chloroform fraction).

The combined ether-soluble material was separated into phenolic and nonphenolic fractions.

Sanguinarine, chelerythrine, chelidonine, corydine, protopine, and allocryptopine were isolated from the nonphenolic fraction, and isocorydine, corydine, N-methyllindcarpine, glaufine [3], isoboldine, and N-methylcoclaurine from the phenolic fraction.

EXPERIMENTAL

For chromatography we used type KSK silica gel and in the case of TLC the following solvent systems: 1) benzene–ethanol (9:1) and 2) chloroform–ethanol (4:1).

The UV spectra were recorded on a Hitachi spectrophotometer in ethanol, the NMR spectra on a JNM-4H-100/100 MHz instrument in $CDCl_3$ with HMDS as standard (δ scale), and the mass spectra on a MKh-1303 instrument.

Isolation and Separation of the Combined Alkaloids. The epigeal part of the plant *C. fimbrilligerum* (13 kg) was extracted with chloroform 10 times. By the usual method, from the concentrated combined extract 66.35 g of total alkaloids was isolated (53.76 g of ether fraction and 12.59 g of chloroform fraction). The combined ether-soluble material was separated into a phenolic fraction (14.12 g of ether-soluble and 0.31 g of chloroform-soluble material) and a nonphenolic fraction (39.33 g).

When the nonphenolic fraction was treated with methanol, a mixture of crystals was obtained (8.48 g) from which 2.54 g of protopine (mp 205-206°C) and 5.90 g of allocryptopine (mp 157-158°C) were obtained by fractional crystallization. Methanol treatment of the mother liquor yielded 9.39 g of (+)-corydine (mp 148-149°C). The residual mother liquor (21.46 g) was chromatographed on a column of silica gel (1:30). Chloroform and mixtures of chloroform and ethanol in various ratios were used as eluents.

The chloroform eluates yielded 0.062 g of dihydrosanguinarine, 0.071 g of (+)-chelidonine (216-217°C), 0.065 g of dehydrocorydine (amorphous), 0.12 g of sanguinarine (mp 240-241°C), and 0.083 g of chelerythrine (mp 206-207°C). The 99.5:0.5 fractions yielded 5.20 g of (+)-corydine, and the 98:2 and 96:4 fractions gave 3.89 g of protopine and 3.61 g of allocryptopine. The combined ether-soluble phenolic fraction was chromatographed on a column of silica gel. The alkaloids were eluted with chloroform and with chloroform–ethanol (200:1, 99:1, 98:2, 96:4, 9:1, and 4:1).

The chloroform-soluble fraction yielded 0.05 g of (−)-isocorypalmine (mp 231-232°C), 0.158 g of (+)-glaufidine, 0.085 g of (+)-isocorydine (mp 183-184°C), and 7.89 g of (+)-corydine.

The 200:1 and 99:1 fractions yielded an additional 0.32 g of corydine and 0.033 g of (−)-scoulerine (mp 191-192°C). The 98:2 fractions gave 0.09 of (+)-N-methyllindcarpine (mp 197-198°C), 0.30 g of (+)-isoboldine (mp 125-126°C), and 0.23 g of (+)-isocorytuberine. The 96:4 fractions yielded 0.035 g of (+)-norisocorydine and also (+)-reticuline (0.032 g; oil) and (−)-N-methylcoclaurine (0.053 g, mp 132-133°C). From the 9:1 and 4:1 fractions were obtained 0.06 g of (+)-norcorydine and 0.11 g of (+)-corydine N-oxide.

The combined chloroform-soluble alkaloids (12.59 g) were chromatographed on a column of silica gel. The fractions eluted by chloroform yielded 6.23 g of (+)-corydine and 0.52 g of (+)-glaufidine. From chloroform–ethanol (9:1 and 4:1) fractions were obtained 0.125 g of glaunine and 0.09 g of glaunidine (mp 230-232°C).

Dihydrosanguinarine, mp 187-188°C (methanol). Mass spectrum, m/e: 333 (M^+), 332 (100%) NMR spectrum: three-proton singlet at 2.55 ppm ($N-CH_3$), two-proton singlets at 4.13 ppm (> CH_2), 5.95 ppm (CH_2O_2), one-proton singlets at 7.03 and 7.62 ppm, one-proton doublets at 6.79, 7.23, 7.42, and 7.63 ppm (J = 8 Hz).

Hydrogenation of Dehydrocorydine. Adams hydrogenation of 20 mg of dehydrocorydine in 2 ml of acetic acid was carried out for 6 h. The acid solution after the separation of the catalyst was made alkaline with 25% ammonia solution, and the reduction product was extracted with chloroform. Distillation of the solvent yielded a product with mp 147-148°C identical with corydine according to TLC and IR spectroscopy.

Methylation of Isocorytuberine. An ethereal solution of diazomethane was added to 30 mg of isocorytuberine in 3 ml of absolute methanol. After a day, the mixture was evaporated to dryness, giving a product identical with corydine.

Norisocorydine, $[\alpha]_D$ +168° (c 0.40, methanol). UV spectrum, λ_{max}: 220, 270, 308 nm (log ε 4.34, 3.84, 3.46). Mass spectrum, m/e: 327 (M^+), 326, 312, 310, 298, 296, 253, 163.5 (M^{++}). NMR spectrum, ppm: 3.67 (OCH_3), 3.85 ($2OCH_3$), 6.81 and 7.03 (d, J = 8 Hz), 6.64.

Methylation of Norisocorydine. Norisocorydine (20 mg) was stirred in 2 ml of Craig's mixture (0.25 ml of 25% CH_2O and 25 ml of CH_3OH) for 1.5 h. Then 0.32 g of sodium tetrahydroborate was added and stirring was continued for 1 h; 5 ml of acetone was added and after 45 min the solution was evaporated to dryness. The residue was dissolved in 15 ml of 2% KOH solution, and the reaction product was extracted with ether. The solvent was evaporated off, giving a product identical with isocorydine according to TLC and mass spectroscopy.

Norcorydine, $[\alpha]_D$ +156° (c 0.43; methanol). UV spectrum, λ_{max}: 223, 270, 310 (log ε 4.36, 3.81, 3.40). Mass spectrum, m/e: 327 (M^+), 326, 312, 310, 298, 296, 253, 163.5 (M^{++}). NMR spectrum, ppm: 3.67 (OCH_3), 3.88 ($2OCH_3$), 6.87 and 7.16 (d, J = 8 Hz), 6.64.

Methylation of Norcorydine. Norcorydine (20 mg) was methylated by Craig's method as described above, and a product identical with corydine was obtained.

Reticuline, $[\alpha]_D$ +47.36° (c 0.32, methanol). UV spectrum, λ_{max}: 286 nm (log ε 4.10). Mass spectrum, m/e: 329 (M^+), 192 (100%), 178. NMR spectrum, ppm: 2.43 ($N-CH_3$), 3.78 ($2OCH_3$), 6.23, 6.52, 6.68 (5 Ar–H).

Corydine N-oxide, $[\alpha]_D$ +154° (c 0.79, methanol).

Reduction of Corydine N-Oxide. Zinc was added to 30 mg of the substance in 5 ml of 10% sulfuric acid solution. After two days, the acid solution was made alkaline with 25% ammonia and was extracted with chloroform. When the solvent had been distilled off a product identical with corydine was obtained.

Isolation and Separation of the Combined Alkaloids of the Roots. By the usual chloroform extraction, 1 kg of the roots yielded 6.39 g of ether fraction and 1.81 g of chloroform fraction. The total ether-soluble material was separated into a phenolic fraction (1.12 g) and a nonphenolic fraction (5.27 g).

Treatment with methanol of the combined nonphenolic alkaloids gave a mixture of crystals (3.31 g) from which 2.55 g of protopine and 0.60 g of allocryptopine were isolated by fractional crystallization from a mixture of methanol and chloroform. The residual mother liquor was chromatographed on a column of silica gel (1:30). The alkaloids were eluted with benzene and benzene–ethanol. The benzene fractions yielded 0.08 g of sanguinarine, 0.09 g of chelerythrine, and 0.04 g of chelidonine, and the benzene–ethanol (99:1 and 98:2) fractions gave 0.25 g of corydine.

From the 96:4 and 9:1 fractions we obtained 0.32 g of protopine and 0.8 g of allocryptopine. The combined phenolic fraction of the ether-soluble material was chromatographed on a column of silica gel (1:30). From the fractions eluted by benzene–ethanol (99:1 and 98:2) we isolated isocorydine (0.043 g) and corydine (0.34 g), and from the 97:3 fractions 0.09 g of N-methyllindcarpine and 0.025 g of glaufine. The 96:4 fraction yielded isoboldine (0.08 g) and the 95:5 and 9:1 fractions 0.035 g of N-methylcoclaurine.

SUMMARY

The epigeal part and roots of the plant *Glaucium fimbrilligerum* have been investigated. From the epigeal part 22 alkaloids have been isolated of which three have proved to be new, and their structures have been determined as d-isocorytuberine, corydine N-oxide, and dehydrocorydine.

Norcorydine, norisocorydine, and reticuline have been isolated from the genus *Glaucium* for the first time, and scoulerine and dihydrosanguinarine have been isolated from the given plant species for the first time. From the roots of *G. fimbrilligerum* 11 known alkaloids have been isolated.

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