413. *The Alkaloids of* Phylica rogersii *Pillans.*

By R. R. Arndt and W. H. Baarschers.

Reticuline (Ia), isocorydine (II), *N*-methyl-laurotetanine (IIIa), and rogersine have been isolated as minor alkaloids of *Phylica rogersii* Pillans (family Rhamnaceae). Rogersine has been characterized as a new aporphine alkaloid, for which structure (IIIb) is suggested.

The isolation of the major alkaloid of *Phylica rogersii* Pillans, and its identification as (—)-*N*-methylcoclaurine (Ib), have recently been reported.[1] The residue obtained after the separation of (—)*N*-methylcoclaurine from the fraction containing the stronger basic alkaloids has now yielded another amorphous alkaloid. The u.v. spectrum was characteristic of a benzyltetrahydroisoquinoline skeleton, and a bathochromic shift in alkaline medium indicated a phenolic nature (dark green colour with ferric chloride). The n.m.r. spectrum of the free base showed the presence of an NMe group (τ 7·52) and 2 OMe groups (τ 6·13). The alkaloid formed a crystalline dimethyl ether with diazomethane, which had properties similar to those reported for laudanosine (Ic).[2] The only crystalline salt which could be prepared from this alkaloid was the perchlorate $C_{19}H_{24}NO_4ClO_4,\frac{1}{2}H_2O$ which had properties, m. p. 211°, $[\alpha]_D$ +80°, similar to those reported for the salt of reticuline.[3] Comparison of the alkaloids liberated from synthetic reticuline picrate [4] and the above-mentioned perchlorate proved them to be identical (paper chromatography and i.r. spectra).*

From the weaker basic part of the crude alkaloid mixture, one amorphous and two crystalline alkaloids were isolated.

The amorphous alkaloid, which had phenolic properties (green colour with ferric chloride), gave, on treatment with diazoethane and methyl iodide, a monoethyl ether methiodide, $C_{23}H_{30}INO_4$, which had a u.v. spectrum characteristic of an aporphine derivative with an unsubstituted 11-position.[5] Its n.m.r. spectrum indicated the presence of an $^+NMe_2$ group (τ 6·70), 3 OMe groups (τ 6·03, 6·13, and 6·27), one OEt group (triplet

* Although Gopinath *et al.*[3] found the perchlorate to be the only crystalline salt, Jain [4] characterized the synthetic (±)-base as its crystalline picrate. Attempts to prepare the picrate from the naturally occurring base were unsuccessful.

[1] Arndt, *J.*, 1963, 2547.
[2] Manske, "The Alkaloids," Academic Press Inc. Publ., New York, 1954, Vol. IV, p. 48.
[3] Gopinath, Govindachari, Pai, and Viswanathan, *Ber.*, 1959, **92**, 776.
[4] Jain, *J.*, 1962, 2203.
[5] Shamma, *Experientia*, 1960, **16**, 484.

at 83 c./sec. and quartet at 253 c./sec. from tetramethylsilane, J 6 c./sec). The presence of only 3 isolated aromatic protons (τ 1·94, 2·82, and 3·16) confirmed a tetrasubstituted aporphine derivative of the glaucine type. This ethyl ether methiodide was proved to be identical (mixed m. p., i.r. spectra, and paper chromatography) with that prepared in the same way from an authentic specimen of *N*-methyl-laurotetanine (IIIa).

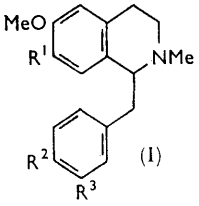
Of the two crystalline alkaloids isolated, the one, $C_{20}H_{23}NO_4$, m. p. 185°, was identified as isocorydine (II) by direct comparison with an authentic specimen.

The other crystalline alkaloid, $C_{20}H_{23}NO_4,\frac{1}{2}MeOH$, m. p. 100—105°, $[\alpha]_D$ +111°, had a u.v. spectrum characteristic of an aporphine alkaloid with an unsubstituted 11-position.[5] Its n.m.r. spectrum showed the pressure of an NMe group (τ 7·47), 3 OMe groups [τ 6·11 (6H), and 6·31 (3H)], and 3 isolated aromatic protons (τ 1·91, 3·18, and 3·39). One-half mole of methanol of crystallization gave a peak at τ 6·55 (intensity 1½H). The fourth oxygen atom was present as a phenolic hydroxy-group, indicated by a green coloration with ferric chloride and a bathochromic shift in the u.v. spectrum in alkaline medium. Methylation with diazomethane afforded glaucine (IIIe) which confirmed a 1,2,9,10-substitution pattern.

Of the four possible mono-*O*-demethyl glaucine alkaloids, three are known, *viz.*, *N*-methyl-laurotetanine (IIIa), glaucentrine (IIIc), and *ON*-dimethyl-laurelliptine (IIId).[6]

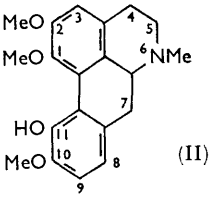
That identifications in this series must be made with caution became apparent when it was found that the i.r. and n.m.r. spectra of *N*-methyl-laurotetanine and the present alkaloid were superimposable.* However, paper chromatography indicated that these two alkaloids were different.

Bick *et al.*[7] showed that in aporphine alkaloids methoxyl groups in position 1, adjacent to two benzene rings, have consistently higher chemical shifts than those at other positions. A methyl resonance at τ 6·31 in the n.m.r. spectrum of the present alkaloid proved that this alkaloid was not glaucentrine (IIIc).

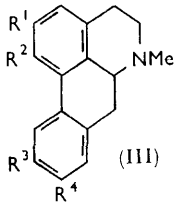


(I)

(Ia: $R^1 = R^3 = OH$, $R^2 = OMe$)
(Ib: $R^1 = OMe$, $R^2 = OH$, $R^3 = H$)
(Ic: $R^1 = R^2 = R^3 = OMe$)

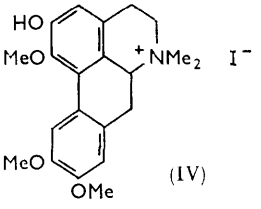


(II)



(III)

(IIIa: $R^1 = R^2 = R^3 = OMe$, $R^4 = OH$)
(IIIb: $R^1 = R^2 = R^4 = OMe$, $R^3 = OH$)
(IIIc: $R^1 = R^3 = R^4 = OMe$, $R^2 = OH$)
(IIId: $R^2 = R^3 = R^4 = OMe$, $R^1 = OH$)
(IIIe: $R^1 = R^2 = R^3 = R^4 = OMe$)



(IV)

Direct comparison of the methiodide with the iodide of the quaternary aporphine base (IV) isolated from *Fagara tinguassoiba*[8] eliminated structure (IIId) for the alkaloid. This leaves only one possible structure (IIIb), which was finally proved by direct comparison of the ethyl ether with a synthetic specimen.[9] The name rogersine is suggested for this new alkaloid.

* During an attempt to isolate more *N*-methyl-laurotetanine as its hydrobromide, it was also found that isocorydine hydrobromide, m. p. 225°, did not depress the m. p. of *N*-methyl-laurotetanine hydrobromide (227°).

[6] Clezy, Nichol, and Gellert, *Experientia*, 1963, **19**, 1.
[7] Bick, Harley-Mason, Sheppard, and Vernengo, *J.*, 1961, 1896.
[8] Riggs, Antoniaccio, and Marion, *Canad. J. Chem.*, 1961, **39**, 1330.
[9] Manske, Charlesworth, and Ashford, *J. Amer. Chem. Soc.*, 1951, **73**, 3751.

Recently Shamma [10] and Clezy *et al.*[6] suggested structure (IIIb) for thalicmidine, a monophenolic aporphine base isolated from *Thalictrum minus*.[11] These suggestions were based on indirect evidence. Apart from differences in the physical constants of rogersine and thalicmidine, the latter was reported [12] to resist methylation by diazomethane, which is not to be expected for an aporphine alkaloid with a hydroxy-group in the 10-position. The direct identification of rogersine now leaves thalicmidine unidentified. This called for a re-investigation of the structure of thalicmidine, which is now in progress.

Experimental

The m. p.s are corrected and were measured in evacuated, sealed, capillaries. Ultraviolet absorption spectra and $[\alpha]_D$ refer to ethanol, and infrared absorption spectra to chloroform solutions. The latter were recorded on a Perkin-Elmer Infracord 137 spectrometer. Nuclear magnetic resonance spectra were determined with a Varian A-60 instrument, for 5—10% deuterochloroform solutions, with tetramethylsilane as an internal standard (τ 10·00). Descending chromatography on Whatmann No. 1 paper was employed; solvent systems were: A, the upper phase of chloroform–benzene–formamide (6 : 4 : 5), with paper impregnated with a 40% methanolic formamide solution; B, the upper phase of cellosolve–toluene–buffer (5 : 5 : 1), with a buffer solution prepared by adding 9·5 ml. of 0·2M-sodium acetate to 90·5 ml. of 0·2M-acetic acid; C, the upper phase of n-butanol–acetic acid–water (16 : 3 : 10).

Isolation of Crude Alkaloids.—Ground, air-dried branches and leaves (49 kg.) of *Phylica rogersii* were soaked with aqueous ammonia and exhaustively extracted with chloroform. The extract was concentrated and shaken with 2% aqueous tartaric acid. The acid solution was made alkaline, and the crude alkaloid mixture (46 g.) was isolated with chloroform. A solution of the crude product in 5% aqueous sulphuric acid (200 ml.) was adjusted to pH 8 with sodium hydrogen carbonate; extraction with chloroform then yielded a crude, weakly basic, fraction (12·5 g.). The aqueous solution was then adjusted to pH 10, and extraction with chloroform afforded a crude, stronger basic, fraction (28 g.).

Reticuline (Ia).—Direct crystallization of the stronger basic fraction from methanol gave (−)-*N*-methylcoclaurine (3 g.). The mother-liquor (25 g.) in chloroform (400 ml.) was extracted with aqueous buffer solution (citric acid–phosphate; pH 7; 1·8 l. in 300-ml. portions). The pH of the aqueous extract was adjusted to 10 with sodium hydrogen carbonate, and (−)-*N*-methylcoclaurine (10 g.) was isolated with chloroform. The original chloroform solution, on evaporation of the solvent, afforded an amorphous substance (15 g.), which was subjected to a 30-tube Craig counter-current distribution between chloroform and aqueous buffer solution (citric acid–phosphate; pH 7·3; 100 ml. of each phase per tube). Tubes 2—4 yielded a brown foam (3·6 g.) of R_F 0·34 (system A), which was treated in ethyl acetate (60 ml.) with activated carbon (1 g.). The product (1·5 g.) with perchloric acid afforded a crystalline perchlorate (600 mg.), m. p. 211° (from methanol) [in open capillary, m. p. 197—199° (decomp.)], $[\alpha]_D$ +80·2° (*c* 1·5), $\lambda_{max.}$ 285 and 225sh, mμ (ε 9037 and 19,050, respectively); $\lambda_{max.}$ in 0·04N-ethanolic potassium hydroxide 300 and 246 mμ (ε 12,020 and 16,600, respectively) (Found: C, 52·1; H, 5·6; N, 3·2; OMe, 14·3. Calc. for $C_{19}H_{24}NO_4ClO_4,\frac{1}{2}H_2O$: C, 52·0; H, 5·7; N, 3·2; 2OMe, 14·2%). The free base (from 130 mg. of perchlorate) in methanol was treated with an excess of ethereal diazomethane. The product was filtered, in chloroform, through alumina and crystallized from hexane; it had m. p. 87—88°, $[\alpha]_D$ +91° (*c* 0·6) [lit.,[2] for laudanosine (Ic), m. p. 87—88°, $[\alpha]_D$ +90°] (Found: C, 70·8; H, 7·8; OMe, 35·0. Calc. for $C_{21}H_{27}NO_4$: C, 70·6; H, 7·6; 4 OMe, 34·6%). The alkaloids liberated from the above perchlorate and from an authentic specimen of synthetic (±)-reticuline picrate, kindly supplied by Professor D. H. R. Barton (Imperial College, London), behaved identically on paper chromatography [R_F 0·79 (ammonia solution–ethanol–water (1 : 5 : 14) and 0·57 (system C)], and had identical i.r. spectra.

Separation of the Weaker Basic Alkaloids.—The weaker basic portion of the crude alkaloid mixture (9·2 g.) was dissolved in chloroform (300 ml.) and extracted with aqueous citric acid–phosphate buffer solution of pH 4·2 (2 × 250 ml.). The aqueous extract was made alkaline and extracted with chloroform to give fraction A (3·78 g.). Further extraction (8 × 200 ml.)

[10] Shamma, *Experientia*, 1962, **18**, 64.
[11] Yunusov and Progressov, *Zhur. obshchei Khim.*, 1950, **20**, 1151.
[12] Yunusov and Progressov, *Zhur. obshchei Khim.*, 1952, **22**, 1047.

of the original chloroform solution with the same buffer solution gave an extract, which was basified and extracted with chloroform to give fraction B (3·2 g.). Finally, the original chloroform solution was exhaustively extracted with 3N-sulphuric acid, the aqueous solution made alkaline, and the product (fraction C; 1·5 g.) isolated with chloroform.

N-*Methyl-laurotetanine.*—Further purification of fraction B was achieved by extraction of its chloroform solution (150 ml.) with aqueous buffer solution of pH 5 (6 × 150 ml.). After treatment of the product (2 g.) remaining in the chloroform solution with activated carbon in ethyl acetate, it failed to form a crystalline hydrochloride, perchlorate, or picrate. A portion (750 mg.) was therefore dissolved in methanol and treated with an excess of ethereal diazoethane solution. Chromatography on alumina and elution with chloroform gave an amorphous ethyl ether (600 mg.), from which a crystalline *methiodide* was prepared by treatment with methyl iodide in methanol; this had m. p. 206—207° (from acetone–methanol), $[\alpha]_D$ +61° (*c* 0·7), $\lambda_{max.}$ 306, 283, and 215 mμ (ε 14,900, 13,290, and 67,280, respectively) (Found: C, 54·2; H, 6·3; N, 2·7. $C_{23}H_{30}INO_4$ requires C, 54·0; H, 5·9; N, 2·7%). This ethyl ether methiodide was identical [mixed m. p., i.r. spectra (in KBr), and paper chromatography (R_F 0·55, system B, and R_F 0·57, system C)] with that prepared from an authentic specimen of *N*-methyl-laurotetanine, which was kindly supplied by Dr. A. Rüegger (Sandoz Ltd., Basle).

Isocorydine.—Fraction C (1·08 g.) was chromatographed on alumina. Elution with chloroform afforded a fraction (740 mg.) which, when crystallized from acetone–hexane, had m. p. 185°, $[\alpha]_D$ +201° (*c* 0·7 in chloroform) [(lit.,[13] for isocorydine, m. p. 185—186°, $[\alpha]_D$ +195° (in chloroform)]; $\lambda_{max.}$ 303, 266, and 221 mμ (ε 5375, 12,815, and 28,390, respectively), $\lambda_{max.}$ in 0·05N-ethanolic potassium hydroxide, 345, 273sh, and 225 mμ (ε 6051, 8384, and 32,420, respectively) (Found: C, 70·2; H, 6·6; N, 3·9; OMe, 27·7. Calc. for $C_{20}H_{23}NO_4$: C, 70·4; H, 6·8; N, 4·1; 3OMe, 27·3%).

The hydriodide, prepared by treatment of the base with sodium iodide in acetic acid, had m. p. 225° (Found: C, 51·0; H, 5·3; N, 2·8; OMe, 20·1. Calc. for $C_{20}H_{24}INO_4$: C, 51·1; H, 5·2; N, 3·0; 3OMe, 19·9%). The free base was identified as isocorydine by comparison with an authentic specimen [mixed m. p., i.r. spectra, and paper chromatography (R_F 0·83, system B, and 0·65, system C)], kindly supplied by Professor M. Shamma (Pennsylvania State University, U.S.A.).

Rogersine.—Fraction A (3·78 g.) was chromatographed through formamide-impregnated cellulose powder (450 g.). Elution with 7 : 3 benzene–hexane (500 ml.) afforded a substance (800 mg.) which was heated with sodium iodide in acetic acid to give a crystalline *hydriodide*, m. p. 245° (Found: C, 50·9; H, 5·3; N, 2·9; OMe, 19·8. $C_{20}H_{24}INO_4$ requires C, 51·1; H, 5·2; N, 3·0; 3 OMe, 19·9%). This was treated with alkali and the free base isolated with chloroform. Recrystallization from methanol gave *rogersine* (IIIb), m. p. 100—105° (sinters at 85°), $[\alpha]_D$ +111° (*c* 0·86), $\lambda_{max.}$ 304, 282, and 219 mμ (ε 25,630, 25,630, and 65,080, respectively); $\lambda_{max.}$ in 0·05N-ethanolic potassium hydroxide, 329 and 223 mμ (ε 39,639 and 50,850, respectively) (Found: C, 68·6; H, 7·3; N, 3·9; OMe, 26·1. $C_{20}H_{23}NO_4,\frac{1}{2}$MeOH requires C, 68·9; H, 7·1; N, 3·9; 3OMe, 26·1%). Drying for 15 hr. *in vacuo* at 40° did not remove the solvent of crystallisation. On paper chromatography, rogersine had R_F 0·80 (system A) and 0·39 [n-butanol–toluene–buffer (3 : 2 : 5), upper phase; buffer prepared as for system B], as compared to R_F 1·00 and 0·45, respectively, for authentic *N*-methyl-laurotetanine. The *methiodide*, prepared by treatment of rogersine, in methanol, with an excess of methyl iodide was recrystallized from acetone–methanol, and then had m. p. 199—200° (Found: C, 52·2; H, 5·2; N, 2·8; OMe, 18·8. $C_{21}H_{26}INO_4$ requires C, 52·3; H, 5·2; N, 2·9; 3 OMe, 19·3%). Rogersine methiodide, R_F 0·42 (system B) and 0·50 (system C), was different from an authentic specimen of the iodide of the quaternary base (IV) from *Fagara tinguassoiba*, kindly supplied by Dr. L. Marion (National Research Council, Ottawa), which had m. p. 229°, R_F 0·37 and 0·35, respectively.

O-*Ethylrogersine* (−)-*Tartrate.*—Rogersine (82 mg.) in methanol (3 ml.) was treated with an excess of ethereal diazoethane solution, and the product (105 mg.), in methanol (2 ml.), warmed with (−)-tartaric acid (60 mg.). The crystals which were precipitated on cooling, were recrystallized from methanol to give *O*-ethylrogersine (−)-tartrate, m. p. 206—207° (decomp.), $[\alpha]_D$ +53° (*c* 0·4) (Found: C, 59·8; H, 6·4; N, 2·8. Calc. for $C_{26}H_{33}NO_{10}$: C, 60·1; H, 6·4; N, 2·7%). This compound was identified [mixed m. p., i.r. spectra in KBr, and R_F 0·56 (system

[13] Boit, " Ergebnisse der Alkaloid Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p. 267.

B) and 0·61 (system C)] by comparison with a synthetic specimen,[9] m. p. 205—206°, kindly supplied by Dr. R. H. F. Manske (Dominion Rubber Research Laboratory, Ontario).

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