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STUDIES ON ARGENTINE PLANTS—XX[1]

THE SYNTHESES OF FARGARINE II

D. GIACOPELLO, V. DEULOFEU and J. COMIN
Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales,
Perù 222, Buenos Aires, Argentina

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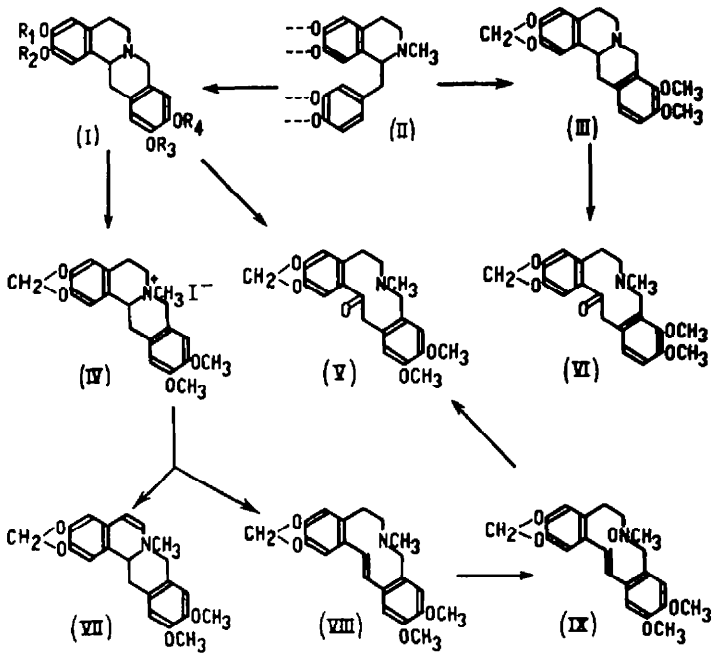
Abstract—Fagarine II has been synthesized starting from tetrahydropseudoberberine and its proposed structure (V) confirmed.

FAGARINE II is a base isolated from the leaves and twigs of *Fagara coco*, (Gill) Engl. (Rutaceae).[2] On the basis of its UV spectrum and the formation of an anhydromethochloride on treatment with phosphoryl chloride, Redeman *et al.*[3] suggested that fagarine II is a protopine alkaloid isomeric with allocryptopine. Comin and Deulofeu[4] transformed it into the tetrahydropseudoberberine (I, $R_1 + R_2 = CH_2$; $R_3 = R_4 = CH_3$) of Haworth *et al.*,[5] and thus showed that while the methylenedioxy group in fagarine II is located at the same carbon atoms as in allocryptopine, the methoxy groups must be at C-10 and C-11 and not at C-9 and C-10 as in allocryptopine.

Although coreximine (I, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$), a protoberberine–protopine alkaloid, and two alkaloids xylopinine, [(−)-norcoralydine][6] (I, $R_1 = R_2 = R_3 = R_4 = CH_3$) isolated from *Xylopia discreta* (L. Fil.) Sprague and Hutchins (Anonaceae),[7] as well as (−)-discretine (I, $R_1 = H$; $R_2 = R_3 = R_4 = CH_3$),[8] which are protoberberine alkaloids, have substituents at C-10 and C-11, fagarine II still remains the only base of the protopine group with this type of substitution. It is, moreover, interesting to note that in *Fagara coco* it is found associated with allocryptopine which is substituted at C-9 and C-10.

It has been pointed out earlier that a hypothetical benzylisoquinoline (II), with substituents at carbon atoms 3′, 4′, 6 and 7, could, by condensation with a "one carbon unit", lead to two bases with a tetrahydroberberine (III) or a tetrahydropseudoberberine (I) type of substitution, which would respectively be precursors of allocryptopine (VI) and fagarine II (V). The report by Barton *et al.*[9] and Battersby *et al.*[10] that the "berberine carbon atom" originates, not as an independent one

[1] Paper XIX. B. Frydman and V. Deulofeu, *Tetrahedron* **18**, 1063 (1962).
[2] G. V. Stuckert, *Investigationes del Laboratorio de Química Biológica*, pág. 109, Vol. I. Córdoba, Argentina (1933); V. Deulofeu and J. Comin, *Il Farmaco* **9**, 340 (1954).
[3] C. E. Redeman, B. B. Wiegarver and G. A. Alles, *J. Amer. Chem. Soc.* **71**, 1030 (1949).
[4] J. Comin and V. Deulofeu, *Tetrahedron* **6**, 63 (1959).
[5] R. D. Haworth, W. H. Perkin and J. Rankin, *J. Chem. Soc.* 1686 (1924).
[6] H. Corrodi and E. Hardegger, *Helv. Chim. Acta* **39**, 889 (1956).
[7] J. Schmutz, *Helv. Chim. Acta* **42**, 335 (1959).
[8] F. Bernoulli, H. Linde and K. Meyer, *Helv. Chim. Acta* **46**, 323 (1963).
[9] D. H. R. Barton, R. H. Hesse and G. W. Kirby, *Proc. Chem. Soc.*, 267 (1963).
[10] A. R. Battersby, R. J. Francis, M. H. Hirst and J. Staunton, *Proc. Chem. Soc.* 268 (1963).



carbon unit from the metabolic pool, but in the N-methyl of a benzylisoquinoline base, and the demonstration by Barton[9] that the correlative carbon atom of protopine has the same origin, has increased the importance of a benzylisoquinoline precursor in the biogenesis of these alkaloids.

The synthesis of fagarine II from tetrahydropseudoberberine[5] has furnished additional proof of its structure. Methylation of tetrahydropseudoberberine produced the two isomeric α- and β-methiodides, the latter being obtained in the larger yield. A mixture of the methochlorides obtained from the methiodides, was transformed into the quaternary hydroxide from which the *anhydrotetrahydropseudoberberines* A (VIII) and B (VII) were prepared. On treating VIII with perbenzoic acid the N-*oxide of the anhydrobase* A (IX) was obtained which on heating in acidic media rearranges to fagarine II (V). This confirms the structure proposed earlier.

A rearrangement of this type was first applied to the syntheses of the protopine alkaloids, allocryptopine,[11] protopine[12] and cryptopine,[13] and also to the preparation of the tetramethoxy analogue of cryptopine, a base named cryptopalmatine, which so far has not been found in anture.[14] Russell,[15] during a reinvestigation of the synthesis of allocryptopine, studied the possible mechanism of the rearrangement.

The preparation of the N-oxide of the anhydrobase A (IX) and its rearrangement to fagarine II (V) are more complex reactions than those observed in the similar synthesis of allocryptopine.[11,15] During the isomerization, coloured products are formed,

[11] R. D. Haworth and W. H. Perkin, *J. Chem. Soc.* 445 (1926).
[12] R. D. Haworth, W. H. Perkin and T. S. Stevens, *J. Chem. Soc.* 1764 (1926).
[13] R. D. Haworth and W. H. Perkin, *J. Chem. Soc.* 1769 (1926).
[14] R. D. Haworth, J. B. Koepfli and W. H. Perkin, *J. Chem. Soc.* 2261 (1927).
[15] P. B. Russell, *J. Amer. Chem. Soc.* **78**, 3115 (1956).

and in several batches fagarine II could be isolated only by counter current distribution of the basic products. Similarly, difficulties were also encountered in the tetrahydropseudoberberine series when the synthesis of fagarine II was attempted by the method of Bentley *et al.*,[16] successfully applied to the synthesis of allocryptopine. *Tetrahydropseudoberberine* N-*oxide* has been prepared, but the oxidation with chromate gave a mixture of products which was found difficult to work up.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in ethanol and IR spectra in a Nujol mull except when otherwise specified. Descending paper chromatography on Whatman paper No. 1 was employed, using as mobile phase the upper layer of a mixture of n-butanol: acetic acid: water (100:4:40) and developing with the Dragendorff reagent as modified by Munier and Macheboeuf.[17]

6,7-*Methylenedioxy*-1-3, (4-*dimethoxybenzyl*)-3,4-*dihydroisoquinoline*. To a solution of 15 g 2-(3,4-dimethoxyphenyl)-N-(3′,4′-methylenedioxyphenylethylacetamide), prepared according to Haworth *et al.*,[5] in 200 ml pure chloroform, 30 g PCl_5 was slowly added with constant shaking and at a temp below 5°. The resulting suspension was left at 0–5° with occasional shaking. After 5 days, when sufficient precipitate had been formed 30 g ice was added for the dissolution of the solid. The solution was evaporated *in vacuo*, leaving an oily residue which was dissolved in 100 ml absolute ethanol. The solution was made alkaline by the addition of 400 ml 20% ethanolic KOH, and then slowly poured, with vigorous stirring, into 7 l. water. A cloudy suspension formed, and on standing for 24 hr the 6,7-methylenedioxy-1-(3,4-dimethoxybenzyl)-3,4-dihydroisoquinoline crystallized out as fine needles (11 g), m.p. 82–84°. It was purified by dissolving in chloroform and filtering through a column of 15 g alumina (Woelm, grade III) employing chloroform for the elution. On evaporation of the chloroform, crystals (10·5 g; 74%), m.p. 87–88°, were obtained.

6,7-*Methylenedioxy*-1-(3,4-*dimethoxybenzyl*)-1,2,3,4-*tetrahydroisoquinoline*. The above-mentioned dihydroisoquinoline (5 g) was dissolved in 250 ml ethanol and hydrogenated at room temp and 1 atm in the presence of 0·5 g platinum oxide to give the tetrahydroisoquinoline (4·4 g; 87%), m.p. 82–84°, hydrochloride m.p. 235°. Haworth *et al.*[5] gave m.p. 84° for the base and 236° for the hydrochloride.

The tetrahydroisoquinoline was also prepared by dissolving 1 g of the dihydrobase in 50% ethanol and slowly adding 100 mg sodium borohydride to the solution. The resulting suspension was refluxed for 15 min, 90 ml water added and the solution obtained extracted thoroughly with ether. The dried ethereal extracts on evaporation yielded an oily residue which crystallized on adding a few drops methanol and scratching (yield 0·70 g; 70%), m.p. 82–84°.

Tetrahydropseudoberberine was prepared from this compound by the method of Haworth *et al.*[5] M.p. 175–176°; λ_{max} 288 mμ (log ϵ 3·95).

Tetrahydropseudoberberine α- *and* β-*methiodides* (IV). To 2·0 g of tetrahydropseudoberberine, 2·0 ml of methyl iodide was added at room temp. The base dissolved and in a few min precipitation of the iodides started. After 2·5 hr (keeping in a dark place avoids discoloration) excess methyl iodide was evaporated off and 2·5 g crystals, m.p. 246–250°, were collected. On recrystallization from methanol, fine needles were obtained (1·76 g 70%), m.p. 266–267°, λ_{max} 290 mμ (log ϵ 3·90). R_f 0·35. This is the β-isomer according to the nomenclature of Jowett and Pyman[18] (Found: C, 52·23; H, 5·17; I, 26·70. Calc. for $C_{21}H_{24}INO_4$: C, 52·40; H, 5·02; I, 26·37%).

The mother liquor from the first recrystallization of the mixture of methiodides was evaporated to dryness (0·74 g) and recrystallized from 25 ml boiling water. On cooling 0·66 g prisms were obtained, m.p. 183–184°, which were recrystallized twice from water and twice from methanol, to give pure α-isomer, m.p. 191–193°, λ_{max} 290 mμ (log ϵ 3.91). R.0.56. (Found: I, 26.06. Calc. for $C_{21}H_{24}INO_4$: I, 26·37%).

Both methiodides decompose on sublimation in high vacuum, giving the original base in 94% yield.

Tetrahydropseudoberberine β-*methochloride*. The original mixture of methiodides (1·42 g) was

[16] K. W. Bentley and A. W. Murray, *J. Chem. Soc.* 2497 (1963).
[17] R. Munier and M. Macheboeuf, *Bull. Soc. Chim. Biol.* **38**, 846 (1951).
[18] H. A. D. Jowett and F. L. Pyman, *J. Chem. Soc.* **103**, 290 (1913).

suspended in 120 ml methanol and, following the method of Phillips and Baltzly,[19] HCl was passed through the suspension until nitrous acid gave a negative test for iodine. The reaction mixture was evaporated to dryness, and the solid residue was thoroughly dried and recrystallized from 20 ml of boiling methanol giving 800 mg needles, m.p. 255–256°, which on further recrystallization from methanol gave the pure β-methochloride, m.p. 256–257°. λ_{max} 235 mμ (log ϵ 4·03); 288 (3·93). R_f 0·38. (Found: N, 3·78; Cl, 9·58. Calc. for $C_{21}H_{24}ClNO_4$: N, 3·60; Cl, 9·09%).

Paper chromatography of the mother liquors of recrystallization showed the presence of another substance with R_f 0·65, which must be the α-methochloride. It could not be obtained in crystalline condition free from the β-methochloride.

N-*Methyl anhydrotetrahydropseudoberberine* A (VIII). The crude solid mixture of methochlorides can be submitted without further purification to the Hofman degradation. To 1·2 g of the methochlorides, dissolved at room temp in 240 ml boiled water (CO_2-free), moist silver oxide prepared from 1·44 g $AgNO_3$, was added and the mixture shaken for 5–10 min. The insoluble silver salts were then filtered off and the clear filtrate evaporated to dryness *in vacuo*, avoiding contact with air and keeping the bath temp at 90–100°. A white solid residue was obtained, which was heated for 30 min to the same temp *in vacuo*, when it was transformed into an oil. This oil was refluxed with 60 ml pet. ether (80–100°), in which it dissolved except for a small fraction which was filtered off. The filtrate was concentrated to 20 ml and on cooling yielded prisms of VIII (610 mg; 57%), m.p. 140–142°, which were recrystallized from cyclohexane for analysis, m.p. 142–143°. R_f 0·41. (Found: C, 71·40; H, 6·7; N, 4·09; O, 18·06. Calc. for $C_{21}H_{23}NO_4$: C, 71·40; H, 6·56; N, 3·97; O, 18·11%).

N-*Methyl anhydrotetrahydropseudoberberine* A N-*oxide* (IX). To a cooled solution of 170 mg perbenzoic acid in 14 ml ethyl ether, a cooled solution of 300 mg VIII in 0·6 ml chloroform was slowly added. The resulting suspension was left for 15 hr at −5° when a semi-solid precipitate of IX formed, which crystallized on scratching. It was collected, (300 mg; 95%), m.p. 150°, and recrystallized from methanol, giving long prisms with the same m.p. (Found: C, 68·06; H, 6·39; N, 3·68; O, 21·80. Calc. for $C_{21}H_{23}NO_5$: C, 68·27; H, 6·28; N, 3·80; O, 21·66%).

Fagarine II (V). One hundred milligram IX was dissolved in 1 ml mixture of one volume HCl and two volumes glacial acetic acid, and the solution kept at 100° for 1 hr. A violet-purple colour developed in the first few minutes, whereas in case of the corresponding product of the tetrahydroberberine series, only a light yellow colour was produced. After heating, 2 ml water was added and the solution made alkaline to pH 10 with 2N NaOH. The resulting brown precipitate was extracted with ether. After washing and drying, the ethereal extract was evaporated to dryness and the amorphous residue dissolved in chloroform and passed through a column of neutral alumina (Woelm, grade III). It was eluted with chloroform with increasing amounts of methanol. The fractions containing 1 to 5% methanol were combined and evaporated. A solid residue (40 mg) was obtained, which on paper chromatography was found homogenous, giving only one alkaloidal spot, R_f 0·52 identical to that of fagarine II.

The alkaloid could not be crystallized and was submitted to a counter current distribution (60 transfers), employing n-butanol as the upper phase and 0·01N HCl aq as the lower phase (K 0·73). The alkaloid was found in tubes 9–26; a coloured impurity moved faster. The solutions containing the base were combined and evaporated to dryness. The white residue obtained was dissolved in water and the solution made alkaline and extracted with ether. The ethereal extract on evaporation gave a residue which was crystallized from ethanol in the form of needles (27 mg m.p. 200–201° which remained undepressed on mixing with natural fagarine II melting at 200°). λ_{max} 232 mμ (log ϵ 4·06); 286 (3·91); identical to the natural base. IR spectra and R_f in three different systems were also identical.

N-*Methyl anhydrotetrahydropseudoberbine* B *picrate* (VII). The crude mixture of methiodides of tetrahydropseudoberberine (420 mg) was suspended in 40 ml 20% ethanolic NaOH and boiled for 3 hr when a clear solution was obtained. After addition of 100 ml water, it was extracted thoroughly with ether. The ether extracts upon evaporation gave 400 mg of an oily residue. The residue was dissolved in 4 ml ethanol, and 1·5 ml ethanolic picric acid was added when a crystalline precipitate separated. On recrystallization from methanol it gave long prisms, m.p. 195–196° (Found: N, 9·52. Calc. for $C_{21}H_{23}NO_4.C_6H_3N_3O_7$: N, 9·62%). The free base gives a positive Lemieux[20] test for

[19] A. P. Phillips and R. Baltzly, *J. Amer. Chem. Soc.* **74**, 5231 (1952).
[20] R. U. Lemieux and E. von Rudloff, *Can. J. Chem.* **33**, 1701 (1955).

vinyl groups. The same picrate, m.p. 195–196°, was also obtained by boiling N-methyl anhydrotetrahydropseudoberberine A for 1 hr with 10% methanolic NaOH and proceeding as described above.

Tetrahydroberberine N-*oxide*. To 360 mg perbenzoic acid in 6 ml chloroform, cooled to 0–5°, 400 mg tetrahydroberberine dissolved in 4 ml chloroform was slowly added and the solution allowed to stand for 12 hr at the same temp. It was then washed with 5 ml 2N NaOH and water. The remaining chloroform solution was well dried and evaporated to dryness, giving an oily residue. On adding methanol and scratching, it crystallized in the form of long needles (200 mg; 46%), m.p. 208–210°, and after several recrystallizations from methanol they melted 210–212°. Analysis of the crystals dried at 80° showed that it retained water rather strongly. (Found: C, 65·19; H, 6·39; N, 3·94; O, 24·42. Calc. for $C_{20}H_{21}NO_5.\frac{1}{2}H_2O$: C, 65·92; H, 6·08; O, 24·15%). This N-oxide has a higher m.p. than the one described by Bentley *et al.*,[16] which melts at 158·5–159°. It gives the same picrate, m.p. 196·5–197·5°, and was reduced to tetrahydroberberine by boiling for 2 hr with Zn powder and 3N HCl. On applying the reactions described by Bentley and Murray,[16] it gave allocryptopine, m.p. 160–161°, the intermediate products being those already described.[16]

Tetrahydropseudoberberine N-*oxide*. To a solution of 460 mg perbenzoic acid in 10 ml chloroform cooled to 0–5°, 500 mg tetrahydropseudoberberine dissolved in 5 ml chloroform was slowly added. The solution left for 12 hr at the same temp, then washed with 2N NaOH and water, well dried and evaporated. The resulting oily residue (500 mg) was crystallized from 20 ml boiling methanol to give fine needles (370 mg), m.p. 220–223°, and after recrystallization from methanol 225°. For analysis it was dried for 5 hr at 80° *in vacuo*. (Found: C, 62·57; H, 6·36; N, 3·40; C, 27·70. Calc. for: $C_{20}H_{21}NO_5.1\frac{1}{2}H_2O$: C, 62·76; H, 6·28; N, 3·66; O, 27·19%).

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