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STUDIES ON ARGENTINE PLANTS—XVII*

THE STRUCTURE OF FAGARINE II

J. COMÍN and V. DEULOFEU
Laboratorios de Química Orgánica, Facultad de Ciencias Exactas y Naturales
Perú 222, Buenos Aires, Argentina

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Abstract—The structure of fagarine II, an alkaloid from *Fagara coco* (Gill.) Engl., has been elucidated through its transformation into tetra-hydro-pseudo berberine.

IN common with other species of the *Rutaceae* family, a number of alkaloids belonging to different chemical types have been isolated from *Fagara coco* (Gill.) Engl.[1] In leaves and twigs, the furoquinoline bases γ-fagarine and skimmianine and the protopine alkaloids *allo*cryptopine (α-fagarine) and fagarine II, have been found.[1-3] From the bark, besides skimmianine and *allo*cryptopine,[4] an aporphine alkaloid, N-methyl-*iso*corydine, has also been isolated.[5] Fagarine III, a minor alkaloid of unknown structure, was found in the extracts from leaves and twigs.[3]

Fagarine II, according to the information given by Stuckert,[1] was first isolated in Merck's Laboratories in Darmstadt. Later, Redemann, Wisegarver and Alles,[3] again obtained the same base.

They suggested that fagarine II was a member of the protopine alkaloids, because its ultraviolet spectrum was very similar to that of *allo*cryptopine, and on treatment with phosphoryl chloride, it gave an anhydromethochloride, a reaction that is considered typical of that group of bases. The same workers showed that it was isomeric with *allo*cryptopine, both having two methoxy- and one methylenedioxy-group. The difference between the bases should then be only one of the location of the substituents.

The experiments reported here show that fagarine II has structure (I). The possibility that fagarine II should have this structure, or the isomeric one (II), was suggested from a comparison of its infrared spectrum (Fig. 1) with that of *allo*-cryptopine (Fig. 2). Both spectra have a certain similarity. However, in the region of out of plane aromatic carbon–hydrogen deformation vibrations, the spectrum of *allo*cryptopine has a strong band at 812 cm^{-1}, a region that has been assigned to two vicinal hydrogen atoms (800–860 cm^{-1}), and the band should arise from the two *ortho* hydrogen atoms present in ring D of the base; this band is totally absent in the spectrum of fagarine II, that should not have *ortho* hydrogen atoms in neither of the aromatic rings A and D. Another difference is found in the region of 855–870 cm^{-1},

* Part XVI: M. J. Vernengo, A. S. Cerezo, G. Iacobucci and V. Deulofeu, *Liebigs Ann.* **610**, 173 (1957); *Anal. Asoc. Quím. Arg.* **46**, 149 (1958).

[1] G. V. Stuckert, *Investigaciones del Laboratorio de Química Biológica*, p. 109, Vol. I, Córdoba, Argentina (1933); V. Deulofeu and J. Comín, *Il Farmaco* **9**, 340 (1954).
[2] V. Deulofeu, R. Labriola and J. De Langhe, *J. Amer. Chem. Soc.* **64**, 2326 (1942).
[3] C. E. Redemann, B. B. Wisegarver and G. A. Alles, *J. Amer. Chem. Soc.* **71**, 1030 (1949).
[4] E. M. Barilari and J. Comín, *Anal. Asoc. Quím. Arg.* **43**, 180 (1955).
[5] J. Comín and V. Deulofeu, *J. Org. Chem.* **19**, 1774 (1954); *Anal. Asoc. Quím. Arg.* **43**, 83 (1955).

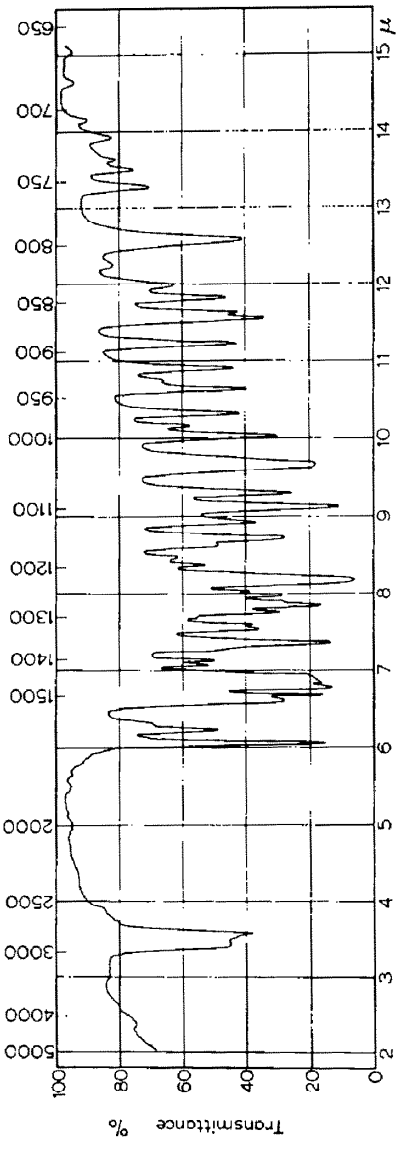


FIG. 1. IR-spectrum of fagarine II (Nujol)

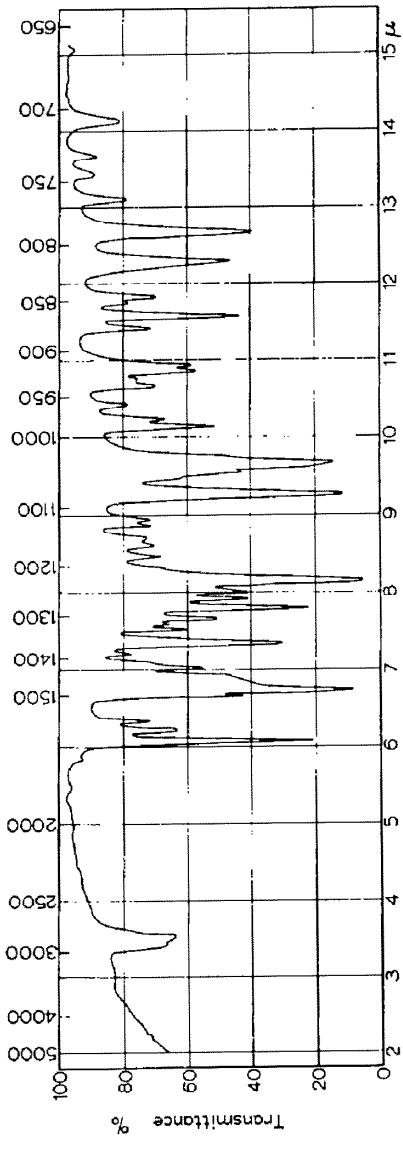
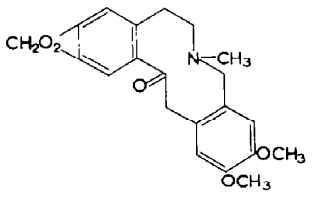


FIG. 2. IR-spectrum of allocryptopine (Nujol)

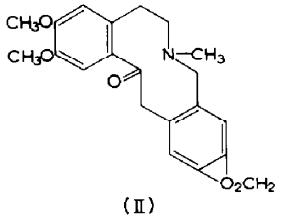
assigned to 1:2:4:5-tetra substituted benzene derivatives.[6,7] The spectrum of *allo*-cryptopine presents a band at 866 cm^{-1} that should originate in the vibration of the two *para* hydrogens atoms of ring A, a band that is stronger in the spectrum of fagarine II (864 cm^{-1}). A little displaced from the assigned region, another band is found at 846 cm^{-1}, which is also stronger in fagarine II than in *allo*cryptopine. The higher absorption in those bands in the case of fagarine II, was interpreted as showing that rings A and D have in this base two hydrogen atoms in *para* position (structure I or II).

To decide on the two alternatives, fagarine II was transformed into the tetrahydro berberine base, by applying the method developed by Späth and Posega,[7] in the synthesis of coptisine from protopine.

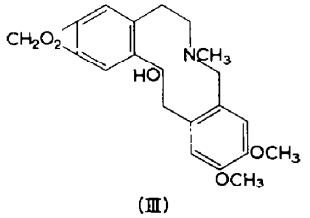
Fagarine II was reduced to the carbinol base (III) with sodium amalgam, the reduced alkaloid dehydrated and cyclized by evaporation to dryness of its slightly acidic solution and the quaternary base (IV) separated as the iodide. The quaternary iodide by high vacuum sublimation yielded a product that was identified by its infrared spectrum and mixed melting point as tetrahydro-pseudoberberine (V), synthesized already by Haworth, Perkin and Rankin.[8] The two methoxy-groups of fagarine II are located in carbons 10 and 11 instead of carbons 9 and 10, the usual position of substituents in the natural protopine and protoberberine groups of bases. Fagarine II has the substituents in the same places as coreximine,[9] a base that stood alone in this respect and Robinson had remarked[10] that it was an exception to the usual places of substitution in the protopine, berberine, phtalide-*iso*quinoline and α-naphthaphenanthridine groups of alkaloids.



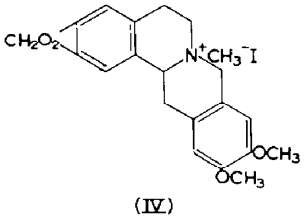
(I)



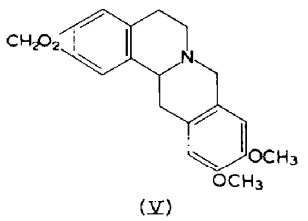
(II)



(III)



(IV)



(V)

Another point is the position of the hydrogen atom in carbon 14 of tetrahydro-pseudoberberine. The *trans*(α, *normal* or *allo*) position to the lone pair of electrons

[6] L. J Bellamy, *The Infra-red Spectra of Complex Molecules*, p. 67. Methuen, London (1954); R. Norman Jones and C. Sandorfy, *Technique of Organic Chemistry* (Edited by W. West) p. 387, Vol. IX, Interscience, New York (1956).
[7] E. Späth and R. Posega, *Ber.* **62**, 1029 (1929).
[8] R. D. Haworth, W. H. Perkin and J. Rankin, *J. Chem. Soc.* 1686 (1924).
[9] R. H. F. Manske, *Canad. J. Res.* **16B**, 81 (1938); *J. Amer. Chem. Soc.* **72**, 4796 (1950).
[10] R. Robinson, *The Structural Relations of Natural Products* p. 86, Oxford Univ. Press (1955).

of the nitrogen atoms, when the carbon hydrogen bond is axial to both rings B and C, must be the most stable and that which will be formed in a preferential way in the transformation of the carbinol base (III) to tetrahydro-pseudoberberine (V). This is in agreement with the infrared spectrum of the last base in the region 2700 to 3000 cm^{-1}.

As Bohlmann and co-workers[11] have pointed out for the *Lupinus* alkaloids and Wenkert and Roychaudhuri[12] for some indole alkaloids, certain neat peaks are observed in the bands around 2800 cm^{-1} in substances with a quinazolidine structure,

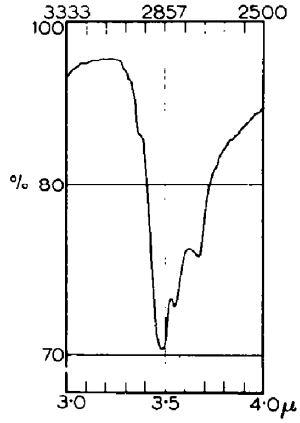
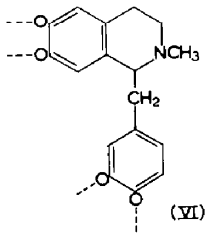


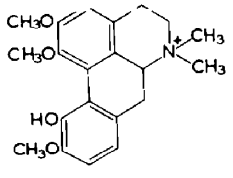
FIG. 3.

when the union of the two quinazolidine rings is *trans*. In the case of tetrahydro-pseudoberberine those peaks are present as shown in Fig. 3. It follows that it must have in carbon-14 an axial hydrogen atom to rings B and C with a *trans* union of the quinazolidine rings.

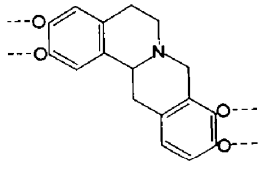
The genesis of three of the alkaloids that have been isolated from *Fagara coco*,



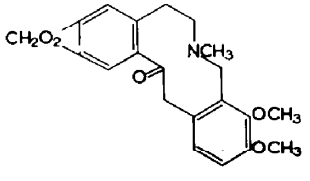
(VI)



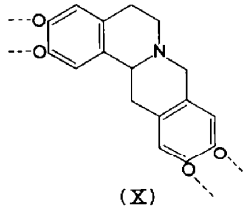
(VII)



(VIII)



(IX)



(X)

[11] F. Bohlmann, W. Weise, H. Sander, H. Hanke and E. Winterfeldt, *Chem. Ber.* **90**, 653 (1957).
[12] E. Wenkert and D. K. Roychaudhuri, *J. Amer. Chem. Soc.* **78**, 6417 (1956).

can be explained by a common four substituted benzyl-*iso*quinoline, precursor (VI). Condensation by dehydrogenation can give rise to an aporphine base with the substituents in the places found in N-methyl *iso*corydine (VII). Condensation with a one carbon unit in *ortho* position to a substituent, produces a protoberberine (VIII) that by oxidation can give rise to *allo*cryptopine (IX). If the condensation takes place in *para* to the same substituent, a tetrahydro-pseudoberberine (X) is produced, that should be the precursor of fagarine II (I). This last type of condensation, that took place in the laboratory, in the synthesis of tetrahydro-pseudoberberine,[8] is represented also in nature by the formation of coreximine.

EXPERIMENTAL

Melting points are uncorrected.

Tetrahydro-pseudoberberine (V) *from fagarine* II (I). Fagarine II, m.p. 195–196° (1 g) was dissolved in 1 N H_2SO_4 (200 ml), 5% sodium amalgam (200 g) added and the mixture heated in a water bath, with stirring, for 2 hr, when the evolution of hydrogen has practically ceased. In order to keep the solution acid, 2 N H_2SO_4 was added from time to time during the operation, in total 125 ml.

The solution, separated from the mercury, was filtered, made slightly alkaline with solid sodium hydrogen carbonate and again faint acid with 2 N HCl. This acid solution was evaporated to dryness, in the water bath at atmospheric pressure, and heated further for 1 hr. The residue was dissolved in water (300 ml), filtered from a small turbidity and the filtrate alkalinized with 2 N NaOH and extracted with ether to eliminate all the non-quaternary bases. The aqueous solution was neutralized with 2 N HCl, sodium thiosulfate (1 g) and sodium iodide (2 g) added, and stirred in the cold. The iodide of the quaternary base, *tetrahydro-pseudoberberine methiodide*, precipitates in crystalline condition and after standing overnight was filtered. 0·5 g were collected, m.p. 175–188°. Recrystallization from water increased the m.p. to 190–205°, but it was never sharp. The methiodide, undoubtedly a mixture, gave a correct value for iodine and was not further purified (Found: I, 25·81; Calc. for $C_{20}H_{21}NO_4 \cdot CH_3I$: 25·13%). The methiodide of tetrahydro-pseudoberberine prepared by Haworth, Perkin and Rankin,[8] m.p. 256°. The methiodide was decomposed by heating at 280° (bath temp) and 0·02 mm pressure.

A reddish sublimate was produced, (150 mg) and recrystallized from a small amount of methanol. After three crystallizations, needles melted at 175–176° were obtained. They gave no depression when mixed with an authentically original sample of tetrahydro-pseudoberberine m.p. 175–176°.

The infrared spectra of the two bases were also identical.

The *picrate* prepared from the sample deriving from fagarine II, melted at 174°. (Haworth, Robinson and Rankin give m.p. 176°.)

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