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# THE ALKALOIDS OF *ZANTHOXYLUM RHETSA* DC

K. W. GOPINATH, T. R. GOVINDACHARI and U. RAMADAS RAO
Department of Chemistry, Presidency College, Madras-5, India

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**Abstract**—The isolation of (±)-evodiamine and the new quaternary alkaloid hydroxyevodiamine from *Zanthoxylum rhetsa* is described.

*Zanthoxylum rhetsa* DC syn *Zanthoxylum budrunga* Wall (Rutaceae) has been the subject of several previous chemical investigations. Khastagir[1] reported the isolation from the bark of this tree, of two alkaloids, budrungaine and budrunginine. Gupta and Seshadri[2] isolated from the heartwood suberosin and skimmianine. From the bark, however, they could isolate only lupeol and no alkaloids.

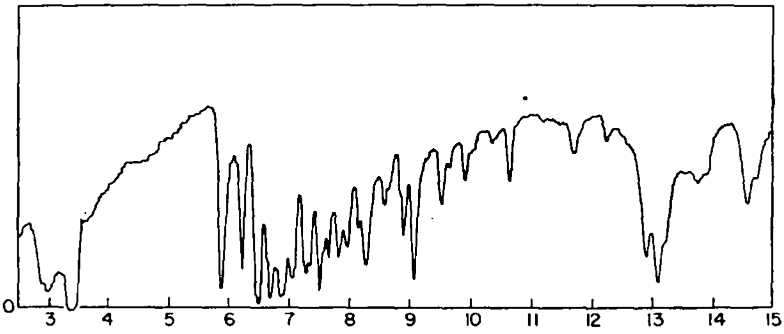

FIG. 1. Dehydroevodiamine chloride (Niyol mull).

In an investigation of the bark collected from Kerala, the presence of lupeol as reported by Gupta and Seshadri was confirmed. In addition, two nitrogen-containing substances were isolated, one of which was basic and the other neutral. The basic product was isolated from the alcoholic extract of the plant, in the form of its chloride, $C_{19}H_{16}ON_3Cl$, m.p. 256–257°, with infra-red absorption (Fig. 1) at 3·0 $\mu$ (>NH), 5·86 $\mu$ $(C = \overset{+}{N}<)$ and 6·2 $\mu$ (benzenoid ring). The chloride on basification with ammonia yielded a base $C_{19}H_{17}O_2N_3$ m.p. 206–207°. On reduction with sodium borohydride the chloride yielded a neutral compound $C_{19}H_{17}ON_3$, m.p. 277–278° with infra-red absorption (Fig. 2) at 3·1 $\mu$ (>NH) 6·12 $\mu$ (tertiary amide) and 6·20 $\mu$ (benzenoid ring). It is interesting to note that the chloride does not have the infra-red band at 6·12 $\mu$; evidently the additional double bond present in the chloride shifts it to longer wavelength so that it merges with the benzenoid absorption at 6·2 $\mu$. The reduction product was found to be identical with (±)evodiamine (I). Further confirmation was obtained by hydrolysis of the reduction product with alcoholic HCl when a compound $C_{19}H_{19}O_2N_3$, m.p. 146–147° yielding a hydrochloride, m.p. 256–257°

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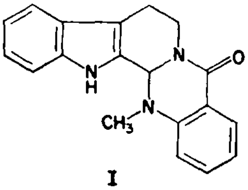
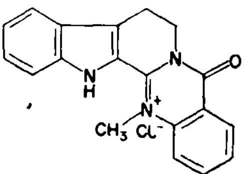
[1] H. Khastagir, *Curr. Sci.* **16**, 185 (1947).

[2] V. N. Gupta and T. R. Seshadri, *J. Sci. Industr. Res. India* **16C**, 71, (1957).

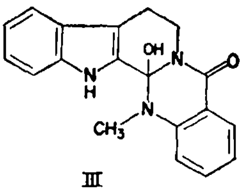
resulted, corresponding to isoevodiamine and its hydrochloride. The chloride should therefore be dehydroevodiamine chloride (II) and the base, hydroxyevodiamine (III). III has not been isolated from any natural source but has been obtained by Asahina and Ohta[3] by the mild oxidation of evodiamine with potassium permanganate in acetone solution.



I



II



III

(±)-Evodiamine was obtained from the acid-insoluble resin left after the removal of hydroxyevodiamine. Although furanoquinoline,[2] 1 : 2-benzophenanthridine[4] and protoberberine[5] alkaloids have been isolated from plants belonging to the genus Zanthoxylum, this appears to be the first reported occurrence, in a plant belonging to this genus, of an indoloquinazoline alkaloid, hitherto encountered only in various species of Evodia.

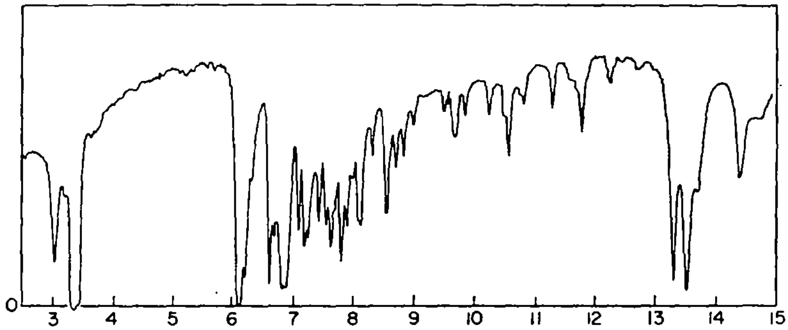


Fig. 2. (±)-Evodiamine (Niyol mull).

## EXPERIMENTAL

*Extraction of* Zanthoxylum rhetsa. The air-dried powdered bark (13·5 kg) was percolated in cold with light petroleum ether (b.p. 40–60°) for three days and the extract decanted. The process was repeated three times and the combined extract distilled to remove the solvent. The yellow residue was triturated with acetone and the pale yellow solid (400 g) filtered. Several crystallizations of the solid

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[3] Y. Asahina and T. Ohta, *J. Pharm. Soc. Japan* No 530, 293 (1926).

[4] H. R. Arthur, W. H. Hui and Y. L. Ng, *Chem. & Ind.* 1514 (1958).

[5] H. A. D. Jowett and F. L. Pyman, *J. Chem. Soc.* **103**, 291, (1913).

from methanol yielded lupeol, m.p. and mixed m.p. with an authentic sample 211–212°. The acetate obtained by heating the compound with acetic anhydride in pyridine at 100° crystallized from dil ethanol in colourless needles, m.p. 215°, undepressed by mixing with an authentic sample of lupeol acetate.

After extraction with light petroleum ether, the plant material was next extracted in cold alcohol containing 1 % acetic acid. The deep yellow alcoholic extract was concentrated to a syrup (water bath) and treated with dil HCl (1 N; 1600 ml). The solution was filtered from the insoluble resin and allowed to remain in a refrigerator for several days when yellow crystals (30 g) deposited. Crystallization from ethanol yielded *dehydroevodiamine chloride* as fine yellow needles, m.p. 255–256° (Ohta[6] reports m.p. 255–256°). (Found: C, 67·6; H, 5·0; N, 12·1. Calc. for $C_{19}H_{16}ON_3Cl$: C, 67·6; H, 4·7; N, 12·4 %). The free base was prepared from the chloride by grinding with conc ammonia. The solid obtained was crystallized from ethanol to give fine yellow plates of *hydroxyevodiamine*, m.p. 206–207°. (Found: C, 71·9; H, 5·6; N, 12·7. $C_{19}H_{17}O_2N_3$ requires: C, 71·4; H, 5·3; N, 13·1 %).

The insoluble resin left behind after acid extraction was triturated with acetone. The pale yellow amorphous powder (45 g) left behind was crystallized several times from ethyl acetate–methanol yielding (±)-evodiamine as colourless plates m.p. 277–278°; $[\alpha]_D = 0°$ (Asahina and Ohta[7] report m.p. 277–278°). (Found: C, 75·5; H, 5·9. Calc. for $C_{19}H_{17}ON_3$: C, 75·2; H, 5·6 %).

*Sodium borohydride reduction of dehydroevodiamine chloride.* The chloride (0·2 g) dissolved in methanol (30 ml) was treated at room temperature with sodium borohydride (0·2 g) in small lots. The yellow colour of the solution was discharged and a colourless solid separated. After remaining for ½ hr the solid was filtered and washed with methanol. Crystallization from ethyl acetate–methanol yielded (±)-evodiamine (0·1 g) as colourless needles, m.p. and mixed m.p. with the sample of evodiamine obtained from the plant source 277–278°. Their infra-red spectra were also superposable.

*Isoevodiamine.* (±)-Evodiamine (0·2 g) was heated under reflux with alcoholic HCl (5 %; 40 ml) for 3 hr. The solution was concentrated to a small volume and allowed to cool. The colourless crystals that separated were crystallized from ethanol to yield colourless needles of isoevodiamine hydrochloride, m.p. 256–257°. (Asahina and Ohta[7] report m.p. 256–257°.)

The base liberated from the hydrochloride by treatment with ammonia crystallized from dil ethanol in fine needles, m.p. 146–147°. (Asahina and Ohta[7] report m.p. 146–147°). (Found: C, 70·6; H, 6·0. Calc. for $C_{19}H_{19}O_2N_3$: C, 71·0; H, 5·9 %).

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[6] T. Ohta, *J. Pharm. Soc. Japan* **65**, No 2A, 15 (1945).

[7] Y. Asahina and T. Ohta, *Ber. Dtsch. Chem. Ges.* **61**, 319 (1928).