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ZANOXYLINE—A NEW ALKALOID FROM STEM BARK OF *ZANTHOXYLUM OXYPHYLLUM*

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Key Word Index—*Zanthoxylum oxyphyllum*; Rutaceae; alkaloids; rhetsinine; zanoxyline; 1-(4′methoxy benzyl)-6,7-dimethoxy *N*:*N* dimethyl 1,2,3,4 tetrahydroisoquinolinium hydroxide.

Abstract—The EtOH extract of stem bark of *Zanthoxylum oxyphyllum* yielded rhetsinine and a new alkaloid 1-(4′methoxy benzyl)-6,7-dimethoxy *N*:*N* dimethyl 1,2,3,4 tetrahydroisoquinolinium hydroxide provisionally named zanoxyline.

INTRODUCTION

Zanthoxylum oxyphyllum Edgew. is a medicinal plant used for the treatment of various ailments in this subcontinent [1]. Two alkaloids, zanthoxyphylline and corydine have been previously isolated from the root of the plant [2], while an alkaloid, rhetsinine, has already been isolated from the stem bark of the same plant [3]. In the present work a re-examination of the stem bark of *Z. oxyphyllum* has shown the presence of rhetsinine and a new alkaloid provisionally named zanoxyline.

RESULTS AND DISCUSSION

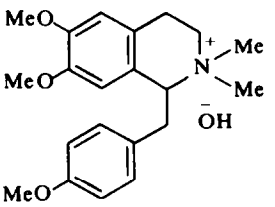
The EtOH extract of the air-dried, powdered stem bark of *Z. oxyphyllum* yielded rhetsinine (mmp and IR) and a new alkaloid provisionally named as zanoxyline, $C_{21}H_{29}NO_4$, mp 210–212°, which on Zn dust distillation yielded isoquinoline indicating the presence of an isoquinoline skeleton in the alkaloid. The nature of the N was quaternary because the compound (i) gave a positive response with citric acid and Ac_2O [4], (ii) did not form methiodide on treatment with MeI and (iii) showed a PMR signal at δ 2.69 ppm corresponding to 6 protons characteristic of N-Me group [5]. The IR band at 3400 cm^{-1} suggested the presence of a —OH group in the compound. The absence of a bathochromic shift, however, with KOH indicated the absence of a phenolic —OH group [6]. The alkaloid on treatment with HI yielded an iodide (**2**), mp 128°, which after passing through Amberlite IR 410 (—OH form) regenerated zanoxyline showing that the —OH group in the alkaloid is attached to the quaternary N atom. The presence of 3 OMe groups in the compound was shown by Zeisel's method [7] and the PMR signal at δ 3.72 ppm corresponding to 9 protons [5]. The alkaloid on $KMnO_4$ oxidation yielded *m*-hemipinic and anisic acids. The formation of these two acids indicates the presence of an isoquinoline nucleus substituted by two —OMe groups at C-6 and C-7 and a benzyl unit substituted by a *p*-OMe group. The iodide (**2**) on Hofmann degradation yielded a methine (**3**), mp 86–87°. Thus zanoxyline may be represented by the tentative structure (**1**), 1-(4′-methoxy benzyl), 6,7-dimethoxy *N*:*N* dimethyl 1,2,3,4 tetrahydroisoquinolinium hydroxide.

The formation of a few more abundant fragments a^+ (**4**), b^+ (**5**), c^+ (**6**), d^+ (**7**) and e^+ (**8**) lends further support to the above structure for zanoxyline [8]. The M^+ appeared at *m/e* 341 instead of 359 probably due to the facile loss of the OH attached to the quaternary N atom as H_2O.

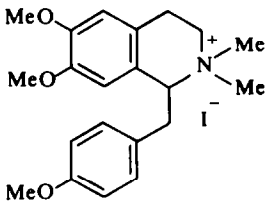
The structure assigned to zanoxyline (**1**) has been confirmed by partial synthesis from coclaurine, which on treatment with MeI and K_2CO_3 in Me_2CO formed its methylated methiodide (**2**). The methiodide (**2**) on passing through a column of Amberlite IR 410 (—OH form) gave a product which was identical with zanoxyline (mmp and IR).

EXPERIMENTAL

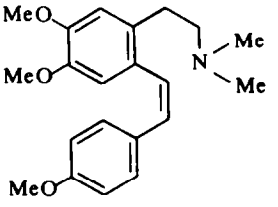
Extraction and isolation. Defatted powdered stem bark (5 kg) of *Z. oxyphyllum* (supplied by United Chemical and Allied Products, Calcutta, identity checked by National Botanical Garden from Herbarium sheet No. P-560) was extracted exhaustively with EtOH. The EtOH extract was concd to a thick



1



2



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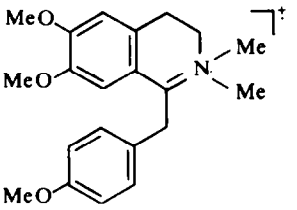
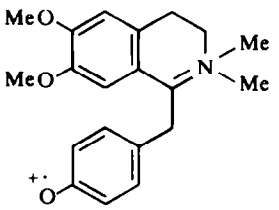
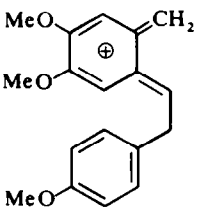


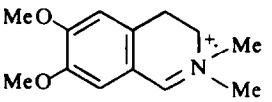
a^+ (4), *m/e* 341



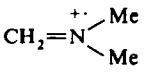
b^+ (5), *m/e* 326



c^+(6), *m/e* 284



d^+ (7), *m/e* 221



e^+ (8), *m/e* 58

viscous mass which was dissolved in H_2O, acidified with a little of HOAc, kept overnight and filtered. The aq. filtrate gave positive tests for alkaloids. It was coned to a thick viscous mass and extracted with $CHCl_3$. The $CHCl_3$ extract on removal of solvent yielded a crystalline alkaloid, rhetsinine (0.26 mg), mp 192°.

The residual viscous mass left after extraction with $CHCl_3$ was dissolved in MeOH and adsorbed onto a column of Al_2O_3 (4 cm dia, length 16 cm) which on elution with a mixture of MeOH–$CHCl_3$ (5:1) yielded a new amorphous alkaloid zanoxyline, $C_{21}H_{29}NO_4$ (4.236 g), mp 210–212°, $[\alpha]_D^{20}$ + 66.34° (MeOH), R_f = 0.80 (Al_2O_3, BuOH–HOAc–H_2O (4:1:5), λ_{max}^{EtOH} nm 257, 293; ν_{max}^{KBr} cm^{-1}: 3400, 1600, 1460, 1380, 1250, 1120, 722, etc.; PMR (CF_3CO_2H) δ 2.69 (*s*, 6H), 2.98 (*s*, 6H), 3.72 (*d*, 9H), 5.37 (*s*, 1H), 6.24 (*s*, 1H), 6.49 (*s*, 1H), 6.63 (*s*, 1H), 6.87 (*s*, 2H), 7.14 (*s* 1H), MS: *m/e* 341, 326, 283, 221, 58 (base peak). (Found: C, 70.26; H, 8.16; N, 3.97; OCH_3 27.21. $C_{21}H_{29}NO_4$ requires: C, 70.19; H, 8.07; N, 3.90; OCH_3, 25.90% for 3 OMe groups.)

Zanoxyline iodide (2). The alkaloid (200 mg) in MeOH (4 ml) on treatment with HI (2 ml) gave zanoxyline iodide (180 mg), mp 128°, lit. 127–129° [9].

Permanganate oxidation of zanoxyline. Zanoxyline (3.5 g) was dissolved in warm H_2O (50 ml), treated with K_2CO_3 (1 g) and oxidized by slowly adding a N soln of $KMnO_4$. Work-up in the usual way yielded *m*-hemipinic acid, mp 174° and anisic acid, mp 184° (mmp).

Hofmann degradation of zanoxyline. The iodide 2 (150 mg) was added to a soln of KOH (0.5 g) in MeOH (7 ml) and the mixture was heated at 100° for 8 hr. H_2O (15 ml) was added to the reaction mixture and the MeOH distilled off. The aq. soln was extracted with Et_2O, the extract dried (KOH) and the solvent evapd. The colourless oily residue (56 mg) crystallized from petrol as fine colourless needles of the methine 3 (22 mg), mp 86°, lit. mp 86–87° [9, 10].

Partial synthesis of zanoxyline. A soln of coclaurine (95 mg) in 0.5 N methanolic KOH (1 ml) and MeI (3 ml) was heated under reflux for 6 6r. Evapn of MeOH and excess MeI left a resinous residue which was crystallized from MeOH to give the methylated methiodide of coclaurine 2 (70 mg), mp 128°, which on passing through Amberlite IR 410 (—OH form) gave zanoxyline (56 mg), mp 210–212° (mmp and IR).

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