

GLYCOZOLINE, A CARBAZOLE DERIVATIVE, FROM *GLYCOSMIS PENTAPHYLLA*^{1,2}

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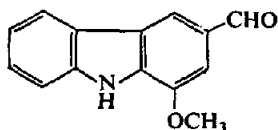
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(Received 30 August 1968, in revised form 29 October 1968)

Abstract—The structure of glycozoline, a carbazole derivative from *Glycosmis pentaphylla*, has been shown to be 3-methyl-6-methoxycarbazole.

INTRODUCTION

Glycosmis pentaphylla (Retz.) DC.^{3a,b} (family Rutaceae; subfamily Aurantieae), an Indian medicinal plant of repute has been reported to elaborate several furoquinoline, quinazoline and acridone bases.^{4,5} These alkaloids which are derivable from anthranilate pathway^{6,7} are characteristic of the family Rutaceae. The anthranilic acid pattern in murrayanine⁸ (I), the first phytocarbazole isolated from *Murraya koenigii* Spreng, prompted Chakraborty⁹ to suggest the anthranilate origin of these compounds. The taxonomic closeness of the genera *Murraya* and *Glycosmis* (both in the subfamily Aurantieae) and the probable common origin of alkaloids and carbazoles of Rutaceae prompted the search for carbazoles in *G. pentaphylla*. The present report relates to the structure of a new carbazole derivative isolated from the root bark of the plant from which three furoquinoline bases were reported.



(I) Murrayanine

RESULTS

The petrol. ether (b.p. 40–60°) extract of the mature dried root bark of *Glycosmis pentaphylla* left a solid residue on removal of the solvent. The residue was extracted with ether and

¹ Part XII in the series "Chemical Taxonomy". Part XI, D. P. CHAKRABORTY and K. C. DAS, *Chem. Commun.* 967 (1968).

² A short communication on the subject appeared in *Tetrahedron Letters* 681 (1966).

³ (a) *Index Kewensis*, Suppl. 12, p. 65, 1951–55, Clarendon Press (1959). (b) In consideration of different views on *G. pentaphylla*, *Index Kewensis*, p. 1039, Clarendon Press (1895); V. NARAYANASWAMI, *Rec. Bot. Survey of India* 14, 2 (1941); G. BRIZCKY, *J. Arnold. Arbor.* 43, 30 (1962); R. N. CHOPRA, S. L. NAYER and I. C. CHOPRA, *Glossary of Indian Medicinal Plants*, p. 126, C.S.I.R., New Delhi (1956), *G. pentaphylla* has been retained instead of *G. arborea*.

⁴ S. C. PAKRASHI and J. BHATTACHARYA, *J. Sci. Ind. Res.* 24, 226 (1965).

⁵ T. R. GOVINDACHARI, B. R. PAI and P. S. SUBRAMANIAM, *Tetrahedron* 22, 3245 (1966).

⁶ J. R. PRICE, in *Chemical Plant Taxonomy* (edited by T. SWAIN), p. 429, Academic Press, New York (1963).

⁷ M. MATSUO and P. KASIDA, *Chem. Pharm. Bull.* 14, 1108 (1966).

⁸ D. P. CHAKRABORTY and B. K. CHOWDHURY, *J. Org. Chem.* 1265 (1968), and references therein.

⁹ D. P. CHAKRABORTY, *Bull. Bot. Soc.* 18, 103 (1964).

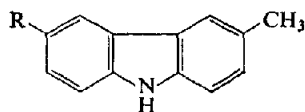
the neutral fraction of the ether extract, on chromatography over Brockmann's alumina, yielded a crystalline nitrogenous constituent glycozoline, m.p. 181–182°. This new compound is soluble in benzene, chloroform, ethanol, methanol but not so in petrol. ether (40–60°). With conc. H_2SO_4 glycozoline gave a greenish tint coloration; with conc. H_2SO_4 and HNO_3 it turned wine red, while with acetic anhydride and H_2SO_4 it gave a greenish tint, which ultimately turned wine red.

From analytical data and mol. wt. determination by mass spectrum (M^+ 211),¹⁰ the molecular formula, $\text{C}_{14}\text{H}_{13}\text{NO}$ has been assigned to the compound. It has one methoxyl group, one C—Me group and an active hydrogen. Glycozoline gave a picrate, $\text{C}_{14}\text{H}_{13}\text{NO}$, $\text{C}_6\text{H}_3\text{N}_3\text{O}_4$, m.p. 182°, but could not be methylated with MeI in acetone in presence of K_2CO_3 . The i.r. spectrum of glycozoline (Nujol) showed absorption peaks at 3500 (—NH— function), 1600, 1595 (aromatic residue), 1380 (C-methyl), 1208 (aromatic ether) and 815 cm^{-1} (substituted benzene derivative).

The NMR spectrum of glycozoline (60 mc in CDCl_3) showed signals for one indolic proton (doublet around δ 7.8); two aromatic protons (doublet around δ 7.5); four aromatic proton multiplets (from δ 6.8 to δ 7.18); three protons of an aromatic methoxyl group (singlet at δ 3.9); three protons of an aromatic C—Me group (singlet at δ 2.5). The NMR data, suggest the presence of a carbazole skeleton in glycozoline.

The u.v. absorption spectrum of glycozoline, max. at 227 ($\log \epsilon$ 4.16), 252 ($\log \epsilon$ 4.16) 264 ($\log \epsilon$ 4.06) and 304 nm ($\log \epsilon$ 4.17), was strikingly similar to that of 3-methoxy-2-methylcarbazole (II),¹¹ 3-methoxycarbazole (III) but distinctly different from those of 1-, 2-, and 4-methoxycarbazoles,¹² indicating that the methoxyl group in glycozoline is in the 3- or 6-position. Since glycozoline was found to be different (mixed m.p., i.r. and u.v. spectra) from 2-methyl-3-methoxycarbazole, it must be a new 3-methoxycarbazole derivative. The inertness of glycozoline towards *N*-methylation (cf. murrayanine and carbazole) may be due to the electron donating mesomeric effect of the methoxyl group at the 3- or 6-position.

On demethylation with HBr in acetic acid, glycozoline furnished a phenol $\text{C}_{13}\text{H}_{11}\text{NO}$ (IV), m.p. 228–230° which, unlike 3-hydroxy-2-methylcarbazole,¹¹ was soluble in 1 N KOH and gave a red colour with FeCl_3 . The phenol could be acetylated to $\text{C}_{15}\text{H}_{14}\text{NO}_2$ (V), m.p. 210°. The u.v. spectrum of this phenol acetate was very similar to that of 3-methylcarbazole, suggesting that the methyl group is in the 3- or 6-position. That the methyl group is in 3-position was confirmed by Zn dust distillation of glycozoline and by reduction with Raney Ni¹³ of phenol (IV), via its tosyl derivative, the product in both cases being 3-methylcarbazole (VI).



(IV) R = OH

(V) R = OCOCH_3

(VI) R = H

(VIII) R = OCH_3

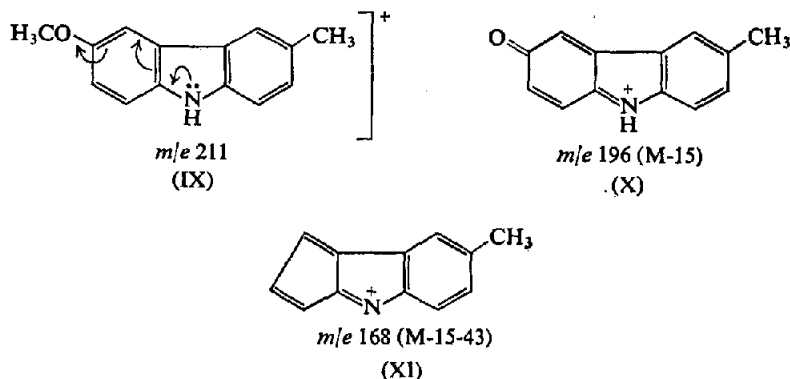
¹⁰ The author is indebted to Dr. B. C. DAS, C.N.R.S., Institut de Chimie des Substances, Gif-Sur-Yvette, France, for mass spectral data, and to Dr. J. L. BOSE of the National Chemical Laboratory, Poona, India, for the NMR spectrum.

¹¹ J. A. CUMMINS, B. F. KAYS and M. TOMLINSON, *J. Chem. Soc.* 1414 (1954).

¹² D. P. CHAKRABORTY, J. DUTTA and A. GHOSH, *Sci. & Cult.* 31, 529 (1965).

¹³ G. W. KENNER and M. A. MURRAY, *J. Chem. Soc.* s178 (1949).

The above data, therefore, lead to the formulation of glycozoline as 3-methyl-6-methoxycarbazole (VIII). The mass spectral fragmentation (IX–XI) of glycozoline is in accord with this structure, which has been confirmed by synthesis (accompanying paper).



Glycozoline is the third carbazole reported from plant source without any basic nitrogen. The occurrence of glycozoline in *G. pentaphylla* provides further credence for the participation of anthranilate in the biosynthesis of phytocarbazoles like murrayanine, girinimbine,¹⁴ glycozolidine¹⁵ and murrayacine.¹⁶

EXPERIMENTAL

All m.p.s are recorded in a Koffler block. Petrol. ether has the boiling range 40–60° unless otherwise mentioned.

Isolation of Glycozoline (VIII)

The air-dried finely powdered mature bark (1 kg) of *Glycosmis pentaphylla* was extracted in a soxhlet for 48 hr. After the removal of the solvent, the residue was extracted with ether. The ether extract was separated into acidic, basic and neutral fractions. The neutral fraction after removal of ether was taken up with benzene and chromatographed over alumina (425 g). The column was first eluted with petrol. ether (three fractions) and then with a mixture of benzene and petrol. ether (1:1), 100 ml being collected in each fraction. Glycozoline was obtained as colourless crystals of m.p. range 170–181° from 4th and 5th fractions. The fractions were combined and repeated crystallization from benzene and petrol. ether furnished a compound, m.p. 181–182° (yield 0.003 per cent). The compound was found to be homogeneous by paper chromatography¹⁷ (R_f 0.65 in 56% alcohol containing 2% acetic acid) and TLC (R_f 0.63 in petrol. ether: benzene, 1:4). (Found: C, 79.53; H, 6.35; N, 6.72; OMe 14.22, mol. wt. 215. $C_{14}H_{13}NO$ required: C, 79.59; H, 6.20; N, 6.63; one OMe, 14.22%, mol. wt. 211). The picrate of glycozoline crystallized from benzene/petrol. ether as brick red needles, m.p. 182°. (Found: N, 13.9. $C_{20}H_{16}N_4O_5$ required: N, 14.28 per cent).

Demethylation of Glycozoline, Formation of (IV)

Glycozoline (100 mg) was heated with acetic acid (1.4 ml) and HBr (48 per cent; 0.5 ml) with frequent shaking (1 hr) at 100° when a further quantity of acetic acid and HBr were added and kept for 5 hr at 100°. On pouring into water, a greenish compound, m.p. 215–220° was obtained. This, on crystallization from benzene, afforded 3-methyl-6-hydroxycarbazole (IV), m.p. 228–230°. It had ν_{max} (KBr) at 3500 (—NH—function), 3400 (phenolic hydroxyl), 1620, 1570, 1495 (aromatic residue), 1380 (C-methyl), 807 cm^{-1} (substituted aromatic system). (Found: C, 79.30; H, 6.02; N, 7.08. $C_{13}H_{11}NO$ required: C, 79.17; H, 5.62; N,

¹⁴ (a) D. P. CHAKRABORTY, B. K. BARMAN and P. K. BOSE, *Sci. & Cult.* **30**, 445 (1964). (b) D. P. CHAKRABORTY and B. K. CHOWDHURY, *Abs. of the IUPAC Sym. on the Chem. of Natl. Prods.*, p. 448 (1968).

¹⁵ D. P. CHAKRABORTY and B. P. DAS, *Sci. & Cult.* **32**, 181 (1966).

¹⁶ D. P. CHAKRABORTY and K. C. DAS, *Chem. Commun.* 967, (1968).

¹⁷ D. P. CHAKRABORTY, K. C. DAS and B. P. DAS, *Indian J. Chem.* **4**, 416 (1966).

7-10 per cent.) The acetate (V) of this phenol crystallized from benzene with m.p. 210°. It had λ_{\max} in EtOH at 230 (log ϵ 4.58), 237 (log ϵ 4.59), 260 (log ϵ 4.20), 296 (log ϵ 4.22) and 330 nm (log ϵ 3.60); and ν_{\max} (KBr) at 3440 (—NH— function), 1750 (acetic group), 1625, 1575, 1495 (aromatic system), 1380 (C-methyl-hump), 813 cm^{-1} (substituted aromatic system). (Found: C, 75.20; H, 5.48; N, 5.85. $\text{C}_{15}\text{H}_{13}\text{NO}_2$ required: C, 75.30; H, 5.48; N, 5.85 per cent.)

Zinc Dust Distillation of Glycozoline: Formation of 3-Methyl Carbazole (VI)

Glycozoline (200 mg) was thoroughly mixed with Zn dust (10 g) previously dried at 250° and heated in a sealed tube in an electrical oven for 2 hr. The ether-soluble portion of the reaction product was dissolved in benzene and chromatographed on alumina (6 g) and elution with benzene/petrol. ether furnished colourless crystals, m.p. 203–204°. On crystallization from benzene and petrol. ether it melted at 208°. On admixture with a pure specimen of 3-methylcarbazole¹⁸ it melted at 208°. It had u.v. and i.r. spectra identical to authentic material. (Found: C, 85.78; H, 6.30; N, 7.50. Calc. for $\text{C}_{13}\text{H}_{11}\text{N}$: C, 86.15; H, 6.12; N, 7.73 per cent.)

Reduction of the Tosyl Derivative to 3-Methyl Carbazole (VI)

The tosyl derivative, m.p. 210–215°, of phenol (IV) (34 mg) was dissolved in spectral alcohol (10 ml) and refluxed for 3 hr with Raney nickel (300 mg) in alcohol. The product was chromatographed on alumina, and eluted with petrol. ether/benzene (2:1) and then with petrol. ether/benzene (1:1). The second solvent fractions gave a colourless solid, m.p. 203–205°, identical with 3-methylcarbazole (u.v. m.m.p.). (Found: N, 7.40. Calc. for $\text{C}_{13}\text{H}_{11}\text{N}$: N, 7.73 per cent.)

Acknowledgements—The author thanks Dr. S. M. Sircar, Director, Dr. D. M. Bose, and Dr. A. Sen, Head of the Dept. of Chemistry, for their interest in the work. The gift of a pure specimen of 3-methoxy-2-methylcarbazole from Dr. M. L. Tomlinson, Oxford, is gratefully acknowledged.

¹⁸ D. P. CHAKRABORTY, K. C. DAS and S. P. BASAK, *J. Indian Chem. Soc.* **45**, 84 (1968).