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CARBAZOLE ALKALOIDS FROM *GLYCOSMIS PENTAPHYLLA*

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Abstract—Three carbazole alkaloids, glycozolicine, 3-formyl carbazole and glycosinine, have been isolated from the roots of *Glycosmis pentaphylla*. The structures of glycozolicine and glycosinine have been established as 5-methoxy-3-methyl carbazole and 2-methoxy-3-formyl carbazole, respectively, from physical and chemical evidence, and synthesis.

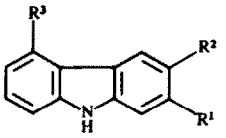
INTRODUCTION

In continuation of our work on the carbazole alkaloids of *Glycosmis pentaphylla* [1], we now report the isolation and structure of the alkaloids glycozolicine (**1**) and glycosinine (**3**), along with the previously reported [2] 3-formyl carbazole (**2**) from the dried roots of *Glycosmis pentaphylla*.

RESULTS AND DISCUSSION

Compound **1**, mp 135°, was found to be homogeneous by TLC. From analytical data and M_r determination by mass spectrometry ($[M]^+$ *m/z* 211) the molecular formula $C_{14}H_{13}NO$ was assigned to it. Zinc dust distillation furnished 3-methyl carbazole (**4**), indicating the presence of a 3-methyl carbazole nucleus. The IR spectrum of **1** showed absorption peaks at 3450 (–NH), 1610, 1590 (aromatic residue), 1380 (C–Me), 1209 (aromatic ether) and 815 cm^{-1} (substituted benzene derivative). The UV absorption spectrum, with λ_{max} at 227 (log ε 4.54), 244 (4.65), 288 (4.10), 325 (3.60) and 330 nm (3.69), was strikingly similar to that of 4-methoxy carbazole [3].

The ^1H NMR spectrum ($CDCl_3$, 100 MHz) of **1** showed signals at δ8.0 (*br s*, 1H, NH exchangeable with D_2O), 8.1 (*d*, *J* = 2 Hz; C-4 proton), 7.1 (*dd*, *J* = 7 and 2 Hz; C-8 proton), 6.7 (*dd*, *J* = 7 and 2 Hz, C-6 proton), three aromatic protons as a multiplet in the region δ7.5–7.2 (C-2, C-1 and C-7 protons), 4.08 (3H, *s*, OMe) and 2.55 (3H, *s*, Me). The C-4 and C-5 protons of the carbazole nucleus are mutually deshielded and appear downfield (δ7.5–8.4) [4]. The presence of only one deshielded proton in the ^1H NMR spectrum of **1** suggests that the other deshielded position is substituted. Since the methyl group occupies the 3-position, the methoxyl group must occupy either position 4 or 5. A doublet at δ8.1, which is not *ortho*-coupled, must be due to the C-4 proton. Therefore, the methoxyl group must occupy position 5, which is also evident from the observation that the C-6 proton appears upfield (δ6.7) due to the presence of the methoxyl group in position 5. The presence of this group in position 5 is also corroborated from the ^{13}C NMR spectrum (Table 1). From all this evidence glycozolicine has been formulated as 5-methoxy-3-methyl carbazole (**1**). The structure of **1** was confirmed by synthesis. 4-Methyl cyclohexane-1,2-dione-1-*m*-methoxyphenyl hydrazone (**5**), prepared by



	R¹	R²	R³
1	H	Me	OMe
2	H	CHO	H
3	OMe	CHO	H
4	H	Me	H
7	OMe	H	H
8	OMe	Me	H

Table 1. ^{13}C NMR data of carbazole and compounds **1** and **3** (in $CDCl_3$)

Carbon no.	Carbazole	1	3
1	110.9 (*d*)	111.1 (*d*)	96.5 (*d*)
2	118.4* (*d*)	119.8 (*d*)	155.5 (*s*)
3	120.1* (*d*)	122.9 (*s*)	116.7 (*s*)
4	125.4 (*d*)	125.5 (*d*)	125.6 (*d*)
5	—	145.8 (*s*)	124.5 (*d*)
6	—	105.9 (*d*)	119.9* (*d*)
7	—	120.1 (*d*)	119.8* (*d*)
8	—	115.7 (*d*)	110.1 (*d*)
10	139.7 (*s*)	140.7 (*s*)	142.8 (*s*)
11	122.5 (*s*)	123.12* (*s*)	117.8 (*s*)
12	—	123.12* (*s*)	122.9 (*s*)
13	—	134.9 (*s*)	139.5 (*s*)
CHO	—	—	193.0 (*d*)
OMe	—	55.44 (*q*)	56.1 (*q*)
Me	—	21.47 (*q*)	—

*Values interchangeable.

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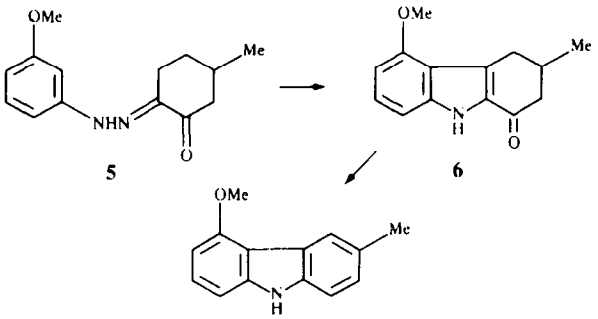

our previous method [5], on indolization furnished a mixture of compounds from which **6**, mp 210°, was separated by CC and characterized from its spectral properties; ^{1}H NMR showed the presence of three aromatic protons as a complex multiplet in the region δ7.5–7.25. Wolff–Kishner–Huang–Minlon reduction of **6** followed by dehydrogenation furnished a compound which was found to be identical with natural glycozolicine in all respects (mp, mmp, UV, IR).

Compound **3**, mp 185°, $C_{14}H_{11}NO_2$, showed an $[M]^+$ at *m/z* 225. The IR spectrum, ν_{max} at 3450, 1680, 1600, 1595, 1208, 765 and 710 cm^{-1}, indicated it to be an aromatic compound with NH, aldehyde and aromatic ether functions. The UV spectrum of **3** showed λ_{max} at 235 (log ε 4.40), 245 (4.25), 275 (4.50), 290 (4.48) and 320 nm (4.06), indicating the presence of a 3-formyl carbazole system [6]. The ^{1}H NMR spectrum ($CDCl_3$, 100 MHz) showed signals at δ11.0 (*br s*, 1H, NH exchangeable with D_2O), 10.10 (*s*, 1H, -CHO) and 3.9 (*s*, 3H, Ar–OMe). The spectrum also showed signals for six aromatic protons of which the relatively deshielded singlet at δ8.2 could be assigned to a C-4 proton, *ortho* to the aldehyde group. The C-4 proton was neither *ortho* nor *meta* coupled, suggesting substitution at these two positions. The other singlet at δ7.0 was assigned to the C-1 proton. The remaining four hydrogens appeared as a complex multiplet in the region δ7.9–7.3, suggesting the lack of substitution in one of the benzene rings of the carbazole moiety. On the basis of the above evidence, structure **3** was suggested for glycosinine, which was further supported by its ^{13}C NMR spectrum (Table 1).

Glycosinine, on decarbonylation with Pd–C, formed 2-methoxy carbazole (**7**), mp 235°, confirming the presence of a methoxyl group in the 2-position. The structure was finally confirmed by its formation from 2-methoxy-3-methyl carbazole (**8**) [7] by oxidation with DDQ.

Compound **2**, mp 158°, was identified as 3-formyl carbazole by comparison with the spectral data reported in the literature [2] and further confirmed by direct comparison with a synthetic specimen.

EXPERIMENTAL

All mps are uncorr. UV and IR spectra were recorded in EtOH and as KBr pellets, respectively. ^{13}C NMR expts were performed at 25 MHz.

Extraction and isolation. Air-dried finely powdered roots (2.5 kg) of *G. pentaphylla* were extd with petrol in a Soxhlet for 48 hr. The solvent was dist. off, the residue dissolved in benzene and chromatographed over silica gel (500 g). The column was eluted with petrol, petrol–benzene (1:1), benzene, benzene–$CHCl_3$ (3:1, 2:1, 1:1) and $CHCl_3$. From the benzene eluate glycozolicine (**1**) was obtained which recrystallized from benzene–petrol, mp 135°, yield 0.01%, TLC on silica gel (benzene–$CHCl_3$, 1:1; R_f 0.39). (Found: C, 79.56; H, 6.30; N, 6.75. Calc. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63.)

From the benzene–$CHCl_3$ (3:1) eluate, a colourless solid was obtained which showed the presence of two compounds by TLC on silica gel (benzene–hexane–EtOAc, 8:9:3; R_f 0.26 and 0.22). The two compounds were sepd by repeated prep. TLC. From R_f 0.26 a compound, mp 158°, was obtained which was identified as 3-formyl carbazole (**2**), yield 0.005%. (Found: C, 79.89; H, 4.55; N, 7.10. Calc. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17%.) From R_f 0.22 another compound, mp 185°, was obtained which was identified as glycosinine (**3**). Yield 0.002%. (Found: C, 74.50; H, 4.91; N, 6.15. Calc. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%.)

Zinc dust distillation of glycozolicine. Glycozolicine (**1**; 50 mg) was thoroughly mixed with Zn dust (3 g) previously dried at 250°, and heated in a sealed tube for 2 hr. The reaction product was dissolved in Et_2O and the solvent dist. off. The residue was dissolved in benzene and chromatographed over silica gel (5 g). The petrol–benzene (1:1) eluate furnished colourless crystals, mp 202°, on recrystallization from benzene, mp 208°. The compound was identified as 3-methyl carbazole by GC and direct comparison with an authentic sample. (Found: C, 86.10; H, 6.20; N, 7.65%. Calc. for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.75%.)

4-Methyl cyclohexane-1,2-dione-1-m-methoxyphenyl hydrazone (**5**). To a soln of 2-hydroxymethylene-5-methyl cyclohexanone (3 g) in MeOH (25 ml), a soln of NaOAc (5 g in 20 ml H_2O) was added. A diazotized soln of *m*-anisidine (2.5 g) was added with constant stirring during 45 min when **5** was obtained. It was recrystallized from EtOH as yellow crystals, mp 186°. Yield 2 g. (Found: C, 68.20; H, 7.40; N, 11.45; Calc. for $C_{14}H_{18}N_2O$: C, 68.27; H, 7.37; N, 11.37%.)

5-Methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**6**). To **5** (1.5 g) in boiling HOAc (10 ml), conc. HCl (3 ml) was added through a reflux condenser. The mixt. was further boiled for 5 min and then poured into crushed ice when a solid product was obtained. TLC showed the presence of two compounds which were sepd by silica gel CC. The column was eluted with petrol, petrol benzene (3:1, 2:1, 1:1), benzene, benzene–$CHCl_3$ (1:1) and $CHCl_3$, successively. From the petrol–benzene (2:1 and 1:1) eluates two compounds were isolated. One, having mp 211°, was identified as 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole by comparison with our previously prepared compound. The other, mp 201°, was identified as 5-methoxy-3-methyl-1-oxo-1,2,3,4 tetrahydrocarbazole (**6**). Yield 0.7 g. (Found: C, 73.30; H, 6.49; N, 6.15. Calc. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11%.)

5-Methoxy-3-methyl-1,2,3,4-tetrahydrocarbazole. Compound **6** (0.6 g) dissolved in ethylene glycol (10 ml) was heated with hydrazine hydrate (0.5 g, 99–100%) and KOH (0.5 g) at 190° for 1 hr and then at 200–210° for 3 hr. The reaction product was then cooled and poured into crushed ice. The reaction product was extd with Et_2O, washed and dried. After removal of solvent an oily mass was obtained which could not be recrystallized. It was filtered through a silica gel column.

5-Methoxy-3-methyl carbazole. The above tetrahydrocarbazole was dissolved in EtOH and Pd–C (10%, 50 mg) was added to it. The mixt. was then sealed in a tube which was evacuated and heated at 230–240° for 6 hr. On working up the reaction product a semi-solid mass was obtained. This was dissolved in benzene and chromatographed over silica gel (5 g). Elution with benzene gave a solid residue which on recrystallization from benzene–petrol furnished a compound, mp 135°, identical with natural glycozolicine (**1**) in all respects.

Decarbonylation of glycosinine. Glycosinine (**3**; 25 mg) was mixed with Pd–C (10 mg) and heated in a sealed tube with 2 ml of dry EtOH for 20 min at 270° under vacuum. The residue obtained after removal of solvent from the EtOH ext. of the reaction product on recrystallization from benzene furnished 2-methoxy carbazole, mp 235°. Yield 10 mg. (Found: C, 79.0; H, 5.5; N, 7.01. Calc. for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10%.)

Oxodation of 2-methoxy-3-methyl carbazole. 2-Methoxy-3-methyl carbazole (25 mg) was dissolved in benzene and stirred with 2,3-dichloro-5,6-dicyanobenzoquinone at room temp. for 30 min. The reaction mixt. was washed successively with 5% HCl and H_2O, and then dried. The residue was dissolved in a small vol. of benzene and chromatographed over silica gel (3 g). Elution with benzene furnished a compound (12 mg), mp 185°, which was found to be identical with natural glycosinine (**3**) (mp, mmp, UV, IR).

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