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GLYCOZOLIDOL, AN ANTIBACTERIAL CARBAZOLE ALKALOID FROM *GLYCOSMIS PENTAPHYLLA*

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Key Word Index—*Glycosmis pentaphylla*; Rutaceae; carbazole alkaloid; glycozolidol.

Abstract—Glycozolidol, a new carbazole alkaloid, has been isolated from the roots of *Glycosmis pentaphylla*. Its structure has been established as 6-hydroxy-2-methoxy-3-methylcarbazole on the basis of physical and chemical evidence. The compound has been found to be active against some Gram-positive and Gram-negative bacteria.

INTRODUCTION

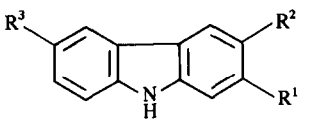
Glycosmis pentaphylla, a reputed Indian medicinal plant, has been reported to elaborate carbazole alkaloids [1, 2]. The present paper reports the structure of a new carbazole alkaloid, glycozolidol, isolated from the roots of the plant.

RESULTS AND DISCUSSION

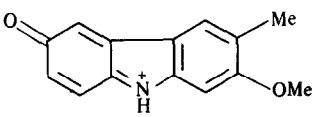
Glycozolidol (**1**), $C_{14}H_{13}NO_2$ ([M]$^+$ 227), mp 240°, was found to be homogeneous by TLC and mass spectrometry. The compound was soluble in alkali and formed a green colour with $FeCl_3$, which indicated the presence of a phenolic hydroxyl group. On zinc dust distillation, glycozolidol furnished 3-methylcarbazole [3, 4], which suggested the presence of a 3-methylcarbazole skeleton. The UV spectrum of **1** in ethanol, with λ_{max} at 232 (log ε 4.50), 260 (4.10) and 305 nm (4.29), also suggested that it was a carbazole derivative. Its IR spectrum showed absorption peaks at ν_{max}^{KBr} 3500 (–OH), 3440 (–NH), 1625, 1600 (aromatic residue), 1380 (C–Me), 1208 (aromatic ether) and 815 cm^{-1} (substituted benzene derivative). The ^{1}H NMR spectrum (100 MHz, DMSO-d_6 solvent) showed signals for one hydroxyl proton as a singlet at δ10.8 (confirmed by D_2O exchange), one NH proton and a broad singlet at δ8.0 (exchangeable with D_2O). The C-1 and C-4 protons appeared as singlets at δ6.92 and 7.45. The C-5 proton appeared as a doublet at δ7.2 (J = 2 Hz), the C-7 proton as a double-doublet at δ6.75 (J = 8 and 2 Hz), the C-8 proton as a doublet at δ7.08 (J = 8 Hz) and the methoxyl proton as a singlet at δ3.7 with the aromatic C-Me at δ2.38 as a singlet. The C-4 proton was not *ortho* or *meta*-coupled, suggesting substitution at positions 3 and 2. The C-5 proton also was not *ortho*-coupled, which suggested substitution at position 6. The hydroxyl proton resonance of glycozolidol is like that of 6-hydroxy-3-methylcarbazole [5].

The mass spectrum of **1** showed a [M]$^+$ at m/z 227. The base peak was at [M – 1]$^+$, represented by the ionic species **2**. This is consistent with the presence of a phenolic hydroxyl group [6]. The other significant peak was at [M – 1 – 28]$^+$, represented by the ionic species **3**.

On acetylation, glycozolidol furnished an acetate **4**, mp 194°, the IR spectrum of which showed the presence of an acetoxy function at 1750 cm^{-1} and the absence of a hydroxyl function at 3500 cm^{-1}. The UV spectrum of **4** in ethanol, with λ_{max} at 236 (log ε 4.53), 257 (4.27), 302 nm



1 R^1 = OMe; R^2 = Me; R^3 = OH
4 R^1 = OMe; R^2 = Me; R^3 = OAc
5 R^1 = OMe; R^2 = Me; R^3 = H
6 R^1 = OMe; R^2 = Me; R^3 = OMe



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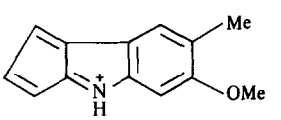

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(4.18), was similar to 2-methoxycarbazole [7], indicating the presence of the methoxyl at position 2. Reduction of the tosyl derivative of glycozolidol with Raney nickel furnished compound **5**, mp 223°. The UV spectrum of **5** in ethanol showed absorptions at 235 (log ε 4.3), 252 (3.8), 300 (3.9) and 325 nm (3.3). Compound **5** was identified as 2-methoxy-3-methylcarbazole [8] by direct comparison (mp, mmp, UV, IR) with a synthetic compound prepared from 2-hydroxy-3-methylcarbazole [9] by methylation with diazomethane. This resolved the position of the methoxyl at 2. On further methylation with diazomethane, glycozolidol furnished compound **6**, mp 160°, which was found to be identical (mp, mmp, UV, IR) to a natural sample of glycozolidine [2].

From all the above evidence, the structure of glycozolidol has been assigned as **1**. Glycozolidol was screened for antibacterial activity against both Gram-positive and Gram-negative bacteria using the standard cup assay method at a concentration of 200 μg/ml. The bacteria used were *Staphylococcus aureus* SH, *Bacillus firmis*, *Sarcina lutea*, *Escherichia coli*, B, *Agrobacterium tumefaciens* and *Proteus vulgaris*. Glycozolidol was active against all the organisms tested except *E. coli*. Gram-positive strains are more susceptible to the compound than Gram-negative ones.

EXPERIMENTAL

All mps are uncorr. UV and IR spectra were recorded in EtOH and as KBr pellets, respectively.

Isolation of glycozolidol. Air-dried, finely powered roots (1 kg) of *G. pentaphylla* were extracted with petrol in a Soxhlet for 48 hr. The solvent was then distilled and the root dried and re-extracted with C_6H_6 for 48 hr. After removal of solvent, the residue was taken up in Et_2O. The Et_2O extract was separated into acidic, basic and neutral fractions. The acidic fraction after removal of Et_2O was taken up in C_6H_6 and chromatographed over silica gel (400 g). The column was eluted with petrol, petrol–C_6H_6 (1:1), C_6H_6 and C_6H_6–$CHCl_3$ (1:1) and $CHCl_3$ in succession. From the C_6H_6–$CHCl_3$ eluate, glycozolidol was obtained, which was crystallized from $CHCl_3$, mp 240°. Yield 0.005%. TLC on silica gel (C_6H_6–EtOAc, 9:1, R_f 0.48). (Found: C, 73.90; H, 5.69; N, 6.10. Calc. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%.)

Zinc dust distillation of **1**. Glycozolidol (100 mg) was mixed thoroughly with Zn dust (5 g) and heated for 2 hr. The Et_2O soluble portion of the reaction product was dissolved in C_6H_6 and chromatographed over silica gel (10 g); elution with petrol–C_6H_6 (1:1) furnished colourless crystals. On crystallization from C_6H_6–petrol, they melted at 208°. The compound was identified as 3-methylcarbazole by direct comparison with a pure specimen.

Acetylation of **1**. Glycozolidol (50 mg) dissolved in pyridine was refluxed with Ac_2O (2 ml) for 2 hr. After reaction, the mixture was poured into crushed ice; a colourless substance separated. It was crystallized form C_6H_6–petrol, when compound **4**, mp 194°, was obtained. Yield 30 mg. (Found: C, 71.30; H, 5.55; N, 5.15. Calc. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20%.)

Reduction of the tosyl derivative of glycozolidol. The tosyl derivative (25 mg) of glycozolidol, mp 172°, prepared by the usual method, was dissolved in EtOH and refluxed for 3 hr with Raney Ni (200 mg) in EtOH. After reaction, the product was chromatographed over silica gel (3 g). The $CHCl_3$ eluate yielded a colourless solid, mp 223°, identical to 2-methoxy-3-methylcarbazole in all respects (mp, mmp, UV, IR).

Methylation of glycozolidol. A MeOH soln (10 ml) of glycozolidol (50 mg) kept at 0° for 16 hr with CH_2N_2 gave a residue after removal of solvent. The residue was washed with 1% aq. NaOH when a colourless solid, mp 160°, was obtained. The compound was found to be identical to natural glycozolidine in all respects.

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