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SYNTHESIS OF GLYCOZOLINE[1,2]

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Abstract—The structure of glycozoline has been confirmed as 3-methoxy-6-methylcarbazole (I) by synthesis.

IN THE accompanying communication, glycozoline, $C_{14}H_{13}NO$, m.p. 181–182°, has been shown to be 3-methyl-6-methoxycarbazole on the basis of its physical properties and the results of degradation experiments.[3] The assignment of the methoxyl group to the 6-position was based only on u.v. spectral evidence and we, therefore, sought to confirm its structure by synthesis. In the present communication, we report the synthesis of glycozoline by two different routes which confirms the aforesaid structure.

The synthesis of glycozoline was readily accomplished by the Fischer method of indole synthesis, as modified by Borsche[4] for tetrahydrocarbazoles. 4-Methoxyphenylhydrazine hydrochloride (II) in ethanol and 4-methylcyclohexanone (III) were condensed in presence of saturated NaOAc to obtain the hydrazone (IV). The hydrazone (IV) could not be crystallized but after a preliminary purification, it was cyclized using 10% aqueous H_2SO_4 as the condensing agent when 3-methyl-1,2,3,4-tetrahydro-6-methoxycarbazole (V) was obtained. The tetrahydrocarbazole was dehydrogenated with chloranil in xylene for 2 hr when 3-methyl-6-methoxycarbazole, m.p. 172–175°, was obtained. On repeated crystallization from benzene/petrol. ether, it melted at 178–179°. It was identical to natural glycozoline (I) (mixed m.p., i.r. spectrum) and the mass spectral fragmentations[5] of the synthetic compound were identical to those of natural glycozoline.

In the above synthesis, the intermediate 4-methylcyclohexane (4′-methoxy)-1-phenylhydrazone (IV) could not be isolated in a crystalline form. Further, the purification of 3-methyl-1,2,3,4-tetrahydro-6-methoxycarbazole from the above reaction mixture offered some difficulties. We therefore tried an alternative method for the synthesis of glycozoline, using the Japp–Klingemann reaction.[6] 2-Hydroxymethylene-5-methylcyclohexanone (VII) was reacted with 4-methoxybenzene diazonium chloride (VI) under Japp–Klingemann conditions, when 4-methylcyclohexane-1,2-dione-1-(4′-methoxy)-phenylhydrazone (VIII) was obtained. The above hydrazone was cyclized with HOAc and conc. HCl to 1-oxo-3-methyl-1,2,3,4-tetrahydro-6-methoxycarbazole (IX). The oxo compound (IX) was reduced

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[1] Part XIII of the series "Chemical Taxonomy". Part XII, D. P. CHAKRABORTY, *Phytochem.* **8**, (1969).

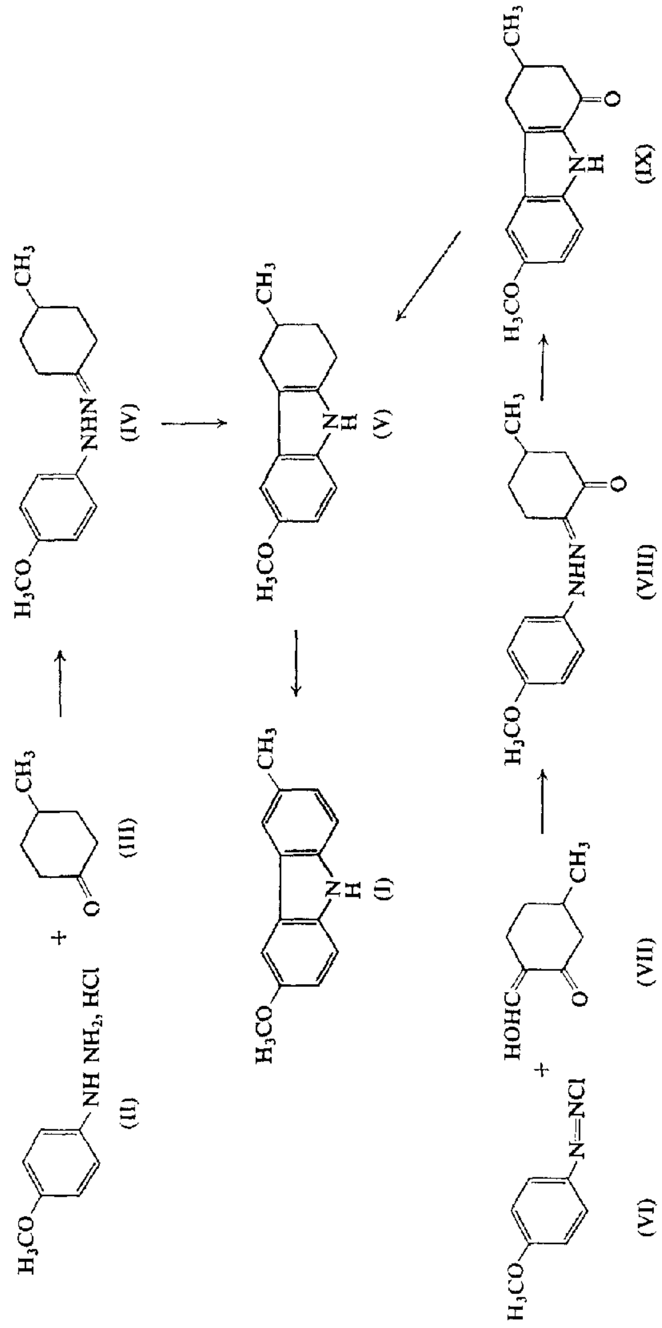
[2] Short communications on the subject appeared in (a) D. P. CHAKRABORTY, K. C. DAS and B. K. CHOWDHURY, *Sci. & Cult.* **32**, 245 (1966); (b) *Chem. and Ind.* 1684 (1966). When the communication (a) was published and (b) was in press W. CARRUTHERS informed us (*Chem. Commun.* 272, 1966) of the synthesis of glycozoline with other work by a different route.

[3] D. P. CHAKRABORTY, *Phytochem.* **8**, 769 (1969).

[4] W. BORSCHE, *Ann.* **359**, 49 (1908).

[5] The authors are indebted to Dr. B. C. DAS for mass spectral measurements.

[6] B. HEATH BROWN and P. G. PHILPOT, *J. Chem. Soc.* 1922 (1965).


H₃CO
NH NH₂, HCl
(II)
+
O
CH₃
(III)
H₃CO
NHN
CH₃
(IV)
H₃CO
N
H
CH₃
(V)
H₃CO
N
H
CH₃
(I)
H₃CO
N=NCl
(VI)
+
HOHC
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CH₃
(VII)
H₃CO
NHN
O
CH₃
(VIII)
H₃CO
N
H
O
CH₃
(IX)

by Wolff-Kishner and Huang-Minlon method to 3-methyl-1,2,3,4-tetrahydro-6-methoxycarbazole (V). The u.v. spectrum of the compound was very similar to that of 6-methoxy-1,2,3,4-tetrahydrocarbazole. The above tetrahydro derivative was dehydrogenated with chloranil to natural glycozoline, m.p. 178–179° (m.m.p. 178–179°, and superimposible i.r. and u.v. spectra).

EXPERIMENTAL*

4-*Methylcyclohexane*(4′-*Methoxy*)-1-*phenyl Hydrazone* (*IV*)

A mixture of 4-methylcyclohexanone (1 g) and NaOAc (1·5 g) was refluxed for 2 hr with *p*-methoxyphenylhydrazine hydrochloride (1·8 g) in aqueous alcohol (30 ml, 50% v/v). After removal of alcohol the hydrazone formed was extracted with $CHCl_3$, purified chromatographically and obtained as a brown oil.

3-*Methyl*-1,2,3,4-*Tetrahydro*-6-*Methoxycarbazole* (*V*)

The above oily hydrazone was cyclized with 10% H_2SO_4 for 10 min. The $CHCl_3$ extract of the product left a semi-solid residue on removal of solvent. This, on crystallization from alcohol, furnished colourless crystals, m.p. 110–112°; λ_{max}^{EtOH} 222 (log ϵ 4·32) and 278 nm (log ϵ 3·84). (Found: C, 77·91; H, 7·74; N, 6·68. Calc. for $C_{14}H_{17}ON$: C, 78·10; H, 7·96; N, 6·51 per cent.)

3-*Methyl*-6-*Methoxycarbazole* (*I*)

3-Methyl-1,2,3,4-tetrahydro-6-methoxycarbazole (200 mg) was dehydrogenated with chloranil (500 mg) in S-free xylene (5 ml). The product on removal of chloranil (with 10% NaOH) and xylene was obtained as a brown residue. It was purified chromatographically, when a colourless compound, m.p. 178–79° was obtained which melted at 178–179° when mixed with natural glycozoline. It had identical u.v. and i.r. spectral max. to natural material.[3] (Found: C, 79·60; H, 6·23; N, 6·75 per cent. Calc. for $C_{14}H_{13}ON$: C, 79·65; H, 6·20; N, 6·67 per cent.)

2-*Hydroxymethylene*-5-*Methylcyclohexanone* (*VII*)

A mixture of 3-methylcyclohexanone (30 g) and ethyl formate (22·8 g) was added to an ethereal suspension of NaOEt (obtained from 6·6 g of sodium).[7] The aqueous layer on acidification with 10% HCl was extracted with ether. On removal of the solvent a brown oily substance was obtained. It was purified by distillation under reduced pressure (3 mm) when 2-hydroxymethylene-5-methylcyclohexanone was obtained, b.p. 90°/3 mm; (lit. b.p. 90°/3 mm).

4-*Methylcyclohexane*-1:2-*Dione*-1-(4′-*Methoxy*)-*Phenylhydrazone* (*VIII*)

An aqueous solution of NaOAc (5·5 g in 14 ml) was added to a solution of 2-hydroxymethylene-5-methylcyclohexanone (3·5 g) in methyl alcohol (36 ml). A diazotized solution of *p*-anisidine (3 g) was added with mechanical agitation during 30 min, when crystals of the compound (VIII) were obtained. On recrystallization from alcohol, this yielded golden yellow flakes, m.p. 194°. ν_{max}^{KBr} 3206 (—NH) and 1653 cm^{-1} (chelated carbonyl). (Found: C, 68·13; H, 7·35; N, 11·52 per cent. Calc. for $C_{14}H_{18}O_2N$: C, 68·27; H, 7·37; N, 11·37 per cent.)

1-*Oxo*-3-*Methyl*-1,2,3,4-*Tetrahydro*-6-*Methoxycarbazole* (*IX*)

Compound (VIII) (1·5 g) was boiled in a mixture of HoAc (12·5 ml) and conc. HCl (3·1 ml) for 3 min. The reaction mixture was poured in ice-water and filtered. The residue obtained was washed, dried and crystallized from benzene when pale yellow crystals of the compound (IX), m.p. 209°, were obtained. λ_{max}^{EtOH} 232 (log ϵ 4·23) and 315 nm (log ϵ 4·39); ν_{max}^{KBr} 3205 (—NH) and 1626 cm^{-1} (chelated $\rangle C{=}O$). (Found: C, 73·17; H, 6·66; N, 6·34 per cent. Calc. for $C_{14}H_{15}O_2N$: C, 73·34; H, 6·59; N, 6·11 per cent.)

3-*Methyl*-1,2,3,4-*Tetrahydro*-6-*Methoxycarbazole* (*V*)

Compound IX (0·8 g) dissolved in $(CH_2OH)_2$ (10 ml) was heated with N_2H_4, H_2O (99–100 per cent, 0·8 g) and KOH (0·8 g) at 190° for 1 hr and up to 200° under reflux for 3 hr. A solid product was obtained which, on recrystallization from alcohol, melted at 112°. This was identical in u.v. max. with compound V, and gave satisfactory analytical figures.

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

[7] P. A. Plattner, P. Treadwell and C. Scholz, *Helv. Chim. Acta* **28**, 771 (1945).

3-*Methyl-6-Methoxycarbazole* (*I*)

The above product was dehydrogenated with chloranil, as previously, when glycozoline, m.p. 177–178°, was obtained. This was found identical in all respect with the natural and synthetic specimens stated above.

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