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STRUCTURE AND SYNTHESIS OF HEPTAPHYLLINE*

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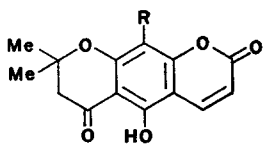
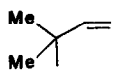
Abstract—A carbazole alkaloid $C_{18}H_{17}NO_2$ designated heptaphylline has been isolated from the roots of *Clausena heptaphylla* Wt. & Arn. On the basis of spectral and chemical evidence it has been constituted as (III). This structure has been confirmed by its unambiguous synthesis. Girinimbine (IX) has also been isolated from this plant.

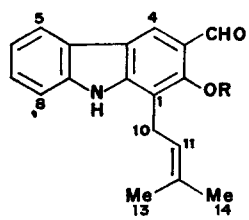
INTRODUCTION

Clausena heptaphylla Wt. & Arn. (Rutaceae) is a medium sized tree growing in the Western Ghats of India. From the hexane extract of the roots, two pyranocoumarins, clausenin and clausenidin were isolated and their structures were shown to be (I) and (II) respectively.[1–4]

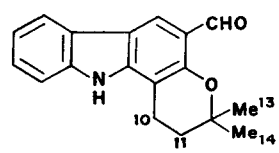


(I) R = H

(II) R = 



(III) R = H
(IV) R = Me



(V)

After separation of clausenin, the residual oil was chromatographed on silical gel when a weakly basic alkaloid designated heptaphylline[5] was obtained in 0·004% yield. Heptaphylline $C_{18}H_{17}NO_2$ (M^+ at *m/e* 279), m.p. 170–171° showed in the UV λ_{max} 234, 278, 298 and 346 nm (log ϵ, 4·42, 4·53, 4·58 and 4·09) and IR (Nujol) bands at ν_{max} 3300 (OH or NH), 2740, 1640 (weak) (chelated aldehyde), 1618 (aromatic). The presence of a formyl group in heptaphylline was inferred by a positive silver test and formation of a red crystalline dinitrophenylhydrazone m.p. 315–316°. Heptaphylline gave a green colour reaction with conc. H_2SO_4 and HNO_3 characteristic of carbazoles and an ethanolic solution showed a deep blue colouration with ferric chloride indicating a chelated phenolic hydroxyl group. The UV spectrum of heptaphylline is characteristic of 3-formyl carbazoles.[5,6] Its NMR spectrum (III; Table 1) indicated the presence of a γ,γ-dimethyl allyl group (two methyl signals integrating for six protons at δ 1·66, 1·83) benzylic methylene doublet (δ 3·6, J = 6 Hz), broad triplet due to a vinyl proton (δ 5·35, J = 6 Hz), a chelated hydroxyl (δ 11·7),

* Contribution No. 268 from CIBA Reserach Centre.

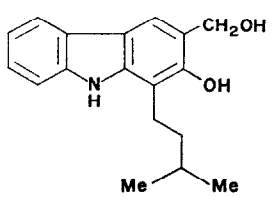
[1] B. S. JOSHI and V. N. KAMAT, *Tetrahedron Letters* 5767 (1966).
[2] B. S. JOSHI, V. N. KAMAT and A. K. SAKSENA, *Tetrahedron* **23**, 4785 (1967).
[3] A. K. GANGULY, B. S. JOSHI, V. N. KAMAT and A. H. MANMADE, *Tetrahedron* **23**, 4777 (1967).
[4] H. FUHRER, T. R. GOVINDACHARI, B. S. JOSHI and B. R. PAI, *Indian J. Chem.* **8**, 198 (1970).
[5] B. S. JOSHI, V. N. KAMAT, A. K. SAKSENA and T. R. GOVINDACHARI, *Tetrahedron Letters* 4019 (1967).
[6] D. P. CHAKRABORTY, B. K. BARMAN and P. K. BOSE, *Tetrahedron* **21**, 681 (1965).

TABLE 1. NMR SPECTRA OF HEPTA-

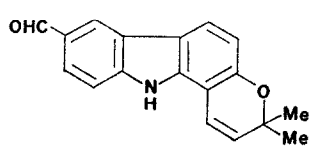
Compound (solvent)	C-1	C-2	C-3	C-4	C-5	C-6
III		11·7	9·9	8·25	8·0	
(CD_3COCD_3)		(s)	(s)	(s)	(dd;6,2)	
V			8·3	8·1	7·95	
(CD_3SOCD_3)			(s)	(s)	(dd;6,2)	
XX	6·73	11·5	9·9	8·2	7·95	
(CD_3COCD_3)	(s)	(s)	(s)	(s)	(dd;7,2)	
XXI	6·82	11·5	9·98	8·25	7·8	
(CD_3COCD_3)	(s)	(s)	(s)	(s)	(br;½w;2)	
XIX		11·8	9·9	7·95	7·85	
($CDCl_3$)		(s)	(s)	(s)	(m)	
XII		8·1	6·8	7·75	7·9	
(CD_3COCD_3)		(s)	(d;8)	(d;8)	(dd;7,2)	
XIII		8·33	6·8	7·9	7·95	
(CD_3COCD_3)		(s)	(dd;8,2)	(d;8)	(dd;7,2)	
XIV	6·95	8·15		7·8	7·93	
(CD_3COCD_3)	(s)	(s)		(s)	(dd;7,2)	
XVI	6·9	11·2	10·1	8·4	8·0	
($CDCl_3$ + CD_3SOCD_3)	(s)	(s)	(s)	(s)	(dd;7,2)	
XVII	7·4	8·7	7·0	7·9	7·95	7·4
(CD_3COCD_3)	(d;2)	(s)	(dd;8·5,2)	(d;8·5)	(dd;8·5, 1·5)	(m)
XVIII	7·4	3·9	7·0	7·9	7·95	7·4
(CD_3COCD_3)	(d;2)	(s;3H)	(dd;8·5,2)	(d;8·5)	(m)	(m)

Spectra were run on a Varian A-60 NMR spectrometer using TMS as an internal standard. Chemical doublet of doublets; m, multiplet; br, somewhat broad singlet; and ½w, line width at half height. Figures in

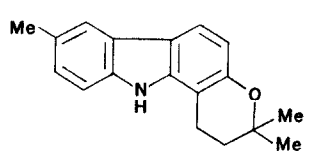
an aldehyde (δ 9·9) and an imine (δ 10·3) functions. Methylation gave monomethoxy heptaphylline m.p. 139–140°. Heptaphylline on treatment with polyphosphoric acid or in better yields with boiling formic acid gave cycloheptaphylline m.p. 250°. Cycloheptaphylline resembled heptaphylline in its UV spectrum and its NMR signals indicated the formation of a 2,2-dimethylchroman. All the above-mentioned spectral data and reactions lead to the



(VI)



(VII)



(VIII)

structure (III) for heptaphylline, (IV) for methoxyheptaphylline and (V) for cycloheptaphylline. Hydrogenation of heptaphylline with PtO_2 as catalyst gave a compound m.p. 130–131° to which the structure (VI) has been assigned on the basis of its elemental analysis, UV and IR spectra.

PHYLLINE AND RELATED COMPOUNDS

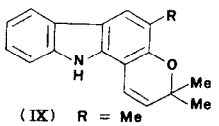
C-7	C-8	C-9	C-10	C-11	C-13	Me C-14
		10·3 (br)	3·65 (d;7)	5·35 (t;6)	1·66 (br;½w;1)	1·82 (br;½w;1)
			2·95 (t;7)	2·0 (t;7)		1·42 (s;6H)
			4·72 (d;7)	5·2 (t;7)	1·66 (br;½w;1)	1·86 (br;½w;1)
7·15 (dd;7·5,2)	7·36 (d;7·5)	10·4 (br)	3·5 (d;7)	5·4 (t;7)		1·75 (s;6H)
			C-10 3·75(m)	5·2 (m)		1·7 (br;½w;1;6H)
			C-10′ 4·9(m)			1·8 (br;½w;1;6H)
			3·68 (d;7)	5·4 (t;7)	1·67 (br;½w;1)	1·83 (br;½w;1)
			4·8 (d;7)	5·25 (t;7)	1·65 (br;½w;1)	1·86 (br;½w;1)
		9·8 (br) 11·5 (br)	3·5 (d;7)	5·5 (t;7)		1·75 (s;6H)
8·0 (m)	7·4 (m)	9·8 (s)				
7·95 (m)	7·4 (m)	9·8 (s)				

shifts are in parts per million. Signals are denoted in the usual way: s, singlet; d, doublet; t, triplet; dd, parentheses are line separations in hertz.

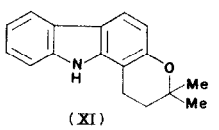
Chakraborty and Das reported the isolation of a carbazole alkaloid murrayacine (VII) from *Murraya koenigii* Spreng. and based the structure proof on its conversion to dihydrogirinimbine which they had constituted as (VIII).[7,8] Since girinimbine has been shown to have the structure (IX) by degradative,[9] spectral[10] and synthetic evidence,[11–13] the structure of murrayacine needed revision to (X).[9] However, the melting point 176° reported for dihydromurrayacine[7] differs from that of cycloheptaphylline (V) m.p. 250°. In order to ascertain the correctness of the structure assigned for cycloheptaphylline, this was decarbonylated by heating with Pd/C to give the compound (XI) m.p. 178°. This was found to be identical in its TLC, m.m.p and IR spectra with the synthetic compound obtained by the following route. 2-Hydroxycarbazole on reaction with 2-methyl-3-butene-2-ol[14] gave three

[7] D. P. Chakraborty and K. C. Das, *Chem. Commun.* 967 (1968).
[8] D. P. Chakraborty, *J. Indian Chem. Soc.* **46**, 177 (1969).
[9] B. S. Joshi, V. N. Kamat and D. H. Gawad, *Tetrahedron* **26**, 1475 (1970).
[10] N. L. Dutta and C. Quassim, *Indian J. Chem.* **7**, 307 (1969).
[11] N. L. Dutta and C. Quassim, *Indian J. Chem.* **7**, 1168 (1969).
[12] S. P. Kureel, R. S. Kapil and S. P. Popli, *Chem. & Ind.* 1262 (1970).
[13] D. P. Chakraborty and A. Islam, *J. Indian Chem. Soc.* **48**, 91 (1971).
[14] A. C. Jain, P. Lal and T. R. Seshadri, *Tetrahedron* **26**, 2631 (1970).

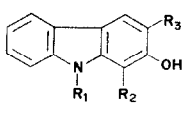
isomeric prenylated products $C_{17}H_{17}NO$ (A) m.p. 134°, (B) m.p. 142–143° and (C) m.p. 172°. On the basis of their NMR spectra (Table 1), the condensation products (A), (B) and (C) have been formulated as (XII), (XIII) and (XIV) respectively. The compound A (XII) on heating with formic acid cyclised to give the dihydropyrano carbazole (XI) m.p. 178–179°. The structure of murrayacine and its dihydro derivative therefore remains to be reinvestigated.

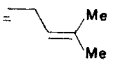


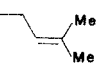
(IX) R = Me
(X) R = CHO

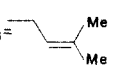


(XI)

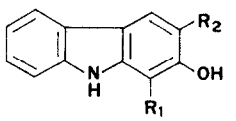


(XII) $R_1 = R_3 = H$, R_2 = 

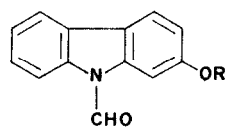
(XIII) $R_2 = R_3 = H$; R_1 = 

(XIV) $R_1 = R_2 = H$, R_3 = 

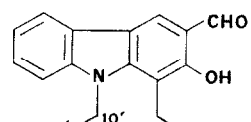
Treatment of 2-hydroxycarbazole with *N*-methyl formanilide and phosphorus oxychloride led to a mixture of 2-hydroxy-1-carbaldehyde (XV), 2-hydroxy-3-carbaldehyde (XVI) and a compound m.p. 210°.[9,15] This compound m.p. 210°, obtained as the major product in the reaction of 2-hydroxycarbazole in dimethyl formamide and phosphorus oxychloride, has been assigned the structure (XVII) on the basis of its UV and NMR data. N-Formyl-2-hydroxycarbazole (XVII) was characterized by preparation of the monomethyl ether (XVIII) m.p. 88° and the *p*-toluenesulphonyl ester m.p. 141°. The compound (XVII) readily hydrolysed with alkali or acid to give 2-hydroxycarbazole.



(XV) R_1 = CHO ; R_2 = H
(XVI) R_1 = H ; R_2 = CHO



(XVII) R = H
(XVIII) R = Me

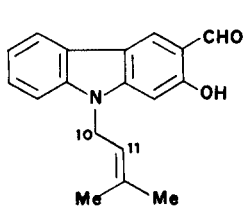


(XIX)

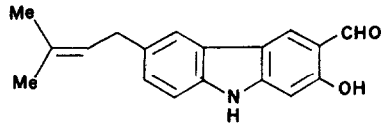
Heptaphylline (III) was synthesized in poor yield by the reaction of (XVI) with 3,3-dimethylallyl bromide at 25° in presence of potassium hydroxide;[16] however, when the reaction was carried out at 100°, a dialkylated compound m.p. 121–122° was formed. This has been assigned the structure (XIX) on the basis of elemental analysis and NMR spectral data. Treatment of (XVI) with 2-methyl-3-buten-2-ol in presence of BF_3-etherate in dioxane led to a mixture of heptaphylline (III) and two isomeric products m.p. 110° (XX) and m.p. 116° (XXI). The structures of these are in agreement with their analytical and spectral data. The compounds (XX) and (XXI) showed one proton singlets respectively at 6·7 and 6·82 δ due to the C-1 proton and at 8·2 and 8·25 δ attributed to the C-4 proton. The compound (XX) showed one proton doublet of doublets in the downfield region at 7·95 δ which should be due to the C-5 proton which carries a neighbouring hydrogen. A complex multiplet around 7–7·5 δ integrating for three protons showed that one of the benzene rings is unsubstituted by the prenyl group. In compound (XX), the broad signal due to the NH group was also

[15] B. S. JOSHI, V. N. KAMAT and D. F. RANE, *J. Chem. Soc.* 1518 (1969).
[16] B. S. JOSHI and D. F. RANE, *Chem. & Ind.* 685 (1968).

absent. The compound (XXI) showed in the downfield region, one proton broad singlet at 7·8 δ which should be due to the C-5 proton having the prenyl substituent in the C-6 position. If the γ,γ-dimethyl allyl group was present at C-7 or C-8, the C-5 proton would have occurred as a clear doublet or as a complex multiplet.



(XX)



(XXI)

After isolation of heptaphylline, the mother liquors on careful chromatographic separation gave girinimbine (IX) which had been isolated earlier from the roots of *Murraya koenigii* Spreng.[9,17]

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined on a Beckmann DK-2A spectrophotometer, and IR spectra were run on a Perkin–Elmer Model 421 spectrophotometer.

Isolation of heptaphylline (III) *and girinimbine* (IX). The powdered roots of *Clausena heptaphylla* (12 kg) were extracted with boiling hexane (3 × 30 l.). The extracts were pooled and concentrated (300 ml). The concentrate on standing overnight deposited clausenin (2 g). The mother liquors, on removal of the solvent, yielded an oil (60 g). This was dissolved in benzene (100 ml) and chromatographed on SiO_2 gel (600 g, 0·2–0·5 mm). The eluted fractions (100 ml) were collected and the progress of the chromatogram followed by TLC. Fractions 10–16 (eluent: benzene), single spot (R_f 0·75; TLC: SiO_2 gel; benzene–$CHCl_3$ 1:1), gave an oily residue (8 g). Crystallization from $CHCl_3$–hexane (40–60°) afforded *heptaphylline* as bright yellow needles (III; 500 mg), m.p. 170–171°. IR (Nujol): 3300, 2740, 1645, 1618, 1590, 1330, 1310, 1280, 1250, 1240, 1230, 1195, 1180, 1150, 1060, 1020, 1015, 970, 930, 880, 870, 850, 820, 780, 770, 735 and 695 cm^{-1}. (Found: C, 77·1; H, 6·1; N, 5·1. MW by MS 279. $C_{18}H_{17}NO_2$ requires C, 77·4; H, 6·1; N, 5·0%. MW 279.)

Heptaphylline formed a dark red 2,4-dinitrophenylhydrazone which crystallized from dimethyl formamide m.p. 315–316°. (Found: C, 62·5; H, 4·7; N, 15·7. $C_{24}H_{21}N_5O_5$ requires: C, 62·7; H, 4·6; N, 15·2%.) It also formed an orange crystalline 1,3,5-trinitrobenzene adduct m.p. 107°.

The mother liquor (after the crystallization of heptaphylline) was freed from the solvent and the residual oil rechromatographed on SiO_2 gel in hexane–benzene (7:3). Fractions 6–12 (50 ml each), on slow evaporation, deposited a waxy solid, which was isolated by filtration and washed with hexane (40–60°). This was recrystallized from CH_2Cl_2–hexane (130 mg), m.p. 173° and was identified as girinimbine by comparison with an authentic sample (TLC, m.m.p. and IR spectrum).

Heptaphylline monomethyl ether (IV). A soln of heptaphylline (III; 100 mg) in dry acetone (100 ml) was refluxed with anhyd. K_2CO_3 (10 g) and dimethyl sulphate (1·2 ml) for 2 hr. The mixture was filtered, acetone removed and the gummy residue extracted with Et_2O. It was washed with aq. $NaHCO_3$, H_2O and dried. Evaporation of the solvent gave a gum (60 mg) which on chromatography of the benzene soln over Si gel and elution with hexane–benzene (1:1) gave (IV; 21 mg) m.p. 139–140°. (MW by MS 293. Calc. for $C_{19}H_{19}NO_2$: MW 293).

[2,2-*Dimethyl*-3,4-*dihydropyrano*-(5,6-*a*)]-3-*formyl carbazole* (*cycloheptaphylline*) (V). A soln of heptaphylline (III; 35 mg) in HCOOH (3 ml) was heated at 100° for 1 hr, when it turned deep blue. It was poured on crushed ice, the ppt collected, washed (H_2O), dried and sublimed at 200°/10^{-3} mm when colourless needles were obtained (V; 20 mg), m.p. 249–250°. λ_{max} 240, 252, 279, 300 and 353 nm; log ε 4·54, 4·34, 4·49, 4·6 and 4·1. (Found: C, 77·1; H, 6·4; N, 5·1. MW by MS 279. $C_{18}H_{17}NO_2$ requires: C, 77·4; H, 6·1; N, 5·0%. MW 279.)

[17] D. P. Chakraborty, B. K. Barman and P. K. Bose, *Sci. & Cult.* **30**, 445 (1964).

1-*Isopentyl*-3-*hydroxymethyl*-2-*hydroxycarbazole* (VI). Heptaphylline (III, 100 mg) in EtOH (20 ml) was hydrogenated using PtO_2 (30 mg) catalyst. The soln was filtered and solvent removed to obtain a yellowish gum which crystallized from Et_2O–hexane (VI; 42 mg) m.p. 131°. λ_{max} 214, 242, 260 and 303 nm; log ϵ 4·54; 4·6, 4·45 and 4·1. (Found: C, 76·5; H, 7·5; N, 5·2. $C_{18}H_{21}NO_2$ requires: C, 76·3; H, 7·4; N, 4·9%.)

1-(*γ,γ-Dimethylallyl*)-2-*hydroxycarbazole* (XII), N-(*γ,γ-dimethylallyl*)-2-*hydroxycarbazole* (XIII) *and* 3-(*γ,γ-dimethylallyl*)-2-*hydroxycarbazole* (XIV). To a stirred soln of 2-hydroxycarbazole (6 g) in a dioxane (40 ml) was gradually added BF_3-etherate (2 ml), and then a soln of 2-methyl-3-butene-2-ol (8 g) in dioxane (10 ml). The reaction mixture was stirred for 3 hr. It was diluted with moist Et_2O (250 ml), the layer separated, washed (H_2O), dried and the solvent removed to give a gum. This was diluted with benzene (200 ml) and filtered to give unreacted 2-hydroxycarbazole (1·5 g). The filtrate was concentrated and chromatographed on SiO_2 gel (60 g); 50 ml fractions were collected. The chromatographic separation was monitored by TLC. (a) Fractions 20–27 (hexane–benzene 1:1) gave a soild which crystallized from Et_2O–hexane (XII; 350 mg) m.p. 134°. λ_{max} 217, 240, 258, and 303 nm; log ϵ 4·5, 4·6, 4·48 and 4·14. (Found: C, 81·5; H, 7·0; N, 5·4. $C_{17}H_{17}NO$ requires: C, 81·2; H, 6·8; N, 5·5%.) (b) Fractions 38–41 (hexane–benzene 1:1), crystallized from Et_2O–hexane (XIII; 200 mg), m.p. 143°, λ_{max} 212, 238, 262 and 303 nm; log ϵ 4·36, 4·68, 4·31 and 4·14. (Found: C, 81·0; H, 6·8; N, 5·6. $C_{17}H_{17}NO$ requires: C, 81·2; H, 6·8; N, 5·5%.) (c) Fractions 60–63 (hexane–benzene 1:3), crystallized from Et_2O-hexane (XIV; 100 mg) m.p. 172°, λ_{max} 238, 259 and 304 nm; log ϵ 4·66, 4·29 and 4·2. (Found: C, 80·7; H, 6·8; N, 5·5. $C_{17}H_{17}NO$ requires: C, 81·2; H, 6·8; N, 5·5%.)

Preparation of 2,2-*Dimethyl*-3,4-*dihydropyrano* (5,6-*a*)-*carbazole* (XI). (a) *From cycloheptaphyline.* Cycloheptaphylline (V; 10 mg) was intimately mixed with 10% Pd/C (25 mg) and heated under N_2 at 170° for 12 min. It was extracted with Et_2O and the solvent extract on evaporation gave a solid, which sublimed under vacuum to give (XI; 6 mg) m.p. 179–180°. (b) *From* (XII). A mixture of (XII; 50 mg) and HCOOH (4 ml) was heated at 100° for 1 hr and poured on crushed ice. The ppt was filtered, washed (H_2O), dried and crystallized from aq. EtOH (XI; 19 mg) m.p. 178–179°. This was found to be identical (m.m p., IR) with a sample obtained by decarbonylation of cycloheptaphylline. λ_{max} 215, 239, 253, 257 and 303 nm; log ϵ 4 4, 4·6, 4·4, 4·4 and 4·1. (Found: C, 81·1; H, 7·1; N, 5·7. $C_{17}H_{17}NO$ requires: C, 81·2; H, 6·8; N, 5·5%.)

2-*Hydroxy*-3-*formyl carbazole* (XVI). To a well-stirred soln of *N*-methyl formanilide (10 g) and $POCl_3$ (10 g) was added in small portions 2-hydroxycarbazole (10 g) at 20–25°. The mixture was stirred for 3 hr, left overnight at r.t. and then heated at 50° for 30 min. It was diluted with H_2O and extracted with Et_2O. The organic layer was washed (H_2O), dried and the solvent evaporated to give a solid, which was chromatographed on SiO_2 gel. Elution with hexane–benzene (1:1) afforded a solid which crystallized from MeOH (1·5 g) m.p. 240°. λ_{max} 234, 247, 278, 298 and 345 nm; log ϵ 4·42, 4·21, 4·54, 4·56 and 4·07. (Found: C, 74·2; H, 4·6; N, 6·7. $C_{13}H_9NO_2$ requires: C, 73·9; H, 4·3; N, 6·6%.)

Heptaphylline (III). 2-Hydroxy-3-formyl carbazole (XVI; 200 mg) was heated with 30% KOH (10 ml) at 85–90° for 15 min and allowed to cool. Me_2SO (2·5 ml) and *γ,γ*-dimethylallyl bromide (1 ml) were added, and the mixture stirred overnight at r.t. It was diluted with H_2O, acidified with conc. HCl and extracted with $CHCl_3$. The extract was washed (H_2O), dried and the solvent removed to give a gum which was chromatographed on SiO_2 gel. Elution with hexane–benzene (1:1) gave a gum which crystallized from CH_2Cl_2–hexane (III, 8 mg) m.p. 169–170°. It was identical with a sample of natural heptaphylline (m.m.p., TLC, IR and NMR spectra).

1,N-*Bis*(*γ,γ-dimethylallyl*)-2-*hydroxy*-3-*formyl carbazole* (XIX). To a soln of (XVI; 1 g) in Me_2SO (5 ml) was added KOH soln (2 g in 2 ml H_2O) and *γ,γ*-dimethylallylbromide (2 ml). The mixture was heated at 80° for 16 hr, cooled, poured over crushed ice and neutralized with HCl. It was extracted with CH_2Cl_2, washed (H_2O), dried and the solvent removed to give a gum. Chromatography on SiO_2 gel, elution with hexane–benzene (1:1), and crystallization from EtOH gave (XIX, 35 mg), m.p. 121°. λ_{max} 237, 252, 281, 305 and 346 nm; log ϵ 4·4; 4·2; 4·55; 4·53 and 4·0. (Found: C, 79·1; H, 7·5; N, 4·6. $C_{23}H_{25}NO_2$ requires: C, 79·5; H, 7·2; N, 4·0%.)

1-(*γ,γ-Dimethyl allyl*)-2-*hydroxy*-3-*formyl carbazole* (*heptaphylline*; III), *N*-(*γ,γ-dimethylallyl*)-2-*hydroxy*-3-*formyl carbazole* (XX) *and* 6-(*γ,γ-dimethyl allyl*)-2-*hydroxy*-3-*formyl carbazole* (XXI). To a stirred soln of 2-hydroxy-3-formyl carbazole (XVI; 6 g) in dioxane (60 ml) was gradually added BF_3-etherate (2·5 ml). A soln of 2-methyl-3-butene-2-ol (8 g) in dioxane (10 ml) was then added and the mixture stirred at r.t. for 4 hr. It was diluted with moist Et_2O (250 ml), the organic layer washed (H_2O), dried and the Et_2O evaporated. The gum (8 g) so obtained was dissolved in benzene and chromatographed on SiO_2 gel (80 g); 50 ml fractions were collected and followed up by TLC. (a) Fractions 26–28 (hexane–benzene, 1:1) gave a residue which crystallized from Et_2O–hexane to give (XX; 60 mg) m.p. 110°. λ_{max} 234, 279, 303 and 347 nm; log ϵ 4·41, 4·57, 4·54 and 4·1. (Found: C, 76·9; H, 6·4; N, 5·2. $C_{18}H_{17}NO_2$ requires: C, 77·4; H, 6·1; N, 5·0%.) (b) Fractions 37–60 (hexane–benzene, 1:1) gave a residue which on crystallization from Et_2O–hexane gave (III; 450 mg) m.p. 170°. This was identical in its m.m.p., TLC, UV, IR and NMR spectra with a sample of natural heptaphylline. (c) Fractions 72–76 (hexane–benzene, 1:3) gave a residue which crystallized from Et_2O–hexane to give (XXI; 60 mg) m.p. 116°. λ_{max} 235, 281, 303 and 350 nm; log ϵ 4·44, 4·49, 4·54 and 4·03. (Found: C, 77·2; H, 6·3; N, 4·9. $C_{18}H_{17}NO_2$ requires: C, 77·4; H, 6·1; N, 5·0%.)

N-*Methyl*-2-*methoxy*-3-*formyl carbazole*. 2-Hydroxy-3-formyl carbazole (XVI; 1·1 g), Me_2SO_4 (1·6 g), anhyd. K_2CO_3 (12 g) and dry acetone (50 ml), were refluxed for 6 hr, and the mixture filtered. Removal

of the solvent gave a gum which was extracted with CH_2Cl_2, washed with $NaHCO_3$, H_2O and dried (Na_2SO_4). Evaporation of the solvent gave a solid which crystallized from CH_2Cl_2–MeOH (350 mg) m.p. 173°. λ_{max} 237, 278, 303 and 355 nm; log ϵ 4·5, 4·5, 4·51 and 4·1. (Found: C, 75·5; H, 5·7; N, 5·4. $C_{15}H_{13}NO_2$ requires: C, 75·3; H, 5·4; N, 5·8%.)

N-*Formyl-2-hydroxy carbazole* (XVII). To a stirred mixture of $POCl_3$ (10 g) and dimethyl formamide (25 ml) was added a soln of 2-hydroxycarbazole (8 g) in dimethyl formamide (25 ml) at r.t. The reaction mixture was then warmed to 45° for 1·5 hr, and poured into H_2O. The ppt was extracted with Et_2O, the extract washed (H_2O), dried and evaporated to give a solid (7·2 g). Crystallization from benzene yielded (XVII; 2 g) m.p. 210°. λ_{max} 220, 235 and 278 nm; log ϵ 4·62, 4·43 and 4·27. (Found: C, 74·2; H, 4·5; N, 6·8. $C_{13}H_9NO_2$ requires: C, 73·9; H, 4·6; N, 6·6%.)

N-*Formyl-2-methoxycarbazole* (XVIII). *N*-formyl-2-hydroxycarbazole (XVII; 500 mg) dissolved in Et_2O (100 ml) was treated with an excess of ethereal CH_2N_2. The Et_2O layer was washed with 5% NaOH, H_2O, dried (Na_2SO_4) and the solvent removed to give a gum which crystallized from MeOH (100 mg) m.p. 88°. λ_{max} 220, 232 and 277 nm; log ϵ 4·68, 4·51 and 4·35. (Found: C, 75·0; H, 5·2; N, 6·4. $C_{14}H_{11}NO_2$ requires: C, 74·6; H, 4·9; N, 6·2%.)

N-*Formyl-2-(p-toluenesulphonyloxy) carbazole*. N-Formyl-2-hydroxycarbazole (XVII, 300 mg), *p*-toluene sulphonyl chloride (300 mg) and pyridine (5 ml) were heated at 100° overnight. The reaction mixture was diluted with CH_2Cl_2, washed with dil. HCl, $NaHCO_3$, H_2O, dried and the solvent removed to give a solid which crystallized from EtOH (170 mg) m.p. 141°. λ_{max} 223, 268 and 310 nm; log ϵ 4·73, 4·37 and 3·75. (Found: C, 66·2; H, 4·6; N, 4·0. $C_{20}H_{15}NO_4S$ requires: C, 65·8; H, 4·1; N, 3·8%.)

2-*Hydroxy carbazole from* XVII. A soln of (XVII; 20 mg) in 5% ethanolic HCl (5 ml) was heated at 70° for 30 min. It was diluted with H_2O, the solvent removed under vacuum and the residual solid extracted with Et_2O. The extract was washed (H_2O), dried and Et_2O evaporated (15 mg); crystallization from benzene gave 2-hydroxycarbazole, m.p. 278°.

N-*Methyl-2-methoxy carbazole*. (a) To a soln of *N*-formyl-2-hydroxycarbazole (XVII, 200 mg) in acetone (25 ml), NaOH (500 mg in 1 ml H_2O), Me_2SO_4 (1 ml) were added, the mixture shaken for 45 min and left overnight at r.t. It was diluted with H_2O, neutralized with conc. HCl, the ppt filtered, washed (H_2O), dried and crystallized from light petroleum (40–60°) (100 mg) m.p. 94°. λ_{max} 210, 238, 260 and 302 nm; log ϵ 4·43; 4·73, 4·33 and 4·19. (Found: C, 79·8; H, 6·3; N, 6·5. $C_{14}H_{13}NO$ requires: C, 79·6; H, 6·2; N, 6·6%.) (b) A soln of 2-hydroxycarbazole (500 mg) in acetone (60 ml) was shaken with NaOH (1·2 g in 2·5 ml H_2O) for 15 min; Me_2SO_4 (2·5 ml) was added, the mixture shaken for further 45 min and left overnight at r.t. It was diluted (H_2O), neutralized with conc. HCl, ppt filtered, washed (H_2O), dried and crystallized from MeOH (320 mg) m.p. 94°. This was identical with the compound obtained in (a).

2-(p-*Toluenesulphonyloxy*) *carbazole*. 2-Hydroxycarbazole (1·5 g), *p*-toluenesulphonyl chloride (1·7 g) and dry pyridine (15 ml) were heated at 100° for 10 hr. The reaction mixture was diluted with $CHCl_3$, washed with dil. HCl, $NaHCO_3$, H_2O, dried and the solvent removed to give a solid which crystallized from acetone–EtOH (700 mg) m.p. 220°. λ_{max} 235, 258, 296, 324 and 336 nm; log ϵ 4·64, 4·31, 4·2, 3·67 and 3·54. (Found: C, 67·8; H, 4·4; N, 4·5. $C_{19}H_{15}NO_3S$ requires: C, 67·6; H, 4·5; N, 4·1%.)

N-*Formylcarbazole*. To a well-stirred soln of $POCl_3$ (10 g) in dimethyl formamide (25 ml) was added a soln of carbazole (7·5 g) in dimethyl formamide (25 ml) at 20–25°. The mixture was stirred at 45° for 1·5 hr and poured on crushed ice. It was extracted with Et_2O, the extract washed with $NaHCO_3$, H_2O dried and solvent removed. The residue crystallized from MeOH (5 g) m.p. 101°. λ_{max} 219, 253, 265, 285, 298 and 310 nm; log ϵ 4·74, 4·23, 4·25, 3·9, 3·76 and 3·79. (Found : C, 79·9; H, 4·7; N, 6·8. $C_{13}H_9NO$ requires: C, 79·9; H, 4·6; N, 7·1%.)

1-*Methyl-2-(p-toluenesulphonyloxy) carbazole*. 1-Methyl-2-hydroxycarbazole (500 mg), *p*-toluene sulphonyl chloride (600 mg) and dry pyridine (5 ml) were heated at 100° for 10 hr. The reaction mixture was diluted with $CHCl_3$, washed successively with dil. HCl, $NaHCO_3$ and H_2O, dried and the solvent removed. The residue was crystallized from CH_2Cl_2–EtOH (500 mg) m.p. 196°. λ_{max} 235, 258, 295, 323 and 335 nm; log ϵ 4·67; 4·3; 4·24; 3·71 and 3·62. (Found: C, 68·2; H, 5·1; N, 4·3. $C_{20}H_{17}NO_3S$ requires: C, 68·3; H, 4·9; N, 3·9%.)

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