Synthesis of Murrayacine

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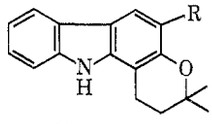
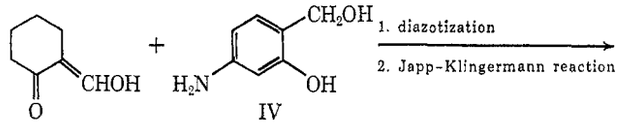
In previous communications[1,2] the structure of murrayacine (I), mp 244–245°, a carbazole alkaloid from the stem bark of *Murraya koenigii* Spreng, was reported. The structure was based on the identity of the reduction product of dihydromurrayacine (II) with dihydrogirinimbine (III). We now report the synthesis of I which confirms the structure.

The synthesis has been accomplished by preparation of a carbazole fragment with a potential aldehyde group and the incorporation of a 2,2-dimethyl-Δ^3-pyran ring into the phenolic substrate, following the method of Chakraborty, *et al.*[3]

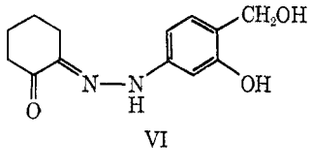
4-Hydroxymethyl-3-hydroxyaniline (IV), mp 110°, on treatment with formylcyclohexanone (V) under Japp–Klingemann condition,[4] furnished cyclohexane-1,2-dione 4-hydroxymethyl-3-hydroxyphenylhydrazone (VI), mp 99–100°. The compound VI, on indoliza-



II, R = CHO
III, R = CH_3

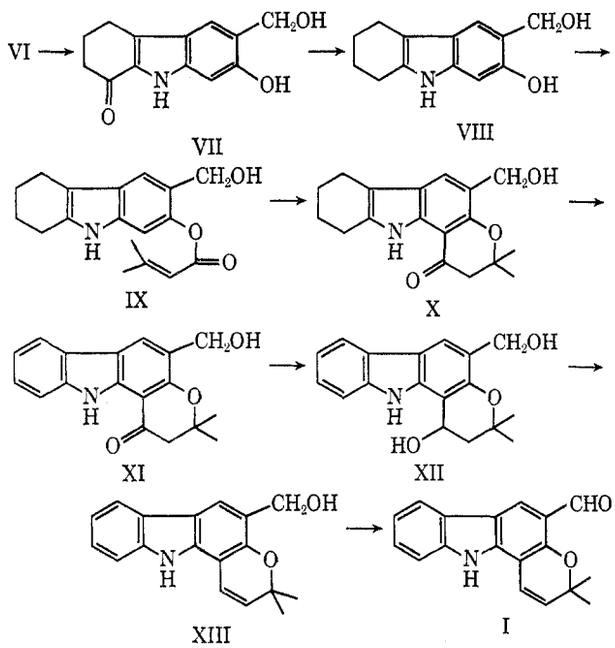


V IV



VI

tion with a mixture of glacial acetic acid and hydrochloric acid, furnished the indole-2-hydroxy-3-hydroxymethyl-8-oxo-5,6,7,8-tetrahydrocarbazole (VII), mp 113–115°. Wolff–Kishner reduction of the keto alcohol VII furnished 2-hydroxy-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole (VIII). The tetrahydrocarbazole VIII was acetylated with 2,2-dimethylacroylyl chloride at 5° in the presence of pyridine when the *O*-acyl compound IX, mp 147–150°, was obtained (ν_{max}^{Nujol} 1740 cm^{-1}). The phenol ester IX on Fries migration and subsequent treatment with hydrochloric acid furnished the chromanone X, mp 125°. The chromanone X was dehydrogenated with palladized charcoal when the indolochromanone XI, mp 160–162°, was obtained. The chromanone derivative was reduced with sodium borohydride when the alcohol XII, mp 114–115°, was obtained. Dehydrotosylation of the tosyl derivative XII in the presence of collidine



VII VIII IX X XI XII XIII I

furnished chromenoindole XIII, mp 199–200°, which had the characteristic uv spectrum [$\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.60), 282.5 (4.57), 302 (4.58)] of a pyranocarbazole like girinimbine.

Oxidation of the chromenoindole XIII with active MnO_2[4] furnished murrayacine, which was identical with natural murrayacine in all respects (uv, ir, tlc, mixture melting point).

Experimental Section

All melting points are uncorrected. Petroleum ether had the boiling point 60–80° unless otherwise mentioned. For chromatography (tlc and column) silica gel supplied by Gouri Chemical, Calcutta, and alumina of M/s Sarabhai Merck, India, were used.

4-Hydroxymethyl-3-hydroxyaniline (IV).—The methyl ester of *p*-aminosalicyclic acid[3] (5 g) in THF (100 ml) was shaken with $LiAlH_4$ (1 g) for 4 hr. After decomposition of $LiAlH_4$ in the usual way and on removal of the solvent from the reaction mixture, a brown gum was obtained. This was dissolved in benzene and chromatographed over silica gel. The benzene–chloroform (1:1) eluent was collected, which furnished IV: mp 110°; yield 3 g; ν_{max}^{Nujol} 3440 (primary alcohol), 3360 (–NH–), 3260 (chelated –OH), 1620, 1600, 1500 cm^{-1} (aromatic).

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.00; H, 6.4; N, 10.41.

Cyclohexane-1,2-dione 4-Hydroxymethyl-3-hydroxyphenylhydrazone (VI).—A diazotized solution of IV (2 g) was gradually added over a period of 45 min to a solution of formylcyclohexanone (3 g) in methanol (35 ml) in the presence of an aqueous solution of sodium acetate (5 g in 10 ml), when a precipitate was obtained. The precipitate was washed acid free and on crystallization from petroleum ether–benzene furnished the hydrazone VI: mp 99–100°; yield 2 g; $\lambda_{max}^{ethanol}$ 380 mμ (log ε 4.46), 332 (2.89), 250 (4.44).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.80; H, 6.51; N, 11.25.

2-Hydroxy-3-hydroxymethyl-8-oxo-5,6,7,8-tetrahydrocarbazole (VII).—Phenylhydrazone (VI, 6.2 g) was boiled in a mixture of acetic acid and concentrated HCl (4 ml) for 2–3 min. The reaction mixture was poured into crushed ice and a solid was obtained after usual work-up. The crude product was dissolved in benzene and chromatographed on silica gel (20 g). The residue of the eluent which was crystallized from petroleum ether–benzene furnished the oxo compound VII: mp 113–115°; yield 1.5 g; $\lambda_{max}^{ethanol}$ 280 mμ (log ε 4.16), 230 (4.40); ν_{max}^{Nujol} 3520 (OH), 3410 (–NH–), 3300 (chelated –OH), 1700 (–CO–), 1610, 1515, 1460 cm^{-1} (aromatic).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.64; N, 6.01.

(1) D. P. Chakraborty and K. C. Das, *Chem. Commun.*, 967 (1968).
(2) D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *J. Org. Chem.*, **36**, 725 (1971).
(3) D. P. Chakraborty, D. Chatterjee, and B. K. Chowdhury, *J. Indian Chem. Soc.*, **48**, 225 (1971).
(4) D. P. Chakraborty and B. K. Chowdhury, *J. Org. Chem.*, **33**, 1265 (1968).

2-Hydroxy-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole (VIII).—Compound VII (1.2 g) dissolved in ethylene glycol (20 ml) was heated with hydrazine hydrate (99–100%, 1 g) and KOH (0.9 g) at 190° for 1 hr and under reflux for 3 hr. After chromatography of the reaction product on silica gel an oil was obtained which could not be crystallized. It responded to ferric reaction.

2-(2,2-dimethylacryloyloxy)-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole (IX).—Compound VIII in pyridine (5 ml) was treated with 2,2-dimethylacroylyl chloride (3 ml) at 5° and kept for 24 hr. The reaction product was poured into crushed ice containing dilute HCl. A solid product was obtained, which on crystallization from alcohol furnished IX, mp 147–150°. It was negative to ferric reaction, yield 1.3 g, ν_{max}^{Nujol} 1740 cm^{-1} (>C=O).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.01; H, 7.08; N, 4.60.

2,3,6,7,8,9-Hexahydro-5-hydroxymethyl-3,3-dimethyl-1-oxopyrano[3,2-*a*]carbazole (X).—Compound IX and powdered anhydrous $AlCl_3$ (2.5 g) were dissolved in freshly distilled nitrobenzene (25 ml) at 0–5° and kept at room temperature for 3 days. Then the product was poured into crushed ice (100 g) containing dilute HCl (25 ml) and extracted with ether. On removal of solvent from the extract a solid (0.7 g) was obtained which was crystallized from alcohol: mp 125°; $\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.54), 282 (4.09), 290 (4.21).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.01; H, 7.08; N, 4.62.

2,3-Dihydro-5-hydroxymethyl-3,3-dimethyl-1-oxopyrano[3,2-*a*]carbazole (XI).—Chromanone (X, 600 mg) was dehydrogenated with Pd/C (10%, 50 mg) at 200° for 5 hr in a sealed tube in the presence of *p*-cymene. The mixture was cooled and filtered. Removal of *p*-cymene furnished a gum which was crystallized from benzene–chloroform and afforded 400 mg of XI: mp 160–162°; $\lambda_{max}^{ethanol}$ 228 mμ (log ε 4.65), 283 (4.08), 290 (4.23); ν_{max}^{Nujol} 3520 (primary alcohol), 3400 (–NH–), 1650 (>C=O), 1600, 1540, 1450 cm^{-1} (aromatic CH).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.18; H, 5.82; N, 4.70.

2,3-Dihydro-1-hydroxy-5-hydroxymethyl-3,3-dimethyl-1*H*-pyrano[3,2-*a*]carbazole (XII).—Compound XI (300 mg) was dissolved in dry methanol (15 ml), and sodium borohydride (50 mg) was added. The solution was kept at room temperature for 20 hr. After the usual work-up a solid was obtained which on crystallization from benzene–petroleum ether yielded 200 mg of XII, mp 114–115°. The tosylate of XII, which was obtained by the usual technique, melted at 135–137°, $\lambda_{max}^{ethanol}$ 238 mμ (log ε 4.56), 288 (4.3), 330 (3.64).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.69; H, 6.40; N, 4.8.

5-Hydroxymethyl-3,3-dimethyl-3*H*-pyrano[3,2-*a*]carbazole (XIII).—The tosyl derivative of XII (80 mg) in collidine (3 ml) was boiled for 6 hr and then poured into crushed ice containing HCl (5 ml). A solid was obtained, which was filtered, washed, and recrystallized from alcohol, yielding 50 mg of XIII: mp 199–200°; $\lambda_{max}^{ethanol}$ 226 mμ (log ε 4.60), 282 (4.57), 302 (4.58); ν_{max}^{Nujol} 3251 (–NH–), 1675 (>C=O), 1640, 1601 (unsaturation and aromatic residue), 895, 740 cm^{-1} (substituted benzene derivative).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 11.46. Found: C, 77.35; H, 6.1; N, 11.5.

Synthetic Murrayacine (I).[5]—Compound XIII (30 mg) was dissolved in CCl_4 (5 ml) and stirred with active MnO_2 (200 mg) for 4 hr. After completion of the reaction the solution was filtered and the solvent was evaporated. The residue was dissolved in benzene and chromatographed on a silica gel column. The benzene–chloroform eluent furnished a solid which melted at 242–244° and was identical with natural murrayacine (uv, ir, mixture melting point).

Registry No.—I, 27300-29-4; IV, 40463-78-3; VI, 40463-79-4; VII, 40463-80-7; VIII, 40463-81-8; IX, 40463-82-9; X, 40463-83-0; XI, 40463-84-1; XII, 40463-85-2; XII tosylate, 40463-86-3; XIII, 27300-31-8; methyl ester of *p*-aminosalicylic acid, 4136-97-4; formylcyclohexanone, 823-45-0; dimethylacryloyl chloride, 3350-78-5.

(5) Since our work was completed, Kapil, *et al.*, reported a different synthesis of murrayacine at IUPAC Symposium on the Chemistry of Natural Products, Feb 1972, confirming the above structure.

Acknowledgment.—The authors thank Professor S. M. Sircar, Ph.D., Director, Bose Institute, and Professor A. Sen, Head of the Department of Chemistry, for their interest in the work.

A Novel Synthesis of 2-Oxo-1,2,3,4-tetrahydrocarbazoles

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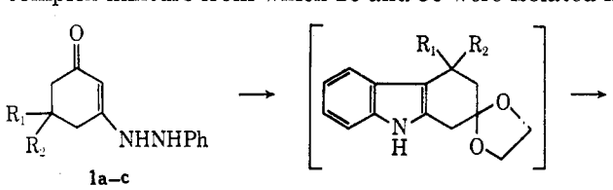
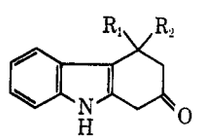
The synthesis of 2-ketotetrahydrocarbazole **2a** *via* a complex multistep sequence has been reported.[2] Based upon our need of this compound for a synthesis under investigation, we sought an alternate route for the preparation of **2a**. We were intrigued by the possibility that we might be able to alter the expected[3] direction of Fisher indole cyclization for 1,3-cyclohexanedione monophenylhydrazone **1a** to obtain **2a** directly. We wish to report that cyclization *via* the ethylene ketal does indeed give the desired 2-ketotetrahydrocarbazole as the only isolable cyclized product.

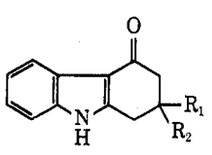
Reaction of hydrazone **1a** with *p*-toluenesulfonic acid in refluxing toluene gave, as expected,[3] the 4-oxo derivative **3a**. However, when the reaction was carried out in a mixture of ethylene glycol and toluene and the crude ketal hydrolyzed with aqueous sulfuric acid, the desired 2-keto derivative **2a** was obtained in 54% yield. In order to test the generality of the method, the two methylated phenylhydrazones **1b** and **1c** were subjected to this cyclization. The monomethyl derivative **1b** was smoothly converted to **2b** in 34% yield. Reaction of the dimethyl derivative **1c** with sulfuric acid–ethylene glycol–toluene, however, resulted in a complex mixture from which **2c** and **3c** were isolated in



1a–c



2a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Me$
c, $R_1 = R_2 = Me$



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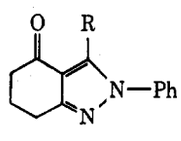

4a, R = H
b, R = Me

(1) (a) Alfred P. Sloan Foundation Fellow; (b) NDEA Title IV Fellow, 1971–1973.

(2) H. J. Teuber and D. Cornelius, *Justus Liebigs Ann. Chem.*, **671**, 126 (1964).

(3) Cyclization of **1a** in aqueous sulfuric acid is reported to give the 4-keto derivative **3a**: G. R. Clemo and D. G. I. Felton, *J. Chem. Soc.*, 700 (1951).