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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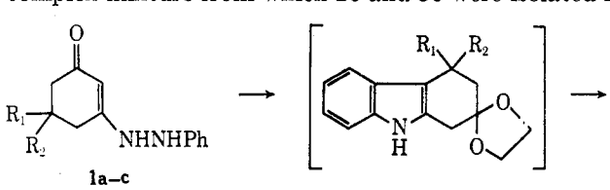
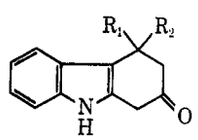
The synthesis of 2-ketotetrahydrocarbazole **2a** *via* a complex multistep sequence has been reported.[2] Based upon our need of this compound for a synthesis under investigation, we sought an alternate route for the preparation of **2a**. We were intrigued by the possibility that we might be able to 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.

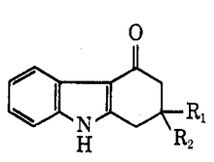
Reaction of hydrazone **1a** with *p*-toluenesulfonic acid in refluxing toluene gave, as expected,[3] the 4-oxo derivative **3a**. However, when the reaction was carried out in a mixture of ethylene glycol and toluene and the crude ketal hydrolyzed with aqueous sulfuric acid, the desired 2-keto derivative **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



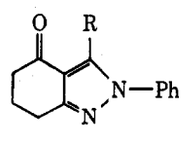
1a–c



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



3



4a, R = H
b, R = Me

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

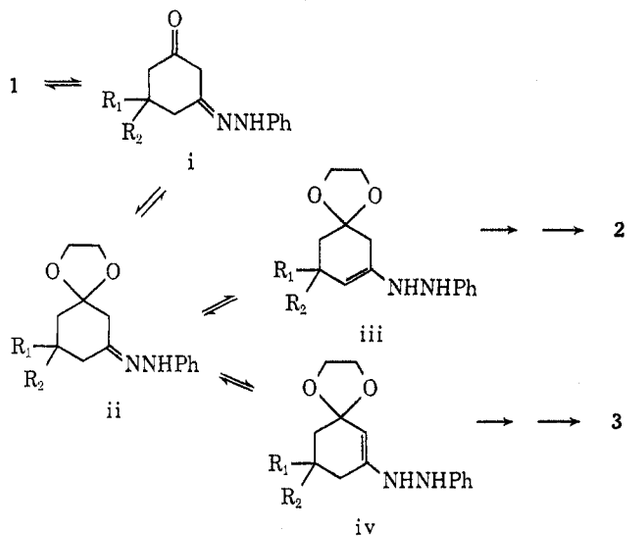
(2) H. J. Teuber and D. Cornelius, *Justus Liebigs Ann. Chem.*, **671**, 126 (1964).

(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).

6 and 5% yields, respectively. Cyclization of **1c** in the absence of glycol gave the expected 4-keto derivative in 38% yield.

We account for these results by assuming that rapid acid-catalyzed conversion of **1** to tautomer i is followed by ketalization to ii (vinylogous amides are generally resistant to ketalization under these conditions). Tautomerization of ii → iii should be more favorable then ii → iv for **1a** and **1b** on steric grounds, thus leading to **2a** and **2b** as the favored products. In the case of **1c**, however, tautomerization of ii to either iii or iv is energetically unfavorable, and thus both **2c** and **3c** are obtained in very low yield.

A brief examination of other ketalizing reagents revealed a different path for reaction of hydrazone **1b** with ortho esters. Thus, reaction of **1a** with triethyl orthoformate and *p*-toluenesulfonic acid (toluene, reflux) followed by hydrolysis of the diethyl ketal gave the tetrahydroindazole **4a**; similarly, triethyl orthoacetate led to the methyl analog **4b**. The assigned orientation of the carbonyl group in **4** adjacent to the pyrazole ring is based on the infrared carbonyl frequency at 1660 cm^{-1} and the ultraviolet absorption at



258 nm characteristic of 4-acyl-1-phenylpyrazoles.[4] The difference in orientation between the ortho ester and the ethylene glycol products suggests that the acylation of the vinylogous amide (either directly or *via* the adduct on the hydrazone nitrogen) by the ortho ester proceeds more rapidly than ketalization.

Experimental Section

2-Oxo-1,2,3,4-tetrahydrocarbazole (2a).—Cyclohexane-1,3-dione monophenylhydrazone[5] (10.10 g, 50 mmol) and *p*-toluenesulfonic acid (11.40 g, 60 mmol) were dissolved in 500 ml of toluene and 25 ml of ethylene glycol. The resulting mixture was refluxed with a Dean–Stark trap for 24 hr. The toluene solution was decanted from the reaction flask, washed with three 30-ml portions of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and freed of solvent *in vacuo* to give 10.51 g of crude ketal. The ketal was dissolved in 165 ml of methanol containing 44 ml of 10% aqueous sulfuric acid and was stirred at room temperature for 6.5 hr. Water (100 ml) was added to the solution, and the resulting mixture was extracted with three 100-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give 9.13 g of crude ketone. This material was purified by elution through a Florisil column (1 × 14 in.), the desired product being eluted in the first 100 ml of 1,2-dichloroethane. The resulting product (7.73 g) was crystallized from ethyl acetate–cyclohexane to give 7.24 g (78%) of **2a**, mp 125–129.5°. Two recrystallizations from ethyl acetate–cyclohexane afforded 4.99 g (54%) of **2a**: mp 131–133° (lit.[2] mp 131–133°); ir (Nujol) 3410, 1715 cm^{-1}; nmr ($CDCl_3$) δ 2.75 (m, 2 H), 3.10 (m, 2 H), 3.55 (s, 2 H), 7.30 (m, 4 H), 7.80 (s, 1 H).

4-Methyl-2-oxo-1,2,3,4-tetrahydrocarbazole (2b) was prepared by the procedure described for **2a** and purified by dry-column chromatography (1 × 22 in. alumina column, chloroform, R_f 0.28). The product, an oil, was obtained in 34% yield: ir (near) 3420, 1715, 1620, 1595 cm^{-1}; nmr ($CDCl_3$) δ 7.88 (s, 1 H), 7.30 (m, 4 H), 3.55 (s, 2 H), 2.68 (m, 3 H), 1.34 (d, 3 H); mass spectrum *m/e* 199 (molecular ion).

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol, mp 221–223°.

Anal. Calcd for $C_{19}H_{17}N_5O_4$: C, 60.14; H, 4.53; N, 18.46. Found: C, 60.23; H, 4.61; N, 18.29.

Attempted Cyclization of 1c.—A mixture of 4.60 g (20 mmol) of phenyl hydrazone **1c**, 2.12 g (21 mmol) of concentrated sulfuric acid, 10 ml of ethylene glycol, and 250 ml of toluene was refluxed with a Dean–Stark trap for 24 hr. The hot toluene solution was decanted from the reaction vessel, and the residue was washed with 30 ml of hot chloroform. The toluene and chloroform solutions were combined, washed with three 40-ml portions of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude product (1.27 g) was chromatographed on a 1.5 × 20 in. silica gel dry column, using chloroform to elute. The band having R_f ~0.2 was removed and the crude ketone **3c** obtained was further purified by preparative tlc (silica gel, 1:4 ethyl acetate–benzene, R_f 0.17) and recrystallization (CH_2Cl_2–CCl_4) to give 190 mg (5%) of **3c**: mp 200–201.5°; ir (KBr) 3250, 1615 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (s, 6), 2.42 (s, 2), 2.80 (s, 2), 7.12 (m, 3), 8.2 (s, 1), 9.08 (s, 1); mass spectrum *m/e* 213 (molecular ion).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.82; H, 7.10; N, 6,57. Found: C, 78.68; H, 6.83; N, 6.33.

The dry column band having R_f ~0.35 was removed to give 440 mg of crude ethylenedioxy ketal. This ketal was dissolved in a mixture of tetrahydrofuran (20 ml) and 10% aqueous sulfuric acid (20 ml) and was stirred for 6 hr at room temperature. The resulting solution was extracted with three 30-ml portions of chloroform. The combined extracts were washed with 20 ml of saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 355 mg of product. Purification by preparative tlc (silica gel, 1:4 ethyl acetate–benzene, R_f 0.36) afforded 260 mg (6%) of **2c** as an oil: ir (neat) 3400, 1705 cm^{-1}; nmr ($CDCl_3$) δ 1.48 (s, 6 H), 2.58 (s, 2 H), 3.52 (s, 2 H), 7.12 (m, 3 H), 7.68 (m, 1 H), 8.08 (s, 1 H); mass spectrum *m/e* 213 (molecular ion).

3-Methyl-2-phenyl-4-oxo-4,5,6,7-tetrahydro(2*H*)indazole (4b).—A solution of 1.14 g (6 mmol) of *p*-toluenesulfonic acid was dissolved in 100 ml of toluene and distilled until 20 ml of toluene and water had been collected. Cyclohexane-1,3-dione monophenylhydrazone (1.01 g, 5 mmol) and triethyl orthoacetate (5 ml) were then added, and the resulting solution was refluxed for 29 hr. The cooled solution was washed with three 30-ml portions of saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo* to give 1.85 g of crude diethyl ketal. This ketal was hydrolyzed by stirring with THF (20 ml) and 10% H_2SO_4 (20 ml) for 44 hr at room temperature. The mixture was then extracted with three 25-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to give 1.28 g of crude product. Purification by preparative tlc (silica gel, 1:4 ethyl acetate–benzene, R_f 0.2) and recrystallization from petroleum ether (bp 30–60°) afforded 325 mg (29%) of **4b**: mp 98–99°; ir (KBr) 1660, 1590, 1555 cm^{-1}; nmr ($CDCl_3$) δ 2.30 (m, 2 H), 2.68 (m, 2 H), 2.75 (s, 3 H), 3.00 (t, 2 H), 7.65 (s, 5 H).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.30; H, 6.25; N, 12.38. Found: C, 74.26; H, 6.30; N, 12.31.

Registry No.—**1a**, 26593-16-8; **1b**, 39554-99-9; **1c**, 26593-17-9; **2a**, 40429-00-3; **2b**, 40429-01-4; **2b** 2,4-dinitrophenylhydrazone, 40429-02-5; **2c**, 40429-03-6; **3c**, 40429-04-7; **4b**, 23894-51-1.

(4) For example, Sadtler reports the infrared and ultraviolet maxima for methyl 5-methyl-1-phenyl-4-pyrazolyl ketone as 1660 cm^{-1} and 252 nm, respectively.

(5) J. B. Hester, *Chem. Abstr.*, **72**, 90425f (1970).