2,5-Dimethylindolo[2,3-*f*]morphan

GLENN C. MORRISON, RONALD O. WAITE, ALBERT N. CARO, AND JOHN SHAVEL, JR.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey

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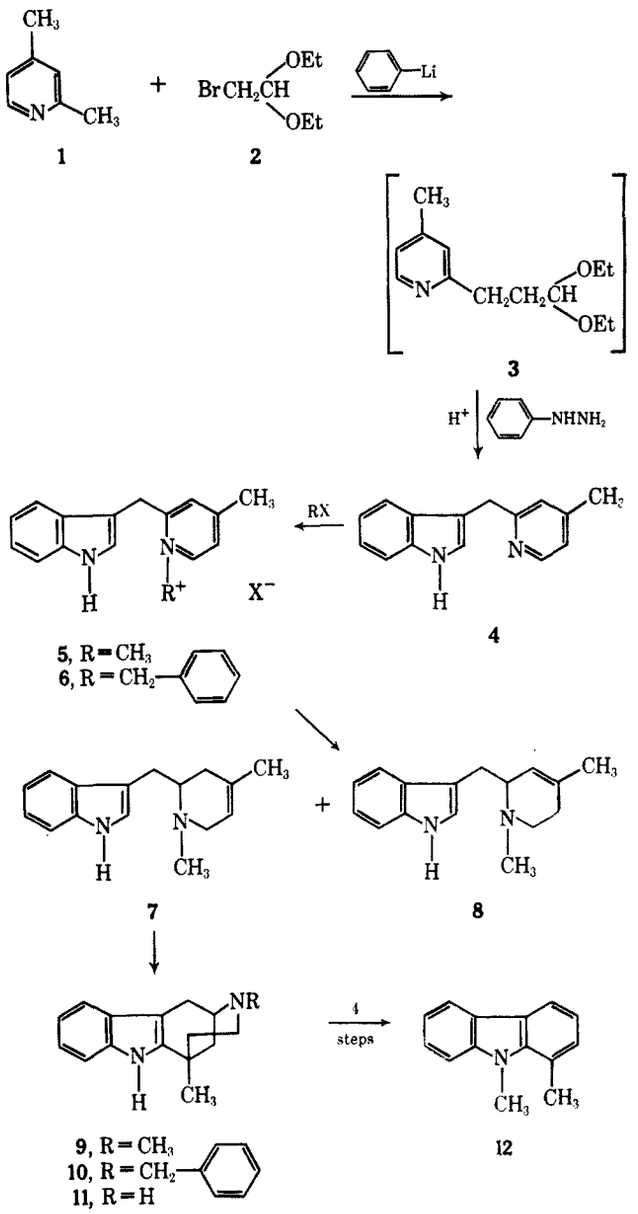
Continuing with our interest in the field of indole analogs[1] of morphine derivatives, we turned our attention to compounds in the morphan series. Benzomorphans have been prepared by the reduction of appropriate 2-benzylpyridines to tetrahydro derivatives which are cyclized with acid.[2] We have adopted this approach for our work; however, the preparation of a 2-(indolylmethyl)pyridine intermediate by the procedures used in the benzene series did not seem feasible. We have utilized an approach which involves building the indole nucleus onto a pyridine side chain.

Wibaut and Beets[3] have described the extension of a pyridine 2-methyl group to a three-carbon aldehyde by treatment with phenyllithium and bromoacetaldehyde diethyl acetal. Cale, *et al.*,[4] have shown that when 2- and 4-methyl groups are present on a pyridine ring, metalation occurs predominantly at the 2 position. We subjected 2,4-lutidine to the phenyllithium–bromoacetaldehyde diethyl acetal procedure to give the pyridyl acetal **3**. Treatment of crude **3** with phenylhydrazine under the conditions of the Fischer indole cyclization produced the indolylmethylpyridine **4**. On standing with methyl iodide, **4** was converted to the quaternary **5**. Reduction of **5** with sodium borohydride led to a mixture of the tetrahydro derivatives **7** and **8** in which **7** was predominant. The $\Delta^{4,5}$ isomer was assigned as the favored product by analogy to the reduction of a 2-picoline quaternary to the $\Delta^{4,5}$-piperidine system.[5] Cyclization of **7** or a mixture of **7** and **8** with phosphoric acid gave the indolomorphan **9**.

We also wished to have the NH indolomorphan available for placing substituents on the basic nitrogen. Since the borohydride reduction can only be carried out on a quaternary, it was necessary to introduce a group which could be removed later in the scheme. For this purpose **4** was converted to the benzyl quaternary **6** by treatment with benzyl bromide. The quaternary was reduced and cyclized to give the N-benzylindolomorphan **10**. The benzyl group was removed by hydrogenolysis, using palladium in acetic acid, to give the desired indolomorphan **11**.

To establish the structure of the indolomorphan ring system, a degradation analogous to the scheme utilized in the cyclohexindolomorphan series[6] was performed. Compound **9** was N-methylated, quaternized, subjected to the Hofmann degradation, and aromatized to 1,9-dimethylcarbazole (**12**) (Scheme I). This material was shown to be identical with an authentic sample prepared from 2-methylcyclohexanone and 1-methyl-1-phenylhydrazine.

SCHEME I



Experimental Section[7]

The melting points were determined using a Thomas–Hoover apparatus which had been calibrated against known standards. The infrared spectra were recorded with a Baird Model 455 instrument on chloroform solutions. The ultraviolet spectra were determined using a Beckman DKI spectrophotometer on 95% ethanol solutions. The nmr spectra were determined with a Varian Associates A-60 spectrometer on deuteriochloroform solutions.

2-(Indol-3-ylmethyl)-4-methylpyridine (4).—To 4.68 g of lithium ribbon suspended in 135 ml of ether was added a solution of 58.0 g of bromobenzene in 68 ml of ether at a rate such that gentle reflux was maintained. Stirring was continued for an additional 2 hr and the solution was allowed to stand overnight. Then 36.1 g of 2,4-lutidine was added at a rate such that the solution just refluxed and after the addition

(1) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).

(2) E. L. May and E. M. Fry, *ibid.*, **22**, 1366 (1957).

(3) J. P. Wibaut and M. G. J. Beets, *Rec. Trav. Chim.*, **59**, 653 (1940).

(4) A. D. Cale, Jr., R. W. McGinnis, Jr., and P. C. Teaque, *J. Org. Chem.*, **25**, 1507 (1960).

(5) M. Ferles, M. Kovarik, and Z. Vondrackova, *Collection Czech. Chem. Commun.*, **31**, 1348 (1966).

(6) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2551 (1967).

(7) The authors are indebted to Mr. A. Lewis and his associates, to Mr. R. Puchalski for the spectral data, and to Mrs. U. Zeek for analytical determinations.

had been completed stirring was continued for an additional 90 min. A solution of 73.2 g of bromoacetal in 135 ml of ether was added with ice-bath cooling at a rate such that the temperature remained between 15 and 20° and then the solution was stirred for an additional 90 min. After standing overnight the reaction mixture was poured into a mixture of 180 g of ice and 270 ml of water. The ether layer was washed with 225 ml of water, dried over sodium sulfate, and the solvent was removed. Distillation of the residue gave 40 g of an oil, bp 87–95° (0.02 mm), which was refluxed for 18 hr with 26 g of phenylhydrazine hydrochloride, 36 ml of sulfuric acid, and 900 ml of water. The reaction mixture was made basic with 40% sodium hydroxide solution and was extracted with ether. The ethereal layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was dissolved in 200 ml of hot benzene and 200 ml of Skellysolve B was added. On standing there was deposited 20.3 g (26%) of a crystalline solid, mp 128–130°. Further recrystallization gave an analytical sample: mp 131–132°; λ_{max} mμ (ε) 220 (36,000), 268 (8000), 280 (7100), 290 (5800); γ_{max} 1560, 1608, 3480 cm^{-1}; δ 2.15 (s, 3 H), 4.25 (s, 2 H), 6.8–7.7 (7 H), 8.4 (d, J = 5 cps, 1 H), and 9.0 ppm (m, 2 H).

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.03; H, 6.53; N, 12.39.

Methiodide.—To a solution of the base in 200 ml of acetone was added 40 ml of methyl iodide. The solution was scratched with a glass rod until crystallization began and was then allowed to stand for 5 hr. There was deposited a crystalline solid, mp 231–236°. Recrystallization from ethanol gave an analytical sample, mp 237–239°.

Anal. Calcd for $C_{16}H_{17}IN_2$: C, 52.76; H, 4.71; N, 7.69; I, 34.84. Found: C, 53.00; H, 5.00; N, 7.74; I, 34.58.

Benzylbromide.—A solution of the base and benzylbromide in 100 ml of ethanol was refluxed for 5 hr. On standing there was deposited a crystalline solid, mp 205–206°.

Anal. Calcd for $C_{22}H_{21}BrN_2$: C, 67.18; H, 5.38; N, 7.12; Br, 20.32. Found: C, 67.22; H, 5.62; N, 7.33; Br, 20.23.

1,2,3,6- and 1,2,5,6-Tetrahydro-2-(indol-3-ylmethyl)-1,4-dimethylpyridine (7 and 8).—To a solution of 5.14 g of sodium hydroxide in 73.6 ml of water was added 124 ml of methanol. The temperature was adjusted to 25° and 34.4 g of 2-(indol-3-ylmethyl)-4-methylpyridine methiodide was added. The mixture was stirred for 15 min and 4.88 g of sodium borohydride was added. The resulting mixture was stirred for 45 min and finally was heated at 50–60° for 2 hr. After cooling to room temperature, filtration gave 20.0 g (87%) of a crystalline solid, mp 144–157°. Three recrystallizations from benzene gave 15.8 g of a crystalline solid, mp 149–158°. This mixture was chromatographed on 1500 g of alumina and eluted with ether. The early ether fractions, after recrystallization from benzene, gave the 1,2,5,6 isomer as a crystalline solid: mp 174–175.5°; λ_{max} mμ (ε) 220 (37,900), 274 sh (5800), 282 (6300), 290 (5500); γ_{max} 3480 cm^{-1}; δ 1.65 (s, 3 H), 2.55 (s, 3 H), 1.6–2.4 (7 H), 5.28 (m, 1 H), 6.9–7.7 (5 H), 8.2 ppm (m, 1 H).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.01; H, 8.55; N, 11.68.

The later ether fractions, after recrystallization from benzene, gave the 1,2,3,6 isomer as a crystalline solid: mp 165.5–166.5°; λ_{max} mμ (ε) 222 (34,700), 274 sh (5400), 282 (5900), 290 (5700); γ_{max} 3460 cm^{-1}; δ 1.6 (s, 3 H), 2.55 (s, 3 H), 1.6–2.3 (7 H) 5.4 (m, 1 H), 6.9–7.7 (5 H), 8.4 ppm (m, 1 H).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.80; H, 8.47; N, 11.47.

2,5-Dimethylindolo[2,3-*f*]morphan (9).—A solution of 35.0 g of a mixture of 1,2,3,6- and 1,2,5,6-tetrahydro-2-(indolylmethyl)-1,4-dimethylpyridine in 350 ml of 85% phosphoric acid was heated at 165° (bath temperature) for 18 hr in a nitrogen atmosphere. The reaction mixture was poured into 1400 ml of cold water, made basic with 40% potassium hydroxide solution, and was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was chromatographed on alumina. Elution with dichloromethane gave, after recrystallization from Skellysolve B, 8.9 g (25%) of a crystalline solid: mp 142.5–143.5°; λ_{max} mμ (ε) 227 (38,300), 282 (7400), 290 sh (6500); γ_{max} 3460 cm^{-1}; 1.27 (s, 3 H), 2.37 (s, 3 H), 1.3–2.7 (7 H), 3.1 (d, J = 17 cps, 1 H), 3.3 (m, 1 H), 6.95–7.2 (3 H), 7.4 (m, 1 H), 7.75 ppm (m, 1 H).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.06; H, 8.57; N, 11.47.

2-Benzyl-5-methylindolo[2,3-*f*]morphan Methanolate (10).—To a solution of 7.16 g of sodium hydroxide in 107 ml of water and 195 ml of methanol, 59 g of 1-benzyl-2-(indol-3-ylmethyl)-4-methylpyridinium bromide was added and the mixture was stirred for 15 min. On the addition of 7.74 g of sodium borohydride an exothermic reaction occurred, after which the mixture was heated at 60° for 1 hr. The reaction mixture was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was refluxed with 1500 ml of hydrobromic acid for 20 hr. The reaction mixture was made basic with 40% sodium hydroxide solution and was extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and the solvent was removed. Chromatography of the residue on alumina gave an oil on elution with methylene chloride. Crystallization of the oil from methanol gave 6.5 g (14%) of a crystalline solid, mp 68–71°. Further recrystallization gave an analytical sample, mp 76–77°.

Anal. Calcd for $C_{22}H_{24}N_2 \cdot CH_3OH$: C, 79.28; H, 8.08; N, 8.03. Found: C, 79.52; H, 7.98; N, 8.23.

5-Methylindolo[2,3-*f*]morphan (11).—To a solution of 3.5 g of 2-benzyl-5-methylindolo[2,3-*f*]morphan in 50 ml of acetic acid was added 350 mg of palladium and the mixture was hydrogenated. After 30 hr 98% of the theoretical amount of hydrogen had been taken up. The catalyst was removed by filtration. After the addition of 150 ml of water, the solution was made basic with 40% sodium hydroxide solution and was extracted with ether. The ether layers were combined, washed with water, and were dried over sodium sulfate. The ether solution was concentrated to 12 ml. On standing there was deposited 1.73 g (77%) of a crystalline solid: mp 183.5–184°; λ_{max} mμ (ε) 226 (37,500) 282 (7500), 289 sh (5800); δ 1.4 (s, 3 H), 1.4–3.0 (8 H), 3.2 (d, J = 17 cps, 1 H), 3.65 (m, 1 H), 7.0–7.3 (3 H), 7.5 (m, 1 H), 7.95 ppm (m, 1 H).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.31; H, 8.17; N, 12.12.

1,9-Dimethylcarbazole (12). A. From 2,5-Dimethylindolo[2,3-*f*]morphan.—To a suspension of 7.0 g of 55% sodium hydride dispersion in mineral oil, 70 ml of dimethylcarbonate, and 300 ml of tetrahydrofuran was added a solution of 6.03 g of 2,5-dimethylindolo[2,3-*f*]morphan in 20 ml of tetrahydrofuran. The mixture was refluxed with stirring for 20 hr. The reaction mixture was poured into 1 l. of cold water, acidified with 20% hydrochloric acid solution, and was extracted twice with 250-ml portions of ether. These etheral solutions were subsequently discarded. The aqueous layer was made basic with 10% sodium hydroxide solution and was extracted twice with 300-ml portions of ether. The ether layers were combined, washed with 150 ml of water, dried over sodium sulfate, and the solvent was removed. There remained 6.0 g of 2,5,13-trimethylindolo[2,3-*f*]morphan which was dissolved in a 15% solution of methyl iodide in ethanol. On standing there was deposited 5.0 g of a methiodide, mp 248–249°. A mixture of the methiodide, 100 ml of ethanol, and 40 ml of 40% sodium hydroxide solution was refluxed overnight. The reaction mixture was diluted with water and was extracted with ether. The ether layer was washed with water and was dried over sodium sulfate. Removal of the solvent gave 2.74 g of 9*b*-(2-dimethylaminoethyl)-1,2-dihydro-9-methyl-9H-carbazole which was dissolved in 120 ml of ethanol, 0.5 g of 5% palladium on carbon was added, and the mixture was hydrogenated. Uptake was constant after 97% of the theoretical hydrogen had been absorbed. The catalyst was filtered and removal of the solvent gave 2.2 g of 9*b*-(2-dimethylaminoethyl)-1,2,3,4-tetrahydro-9-methyl-9H-carbazole as an oil. A mixture of the oil and 2 g of palladium on carbon in a test tube was immersed in a bath at 250°, the temperature raised to 310° over a 10-min interval, and then held there for 20 min. The reaction mixture was treated with 5 ml of chloroform and filtered. After removal of the solvent there remained 0.85 g of a solid. Recrystallization from ethanol–water gave an analytical sample, mp 108–109°.

Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.32; H, 6.89; N, 7.43.

B. From 2-Methylcyclohexanone and 1-Methyl-1-phenylhydrazine.—To a refluxing solution of 7 ml of hydrochloric acid in 20 ml of water was added 5.0 g of 1-methyl-1-phenylhydrazine. After stirring for 5 min, 4.6 g of 2-methylcyclohexanone was added dropwise and then heating was continued for an additional 3 hr. The reaction mixture was made basic with

10% sodium carbonate solution and was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was mixed with 7.5 g of 5% palladium on carbon in a test tube, placed in a bath at 250°, and the temperature was raised to 285° over a 10-min interval. The reaction mixture was treated with chloroform, filtered, and the solvent was removed. There remained 4.0 g (83%) of a solid. Recrystallization from ethanol gave an analytical sample, mp 113–114°.

Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.11; H, 8.86; N, 6.94.

The samples from A and B were shown to be identical by the methods of mixture melting point and infrared analysis.

Registry No.—**4**, 7551-08-8; **5**, 14128-30-4; **6**, 14128-31-5; **7**, 7546-56-7; **8**, 7551-09-9; **9**, 7546-57-8; **10**, 14171-84-7; **11**, 14128-34-8; **12**, 14171-85-8.

1-Acylindoles. III. A Novel Synthesis of 9-Acyltetrahydrocarbazole and 5-Acyl-γ-carboline Derivatives

HISAO YAMAMOTO

Pharmaceutical Division, Sumitomo Chemical Company, Ltd., Konohana-ku, Osaka, Japan

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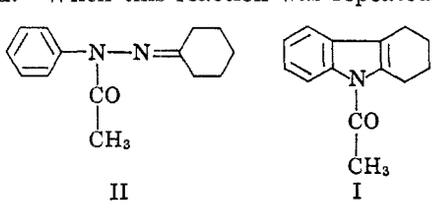
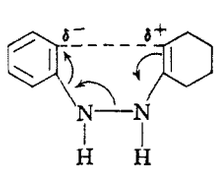
Perkin and Plant[1] claimed to have prepared 9-acetyl-1,2,3,4-tetrahydrocarbazole (I) by boiling cyclohexanone N^1-acetylphenylhydrazone (II) in dilute sulfuric acid. When this reaction was repeated by Suvorov and Sorokina,[2] the deacylated 1,2,3,4-tetrahydrocarbazole (III), mp 117–119°, but not the 9-acetyl compound I, was found to be the product. Suvorov and Sorokina stated that acylation of the N^1 atom of the hydrazone derivative should stabilize the p-electron pair of that nitrogen atom and thus retard formation of a new C–C bond. This would make Fischer carbazole formation difficult. Therefore they concluded that hydrolysis of the acetyl group precedes Fischer cyclization.



II I

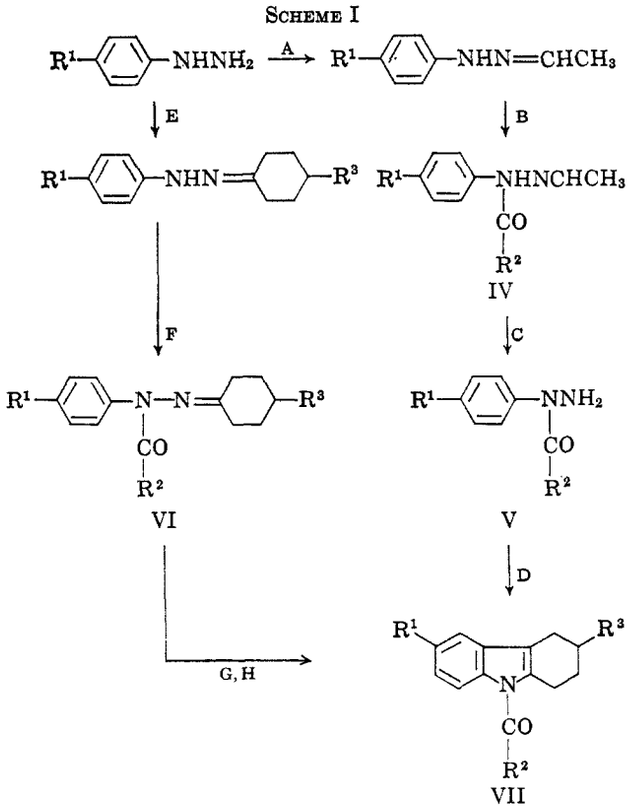


This work was then repeated by the present author, who obtained both the 9-acetyl derivative (I), mp 77–78°, and the deacylated material, mp 115–118°, as products.

In a previous publication,[3] the author has shown that deacylation of the N^1 atom of hydrazones is not necessary for Fischer indole cyclization and therefore participation by the p-electron pair of that atom in the formation of the new C–C bond is not important. This same conclusion may be applied in the case of tetrahydrocarbazole formation. Thus the deacylation observed during tetrahydrocarbazole formation from hydrazones may not be a step which necessarily precedes cyclization as postulated by Suvorov and Sorokina.

When the aqueous sulfuric acid reaction medium was replaced with glacial acetic acid and gaseous hydrogen chloride in the cyclization of cyclohexanone-N^1-benzoylphenylhydrazone, a good yield of 9-benzoyl-1,2,3,4-tetrahydrocarbazole was obtained, but no deacylated product was observed (Scheme I, step G).

SCHEME I



We have also found that 9-acyl-1,2,3,4-tetrahydrocarbazoles (VII) may be produced directly from the interaction of N^1-acylarylhydrazine hydrochlorides (V) with cyclohexanone and substituted cyclohexanones (step D).

This method for the synthesis of 9-acyl-1,2 3,4-tetrahydrocarbazoles is smooth and rapid, resulting in a high and in some cases quantitative yield of product. These results support the view that participation by the p-electron pair of the acylated nitrogen atom of the hydrazone is negligible in Fischer carbazole formation.

The intermediate N^1-acylarylhydrazine hydrochlorides (V) may be produced quantitatively from acetaldehyde N^1-acylarylhydrazones (IV) by cleavage with hydrogen chloride in absolute ethanol or in a mixture of ethanol and a second inert organic solvent.

In addition to the preparation of several 9-acyl-1,2,3,4-tetrahydrocarbazole derivatives by this new method, 5-*p*-chlorobenzoyl-2-methyl-8-methoxy-γ-car-

(1) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 119, 1825 (1921).
(2) N. N. Suvorov and N. P. Sorokina, *Dokl. Akad. Nauk SSSR*, **136**, 840 (1961).
(3) H. Yamamoto, *Bull. Chem. Soc. Japan*, **40**, 425 (1967).