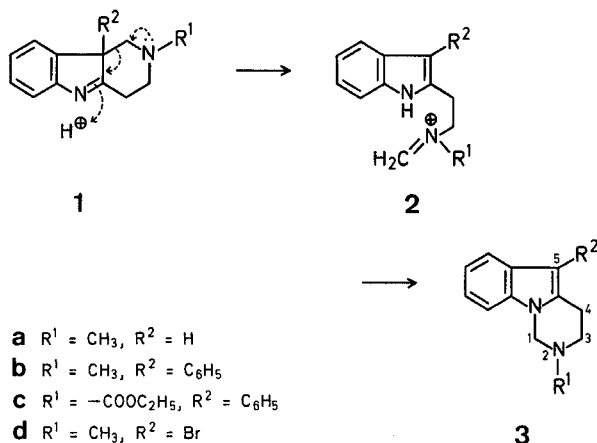


A Convenient Synthesis of the 1,2,3,4-Tetrahydro-pyrimido[3,4-*a*]indole System

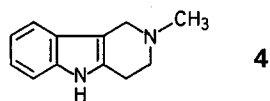
Kuldip S. BHANDARI and Victor SNIIECKUS

Department of Chemistry, University of Waterloo, Waterloo, Canada

The retro-Mannich reaction in compounds possessing a 3-aminomethyl-3*H*-indole system is well documented particularly within the molecular framework of indole alkaloids¹. The most recent examples² of this reaction have been observed during the Fischer indole cyclization of 3-substituted 4-piperidones in which the normal ultimate event (loss of a proton in **1a**) is blocked by the presence of a 3-substituent (e.g. **1b**, **1c**) forcing to a large extent the Mannich fragmentation pathway (**1**→**2**) in order to achieve a similar aromatic stabilization. In these cases, the major isolated products were derivatives of the hitherto unknown 1,2,3,4-tetrahydropyrimido[3,4-*a*]indole system (**3b** and **3c**) presumably resulting from cyclization of the intermediates **2b** and **2c**, respectively:



We report that this type of rearrangement may be conveniently effected on 2-methyl-1,2,3,4-tetrahydro-5*H*-pyrimido[4,3-*b*]indole (3-methyl-1,2,3,4-tetrahydro- γ -carboline, **4**) by *N*-bromosuccinimide (NBS) to yield **3d** and that



the net reversal of this transformation (**3**→**4**) may be accomplished after reductive removal of the 5-bromo function in **3d**. Since derivatives of tetrahydro- γ -carbolines are readily available³, the reaction **4**→**3** offers a potential general entry into the new heterocyclic ring system **3**.⁴

5-Bromo-2-methyl-1,2,3,4-tetrahydro-pyrimido[3,4-*a*]indole (**3d**):

A solution of 3-methyl-1,2,3,4-tetrahydro- γ -carboline⁵ (**4**; 186 mg, 1 mmol) in anhydrous benzene (25 ml) was treated with *N*-bromosuccinimide (178 mg, 1 mmol) and the reaction mixture was stirred at room temperature for 20 minutes. The precipitate was removed by filtration and the filtrate was quickly washed with consecutive solutions of dilute sodium hydroxide and water. The benzene layer was briefly dried (sodium sulfate) and evaporated *in vacuo* to yield a brown gummy residue which was chromatographed on silica gel (chloroform/methanol, 20:1) to furnish 119 mg (45%) of **3d** as a homogeneous semisolid.

I.R. (CHCl_3): no NH, $\text{C}=\text{O}$.

N.M.R. (CDCl_3): $\tau = 2.45$ – 2.95 (m, 4H, aromatics), 5.31 (s, 2H, $\text{N}-\text{CH}_2-\text{N}$), 7.02 (s, 4H, CH_2-CH_2), 7.58 (s, 3H, $\text{N}-\text{CH}_3$). The semisolid compound **3d** was converted into the methiodide which crystallized from ethanol/water to give pale yellow needles; m.p. 210–215°.

$\text{C}_{13}\text{H}_{16}\text{N}_2\text{BrJ}$ calc. C 38.33 H 3.93 N 6.88 J 31.20
found 38.68 4.27 7.03 32.04

U.V. (methanol): $\lambda_{\text{max}} = 291$ ($\epsilon = 5400$), 281 (7800), 273 (8600) m μ .

2-Methyl-1,2,3,4-tetrahydro-pyrimido[3,4-*a*]indole (**3a**):

To a slurry of lithium aluminum hydride (76 mg, 2 mmol) in dry tetrahydrofuran (25 ml) was added dropwise with stirring a solution of **3d** (132.5 mg, 0.5 mmol) in dry tetrahydrofuran (25 ml) and the reaction mixture was stirred at room temperature for 15 hr. Normal isolation procedure gave **3a** as a homogeneous oil; yield: 52 mg (85%).

I.R. (CHCl_3): no NH, $\text{C}=\text{O}$.

N.M.R. (CDCl_3): $\tau = 2.25$ – 3.05 (m, 4H, aromatics), 3.81 (s, 1H, indole-3H), 5.36 (s, 2H, $\text{N}-\text{CH}_2-\text{N}$), 7.15 (broad s, 4H, CH_2-CH_2), 7.43 (s, 3H, $\text{N}-\text{CH}_3$).

The methiodide crystallized from ethanol/ethyl acetate to give colorless needles; m.p. 195–200°.

$\text{C}_{13}\text{H}_{17}\text{N}_2\text{J}$ calc. C 47.56 H 5.19 N 8.53 J 38.72
found 47.24 5.47 8.58 38.51

U.V. (methanol): $\lambda_{\text{max}} = 292$ ($\epsilon = 5800$), 280 (7900), 272 (8500) m μ .

2-Methyl-1,2,3,4-tetrahydro-5*H*-pyrimido[4,3-*b*]indole (3-Methyl-1,2,3,4-tetrahydro- γ -carboline, **4**):

Compound **3a** (93 mg, 0.5 mmol) was dissolved in 50% aqueous acetic acid (15 ml) and heated on a steam bath for 4 hr. After basification with sodium carbonate, the reaction mixture was extracted with dichloromethane and the dichloromethane extract was washed with water and dried (sodium sulfate). Evaporation to dryness *in vacuo* left 74 mg (80%) of **4** which was shown to be identical to an authentic sample⁵ on the basis of comparison of N.M.R. spectra and m.p. and mixture m.p. determinations of the corresponding methiodide derivatives.

We are very grateful to the National Research Council of Canada and Bristol Laboratories for financial support.

Received: May 2, 1971

¹ A. Z. BRITTEN, G. F. SMITH, G. SPITELLER, *Chem. & Ind.* **1963**, 1492.

G. F. SMITH, M. A. WAHID, *Chem. & Ind.* **1963**, 4002.

K. BIEMANN, G. SPITELLER, *J. Amer. Chem. Soc.* **84**, 4528 (1962).

J. A. JOULE, G. F. SMITH, *J. Chem. Soc.* **1962**, 312; *Proc. Chem. Soc.* **1959**, 322.

P. N. EDWARDS, G. F. SMITH, *J. Chem. Soc.* **1961**, 1458.

G. F. SMITH, J. T. WROBEL, *J. Chem. Soc.* **1960**, 792.

² E. EBNÖTHER, P. NIKLAUS, R. SÜESS, *Helv. Chim. Acta* **52**, 629 (1969).

C. G. CATTANACH, A. COHEN, B. HEATH-BROWN, *J. Chem. Soc. [C]* **1971**, 359.

see also A. JACKSON, N. D. V. WILSON, A. J. GASKEL, J. A. JOULE, *J. Chem. Soc. [C]* **1969**, 2738.

³ R. A. ABRAMOVITCH, I. D. SPENSER, *Advan. Heterocyclic Chem.* **3**, 79 (1964).

⁴ A similar rearrangement was discovered by Ebnöther² in the reaction of **4** with butyllithium and diphenyliodonium chloride but the nature of the resulting product (**3b**) precludes attempts to effect further functionalization at C-5 and/or the reverse process **3**→**4**.

⁵ V. BOEKELHEIDE, C. AINSWORTH, *J. Amer. Chem. Soc.* **72**, 2132 (1950).