The Synthesis of 5,10-Dimethylnaphtho[2,3-c]pyridine (1)

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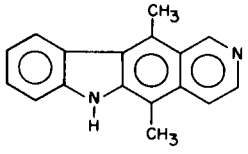
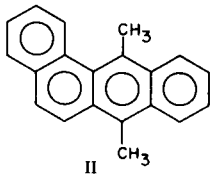
Considerable effort has been expended during the last few years in the synthesis and biological evaluation of isosteres of the indole alkaloids of the type ellipticine (I) (2) and 7,12-dimethyl-1,2-benzanthracene (II) (3). A desirable analog of these two systems for testing is 5,10-dimethylnaphtho[2,3-c]pyridine (III), described herein, in which the indole portion of the ellipticine molecule is replaced by a linearly fused benzene ring as in II.

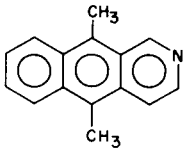
1,4-Dimethylnaphthalene (IVa) was brominated in good yield to 2-bromo-1,4-dimethylnaphthalene (IVb); however attempts to convert this compound to the corresponding aldehyde (IVc) by lithium exchange were unsuccessful. Formylation of IVa using the Rieche reagent butyl dichloromethyl ether (4) gave 2-formyl-1,4-dimethylnaphthalene (IVc) in high yield. That formylation had occurred in the substituted ring was shown by a sharp singlet (δ 7.52) in the 100 MHz nmr spectrum of IVc associated with H-3.



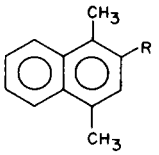
I



II



III



IVa) R = H
b) R = Br
c) R = CHO
d) R = $CH{=}NCH_2CH(OEt)_2$

Also the methyl resonances in IVc were resolved, the C-1 methyl group resonance being deshielded by *ca.* 40Hz from the corresponding resonance in IVa, consistent with an *ortho* related formyl group. Condensation of IVc with aminoacetaldehyde diethyl acetal gave 1,4-dimethyl-2-(2′,2′-diethoxyethylimino)methylnaphthalene (IVd) which upon cyclization in superphosphoric acid gave 5,10-dimethylnaphtho[2,3-c]pyridine (III) as yellow plates in 28% overall yield.

EXPERIMENTAL

Melting points were determined on a Bucci oil bath instrument and are uncorrected. Infrared spectra were determined on a Perkin Elmer Model 257 spectrometer. NMR spectra for which we thank Mr. D. Barraclough of the University of Salford were measured on a Varian H.A. 100 spectrometer (deuteriochloroform) and are relative to TMS (internal). In reporting the nmr spectra the following abbreviations are employed, s = singlet, d = doublet, dd = double doublet and m = multiplet. Integration of spectra were carried out routinely and in all cases support the given structures. Elemental analysis were performed by the University of Salford microanalytical laboratory.

2-Bromo-1,4-dimethylnaphthalene (IVb).

A solution of 1,4-dimethylnapthalene (5) (5.0 g., 0.032 mole) in carbon disulfide (50 ml.) was cooled to 0° and bromine (5.11 g., 0.032 mole), in carbon disulfide (10 ml.), was added dropwise with stirring over a thirty minute period. The resulting solution was allowed to stir until it reached room temperature. The solvent was removed, leaving a light yellow oil which was fractionally distilled *in vacuo*, b.p. 140-142°/0.2 mm. This oil was dissolved in absolute ethanol and cooled overnight, resulting in 5.7 g. (76%) of crystalline product, m.p. 51-53°. An analytical sample had a m.p. 53.5-54° (6).

Anal. Calcd. for $C_{12}H_{11}Br$: C, 61.30; H, 4.73; Br, 33.97. Found: C, 61.47; H, 4.87; Br, 33.93.

2-Formyl-1,4-dimethylnaphthalene (IVc).

Anhydrous stannic chloride (1.02 ml.) was added to a solution of IVa (0.91 g., 0.00583 mole) in methylene chloride (15 ml.) at 0°, and dichloromethyl butyl ether (1.36 g.) was added to the stirred solution over 5 minutes. The resultant pink solution was kept at 0° for 1 hour and then stirred at room temperature overnight. After pouring the mixture into water (80 ml.), the organic phase was separated and the aqueous phase extracted with methylene chloride (2 x 50 ml.). The combined extracts were washed with aqueous sodium bicarbonate, water and dried. Removal of the solvent gave a green solid which was crystallized from aqueous ethanol as colorless plates m.p. 84-85° (0.80 g., 73%). An analytical

sample has m.p. 87°; ir μ 5.97 (CHO) and 13.2 (sharp doublet, *ortho* substituted benzene); nmr δ 2.50 (s, 4-CH_3), 2.77 (s, 1-CH_3), 7.52 (s, 3-H), 7.46, 7.8 and 8.0 (Multiplets, H-5,6,7 and 8), and 10.33 (s, CHO). The spectrum of 1,4-dimethylnaphthalene had δ 2.37 (s, CH_3) 6.87 (s, H-2,3), 7.2 (m, H-5,8) and 7.68 (m, H-6,7).

Anal. Calcd. for $C_{13}H_{12}O$: C, 84.8; H, 6.52; M.W. 184. Found: C, 84.4; H, 6.55; M.W. 184 (Mass spectrometry).

1,4-Dimethyl-2-(2',2'-diethoxyethylimino)methylnaphthalene (IVd).

A mixture of IVc (8 g., 0.0435 mole) and aminoacetaldehyde diethyl acetal (9.26 ml.) was heated at 95-100° for 2 hours. Four portions of benzene (15 ml.) were added and distilled to remove traces of water. The resultant oil was crystallized from petroleum (b.p. 100-120°) with the aid of an acetone-solid carbon dioxide cooling bath (8.3 g., 65%) m.p. 43°; ir μ 6.06 (imine). An analytical sample of IVd had m.p. 46-47°.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.2; H, 8.4; N, 4.7. Found: C, 75.8; H, 8.4; N, 4.4.

5,10-Dimethylnaphtho[2,3-*c*]pyridine (III).

A sample of IVd (7 g., 0.0234 mole) was added with stirring to superphosphoric acid [prepared from orthophosphoric acid (90%) (140 g.) and phosphorus pentoxide (56 g.)] at 140°. The mixture was kept at this temperature for 0.5 hour and then poured onto ice (200 g.). The insoluble phosphate salt of the product was allowed to coagulate for one hour and then filtered. The phosphate was extracted with boiling 6*N* hydrochloric acid (2 x 200 ml.), filtered hot, basified with sodium hydroxide and extracted with methylene chloride (3 x 200 ml.). Removal of the solvent gave yellow crystals of III which were crystallized from benzene (3 g., 61%) m.p. 160-161.5°; ir μ 12.4 and 13.4; nmr δ 9.68 (d, $J_{1,3}$ 1 Hz; H-1), 8.31 (d, $J_{4,3}$ 6.5 Hz; H-4), 7.79 (dd, $J_{3,4}$ 6.5 Hz; $J_{3,1}$ 1 Hz; H-3), 7.43 and 8.18 (multiplets, H-5,6,7 and 8) and 3.03, 2.87 (singlets, C-9, C-10 methyls).

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.8; H, 6.3; N, 6.8; M.W. 207. Found: C, 86.6; H, 6.1; N, 6.4; M.W. 207 (Mass spectrometry).

REFERENCES

(1) Contribution No. 1911. This work was supported in part by Public Health Service Research Grant GM-10366 to Indiana University.

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(4) A. Rieche, H. Gross and E. Höft, *Chem. Ber.*, **93**, 88 (1960).

(5) Available from Aldrich Chemical Company, U.S.A.

(6) We are indebted for the bromination experiment to D. McClure, Indiana University Chemistry Laboratories.