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Formation of a 1,2-Azaphosphorine Under the Conditions of the Bischler-Napieralski Reaction

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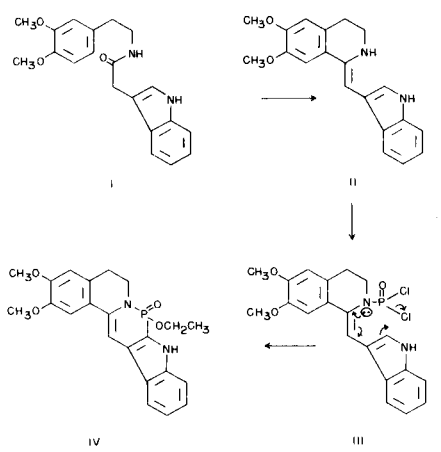
The normal product of the Bischler-Napieralski (1) cyclization of an amide such as I is a 3,4-dihydro-β-carboline which is in equilibrium with the methylidene form (II). However, on refluxing I in phosphorus oxychloride, followed by recrystallization from ethanol, we obtained a neutral compound which analyzed for the empirical formula of II plus a $PO_2C_2H_3$ residue. The infrared spectrum showed strong absorption at 1038 and 1202 cm^{-1} typical of P-O-C (aliphatic) and P=O groups (2). The ultraviolet spectrum (λ max (EtOH) mμ (ϵ) 215 (41,000), 267 (37,000), 310 (27,600)) indicated a more highly conjugated system than was present in the starting material.

CHART I



The elemental analysis and spectral data suggested that the unknown had been formed by a double condensation of phosphorus oxychloride with II followed by displacement of the remaining halogen by ethanol during recrystallization. It seemed probable that the initial condensation would occur on the basic nitrogen to give the phosphoramide (III). Subsequent cyclization onto the α-position of the indole nucleus now appeared likely since the high electronegativity of that position is even further enhanced by the vinyl nitrogen system in the β-position.

This proposal is substantiated by the pmr spectrum (3) of IV which shows the expected relative intensities, coupling constants, and chemical shifts (4). The hydrogen of the indole nitrogen appears at 9.00 ppm, one of the aromatic hydrogens of indole at 7.82 ppm (broad doublet, J = 6 cps), the other three at 7.17 ppm (unresolved multiplet), the hydrogen of the dimethoxybenzene ring adjacent to the double bond at 7.42 ppm and the other at 6.94 ppm, the olefinic hydrogen at 7.30 ppm (doublet, J_{PH} = 5 cps (5)) the methylene of the ester at 4.34 ppm (quintet, J_{PH} = 7 cps (6), J_{HH} = 7 cps) the hydrogens of the two methoxy groups at 3.80 and 3.90 ppm, the methylene adjacent to nitrogen at 3.66 ppm (two triplets, J_{PH} = 18 cps (7), J_{HH} = 7 cps) the benzyl hydrogens at 3.08 ppm (triplet, J = 7 cps) and the methyl group of the ester at 1.11 ppm (triplet, J = 7 cps).

The starting amide was obtained from the thermal condensation of homoveratryl amine and indole-3-acetic acid.

EXPERIMENTAL (8)

N-(3,4-Dimethoxyphenethyl)indole-3-acetamide (I).

A mixture of 71.5 g. of 3,4-dimethoxyphenethylamine and 64.2 g. of indole-3-acetic acid was heated at 175° for 20 hours under a stream of nitrogen. The reaction mixture was dissolved in chloroform. The chloroform solution was washed with 5% hydrochloric acid, 5% sodium carbonate solution, and water, dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from ethyl acetate gave 84 g. (63%) of a solid, m.p. 117-119°. Further recrystallization gave an analytical sample, m.p. 121-122.5°.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.70; H, 6.63; N, 8.57.

8-Ethoxy-5,6-dihydro-2,3-dimethoxy-9*H*-indolo[2,3-*c*]isoquino[1,2-*f*]-[1,2]azaphosphorine 8-Oxide (IV).

A solution of 15.0 g. of *N*-(3,4-dimethoxyphenethyl)indole-3-acetamide in 48 ml. of phosphorus oxychloride was refluxed for 20 hours. The reaction mixture was stripped *in vacuo* on the steam bath and the residue treated with 100 ml. of ethanol giving 4.2 g. of a solid, m.p. 300°. A solution of the solid in 700 ml. of ethanol was refluxed for 2.5 hours and then concentrated to 100 ml. On standing there was deposited 2.3 g. (13%) of a crystalline solid, m.p. 285.5-286.5°.

Anal. Calcd. for $C_{22}H_{23}N_2O_4P$: C, 64.38; H, 5.65; N, 6.83; P, 7.55. Found: C, 64.36; H, 5.88; N, 6.71; P, 7.82.

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(8) Melting points are corrected. 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.

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