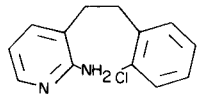
A 2-Aminopyridine Functioning As a Diene in a Diels-Alder Reaction

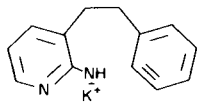
Lewis A. Walter

Medicinal Chemistry Research Department, Schering Corporation

In an attempted conversion of 2-amino-3-(*o*-chlorophenethyl)pyridine (I) to 5,6-dihydro-11*H*-pyrido[2,3-*b*]-1-benzazepine (III) (1) *via* the benzyne intermediate II in liquid ammonia, only acenaphthene (VI) and a mixture of 2-amino-3-(*o*- and *m*-aminophenethyl)pyridines were isolated. It is postulated that to obtain acenaphthene from this reaction, the anion II or its tautomer IV must have reacted as a diene in an intramolecular Diels-Alder condensation with the benzyne. The resulting intermediate V was not isolated and the "amidine" bridge was presumably eliminated during the reaction or its workup to give VI. The reaction of II with the solvent ammonia gave the aminophenethylpyridines.



I



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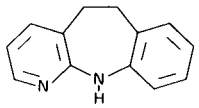
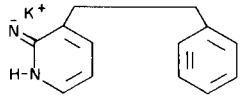
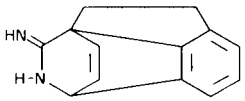


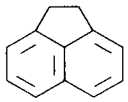
III



IV



V



VI

EXPERIMENTAL (2)

3-(*o*-Chlorophenethyl)picolinamide.

3-(*o*-Chlorophenethyl)picolinonitrile (3) (4), 20 g., m.p. 90-93°, was refluxed with 10 g. of sodium hydroxide in 200 ml. of 50% alcohol for 40 minutes. The methanol was removed *in vacuo* and the residue was chilled, filtered, and washed with water to give 18 g. (84%) of product, m.p. 119-120° after prolonged drying *in vacuo*.

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; N, 10.74. Found: C, 64.38; H, 5.31; N, 10.78.

Methyl *N*-2-[3-(*o*-chlorophenethyl)pyridyl]carbamate.

Sodium methylate from 3 g. of sodium in 150 ml. of methanol was cooled to 5° and 17 g. of finely powdered 3-(*o*-chlorophenethyl)picolinamide was added. The mixture was stirred vigorously and kept below 5° by a dry ice-acetone bath while 10.4 g. of bromine was added in 30 seconds. The mixture was kept at 0-5° until all the solid had dissolved and then was refluxed for two hours. The methanol was distilled and the residue triturated with water, filtered and washed. The product was crystallized from methanol, yield 15 g. (83%) m.p. 113-115°.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 61.96; H, 5.20; N. 9.63. Found: C, 61.70; H, 5.32; N, 9.63.

2-Amino-3-(*o*-chlorophenethyl)pyridine (I).

Methyl *N*-2-[3-(*o*-chlorophenethyl)pyridyl]carbamate (15 g.) and 200 ml. of concentrated hydrochloric acid were refluxed for 16 hours and evaporated to dryness *in vacuo*. The crude hydrochloride was crystallized from water, m.p. 132-134.5°.

Anal. Calcd. for $C_{13}H_{13}ClN_2 \cdot HCl$: C, 58.00; H, 5.24. Found: C, 58.18; H, 5.29.

The free base was crystallized from ether, m.p. 92-94°.

Anal. Calcd. for $C_{13}H_{13}ClN_2$: C. 67.09; H, 5.63; N, 12.04. Found: C, 67.23; H, 5.56; N, 11.83.

Reaction of 2-Amino-3-(*o*-chlorophenethyl)pyridine (I) with Potassium Amide.

Five grams of I, added in small portions to a stirred solution of the potassium amide from 3.5 g. of potassium in 300 ml. of liquid ammonia, gave a greenish-black mixture. After one hour, 7 g. of ammonium nitrate was added in small portions followed by 100 ml. of ether and the ammonia was evaporated. Ether (200 ml.) and 50 ml. of water were added, the aqueous layer and emulsion were separated, filtered, and extracted with additional ether. The combined extracts were dried (potassium carbonate), filtered and evaporated on a steam bath leaving 4.1 g. of brown semisolid residue. This material was stirred with 40 ml. of hot isopropyl ether, cooled, filtered and washed to give 2 g. of crystals, m.p. 100-110°, nitrogen content 19.24%. The nmr spectrum indicated it to be a mixture of 2-amino-3-(2-aminophenethyl)pyridine (1) and 2-amino-3-(3-aminophenethyl)pyridine. Repeated crystallization from benzene and from methanol gave the latter compound, m.p. 125-128°.

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.20; H, 7.08; N, 19.70. Found: C, 73.34; H, 7.29; N, 19.44.

Nmr spectra were taken on a Varian A-60A spectrometer in deuteriodimethylsulfoxide with tetramethylsilane (δ 0.00) as an internal standard. Signals are described as singlet (s), doublet (d), triplet (t), and quartet (q).

2-Amino-3-(3-aminophenethyl)pyridine, δ 7.82 q (H, 6-pyridyl, J 6,5 = 4.8, J 6,4 = 2); δ 7.32 q (H, 4-pyridyl, J 4,5 = 7); δ 6.95 t (H, 5-phenyl); δ 6.3-6.8 m (4H, 2,4,6-phenyl and 5-pyridyl); δ 5.6 broad s (2H, N); δ 4.8 broad s (2H, N); δ 2.70 s (4H, methylene).

2-Amino-3-(2-aminophenethyl)pyridine (1), δ 7.82 q (H, 6-pyridyl, J 6,5 = 5, J 6,4 = 2); δ 7.29 q (H, 4-pyridyl, J 4,5 = 7); δ 6.50 q (H, 5-pyridyl); δ 6.4-7.1 m (4H, phenyl); δ 5.6 broad s (2H, N); δ 4.7 broad s (2H, N); δ 2.69 s (4H, methylene).

The gummy residue from the isopropyl ether was dissolved in 5 ml. of benzene and chromatographed on 40 g. of alumina. Benzene eluted a rapidly moving yellow band and evaporation of the benzene eluate gave 1.2 g. of a yellow oil which solidified to a waxy solid, m.p. 73-90°, nitrogen 2.31%. Crystallization from acetonitrile, the only solvent found suitable, effected no purification. When sublimed at 60°/2mm. the wax gave 0.4 g. of pale yellow crystals, m.p. 92-93°. The color was not removed by repeated sublimation or by crystallization from acetonitrile.

The uv, infrared (chloroform) and nmr (deuteriochloroform) spectra of this solid were identical to those of acenaphthene, m.p. 95-95.5°, and a mixed m.p. was not depressed.

Anal. Calcd. for $C_{12}H_{10}$: C, 93.46; H, 6.54. Found: C, 93.15; H, 6.75.

Acknowledgment.

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REFERENCES

(1) Subsequently prepared by another procedure, see F. J. Villani and T. A. Mann, *J. Med. Chem.*, 11, 894 (1968).

(2) Melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

(3) Derivatives of 10,11-Dihydro-5*H*-Dibenzo[*a*,*d*]cycloheptenes III. "Aza Ketones," a paper presented by F. J. Villani, P. J. L. Daniels, C. A. Ellis, T. A. Mann and K. Wang before the Medicinal Division meeting of the American Chemical Society, New York, N. Y., Sept. 1966. A manuscript is in preparation for submission to the *J. Org. Chem.*

(4) *o*-Chlorobenzyl 3-pyridyl ketone, prepared from *o*-chlorophenyl acetonitrile by the general procedure of A. Burger and C. R. Walter, *J. Am. Chem. Soc.*, 72, 1988 (1950), was reduced (Wolff-Kischner) to 3-(*o*-chlorophenethyl)pyridine. The latter was oxidized and converted to the nitrile by the general method of W. E. Feeley and E. M. Beaver, *ibid.*, 81, 404 (1949).

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