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SYNTHESIS OF 2,3-DIMETHYL-1,4-DIAZACYCL[3.2.2]AZINE. A NOVEL HETEROAROMATIC SYSTEM

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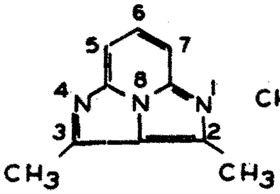
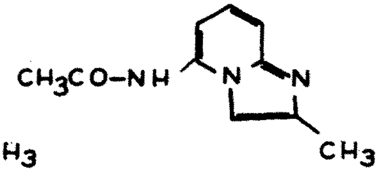
We wish to report reactions leading to a new heterocyclic system of 1,4-diazacycl[3.2.2]azine (I). We use the nomenclature proposed by V. Boekelheide in his definitive paper on cyclazines (1).

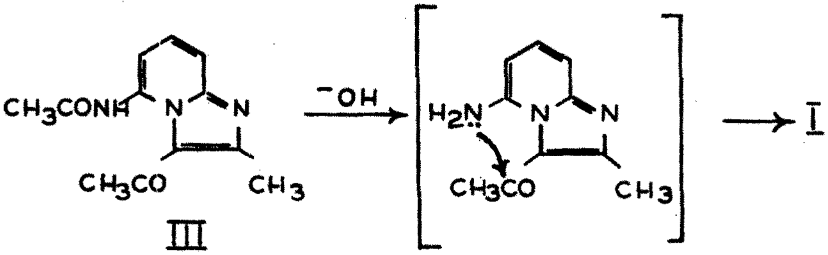
5-Amino-2-methylimidazo[1,2-a]pyridine (2) was acetylated with acetic anhydride. The reaction mixture was poured on ice and neutralized with ammonium hydroxide. Two products were obtained, the expected acetamide (II) and 5-acetamido-3-acetyl-2-methylimadazo[1,2-a]pyridine (III). The solution containing II and III was continuously extracted with ether. From the ether extract yellow needles of III, m.p. 145.5-146.5°, were obtained (0.54 g.; 17% yield). The compound fluoresced yellow in ultraviolet light. Its n.m.r. spectrum consisted of eleven lines (an AMX system with two overlapping lines) in the 7-8 p.p.m. region. There were also three separate bands at 2.25, 2.69 and 2.78 p.p.m., assigned to the methyl groups. The NH absorption was observed at an unusually low field, 12.66 p.p.m.


6
5
7
4
N
8
N
N
1
3
2
CH3
CH3

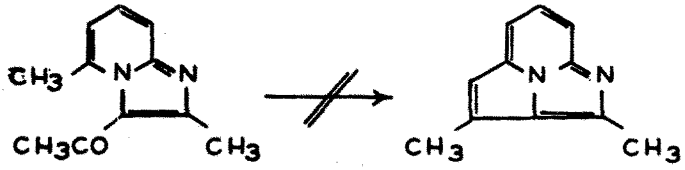
I


CH3CO–NH
N
N
CH3

II


CH3CONH
N
N
CH3CO
CH3
⁻OH
H2N
N
N
CH3CO
CH3
I

III


CH3
N
N
CH3CO
CH3
N
N
CH3
CH3

IV

Anal. Calcd. for $C_{12}H_{13}N_3O_2$ (Compound III): C, 62.34; H, 5.63; N, 18.18. Found: C, 62.12; H, 5.78; N, 18.07.

It is believed that compound III was formed by acetylation at position 3 in a Friedel-Crafts type of reaction. Such reaction is not unexpected since position 3 in the imidazo-[1,2-a]pyridine ring carries high electron density and is readily attacked by electrophilic reagents (3). The diacetyl compound III can also be obtained from the acetamide II on treatment with acetic anhydride.

The aqueous layer after extraction of III was evaporated to dryness and, from the residue, 5-acetamido-2-methylimidazo-1,2-a]pyridine (II) was extracted with ether. The yield was 1.39 g. 37%). Its n.m.r. spectrum consisted of two lines at 2.23 and 2.33 p.p.m. caused by absorption of the methyl groups. Eight lines are observed in the region of 6.6-7.6 p.p.m. with a total area proporional to four protons. The NH band occurs at 9.0 p.p.m.

5-Acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine III) (0.50 g.) was dissolved in 25% aqueous sodium hydroxide olution and alcohol mixture. The mixture was refluxed for one our, acidified with dilute hydrochloric acid and made slightly lkaline with ammonium hydroxide. The solution was evaporated to ryness and from the residue the reaction product, 2,3-dimethyl-1,4-iazacycl[3.3.2]azine (I) was extracted with carbon tetrachloride. was obtained in the form of yellow needles, m.p. 113-114° (from cyclohexane). The yield was 0.288 g. (77%). The compound I did not show fluorescence in ultraviolet light.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found C, 70.16; H, 5.79; N, 24.49. Ultraviolet absorption (solvent: absolute ethanol), λ_{max} in mμ and log ε: 377 (2.43) 343 (4.23); 337 (4.01) 320(sh) (3.81); 292 (4.02) 284 (4.01); 230 (5.00).

The structure of 2,3-dimethyl-1,4-diazacycl[3.2.2]-azine (I) is evident from the following data: 1) The n.m.r. spectrum contains seven lines in the aromatic region, at 8.16, 8.07, 8.00, 7.91, 7.77 and 7.70 p.p.m., forming a pattern characterisitc of an AB_2 system with an overlap of lines 5(B) and 6(B) and 7.85 p.p.m. The chemical shift of proton A, as given directly by line 3(A), is 8.00 p.p.m., whereas protons B would absorb at 7.81 p.p.m., if not modified by spin coupling. The coupling constant, J_{AB}, was calculated to be 7.98 c.p.s. (4). Preliminary molecular orbital calculations of electron densities in the 1,4-diazacycl[3.3.2]azine system indicate a lower electron density for position 6 than for positions 5 and 7, a result which is in accordance with the observed proton chemical shifts. A single absorption line with an area equivalent to six protons was observed at 2.95 p.p.m. indicating a symmetrical structure of I and magnetic equivalence of both methyl groups. 2) Mass spectrometric data indicate the correct molecular weight of 171, as well as the formula $C_{10}H_9N_3$.

This synthesis of I demonstrates that an amino group is capable of reacting with a carbonyl group at 3-position of the imidazo[1,2-a]pyridine system. It is worth noting that the carbonyl group in this position is deactivated for a nucleophilic attack. By contrast, it was not possible to induce an intramolecular cyclization between a methyl group and carbonyl group in 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine (IV) (5) to give a 1-azacycl[3.2.2]azine derivative.

2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide (1,3 g) which was obtained by the quaternization of 2-acetamido-6-methylpyridine with bromoacetone, was heated for 30 minutes with a saturated solution of sodium bicarbonate. On cooling of the solution, 3-acetyl-2,5-dimethylimidazo[1,2-a]-pyridine (IV) crystallized in flakes m.p.105^{o} (from abs. ethanol and hexane). Yield 0.45 g. (53%). Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.17; H, 6.53; N, 14.52. Molecular weight determined by mass spectrum: 188; formula $C_{11}H_{12}N_2O$. When IV was dissolved in tert-butyl alcohol and refluxed with sodium tert. -butoxide for several hours, there was no cyclization and the acetyl compound was recovered unreacted.

The NMR spectra of compounds I, II and III were run in deuterochloroform solution with TMS as internal standard on a Varian A-60 spectrometer.

Future efforts are being directed towards the synthesis of the unsubstituted parent compound, 2,4-diazacycl-

[3.32]azine, and a correlation of the proton chemical shifts with the calculated electron densities.

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