The Synthesis of 1,4-Diazacycl[3,2,2]azine

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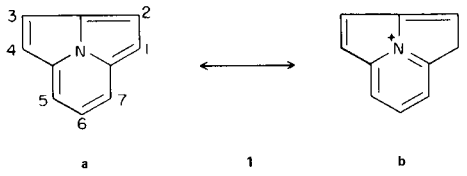
The diazaanalog of "cycl[3,2,2]azine", "1,4-diazacycl[3,2,2]azine" (1,4,7b-triazacyclopent-[*cd*]indene) and its 2-methyl derivative were prepared. These compounds are subject to facile acid-catalyzed hydrolysis affording substituted imidazo[1,2-*a*]pyridines.

Some years ago, Boekelheide and co-workers described the synthesis of a new heteroaromatic ring system, cycl-[3,2,2]azine (**1**) (1). This compound has been shown to

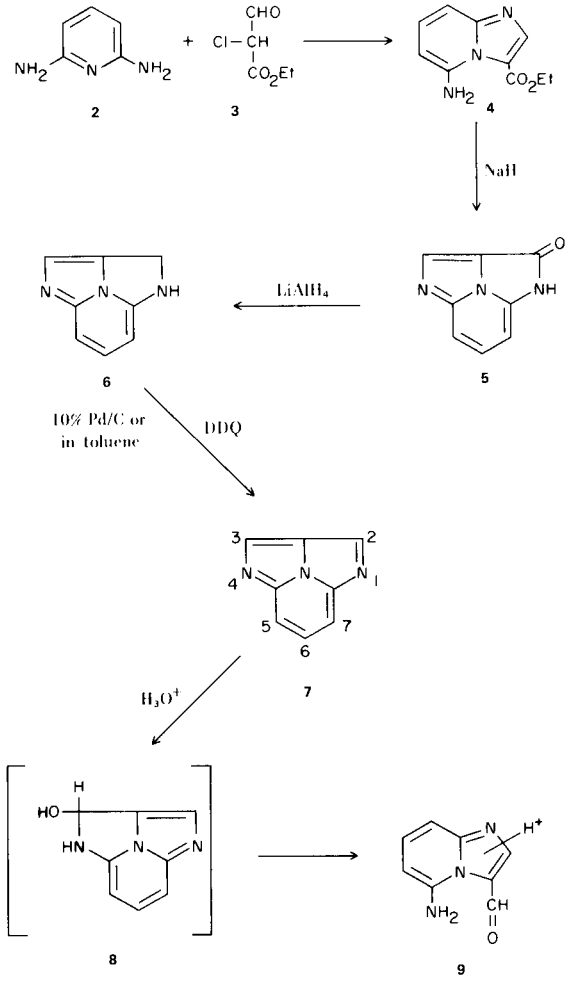


a 1 b

be "aromatic" in the sense that it undergoes electrophilic substitutions, at position 1 (4), and sustains a ring current when placed in a magnetic field. Resonance theory, and various LCAO approximations (Table I) place a substantial negative charge at positions 1 and 4 of this molecule, thus implicating structures such as b as contributing to the ground-state structure of this molecule (1,2).

We became interested in examining any changes in the properties of this type of heteroaromatic system that might occur when those carbon atoms (1 and 4) where an excess negative charge exists, are replaced by the inherently more electronegative nitrogen atoms. Thus we undertook to prepare the parent 1,4-diazacycl[3,2,2]-azine (**7**) (3) (Scheme I). In view of our experience dealing with the chemistry of polyazaindenes, the imidazo-[1,2-*a*]pyridine **4** appeared to be an attractive starting material containing all of the necessary carbon and nitrogen atoms. The synthesis of compound **4** was accomplished as shown in Scheme I with its structure being established by its elemental analysis, mass spectrometric molecular weight, pmr spectrum and mode of formation. The conversion of this amino ester to the lactam **5** occurs in high yield upon treatment with sodium hydride. Finally, reduction of this lactam to the 1,2-dihydro-1,4-diazacycl-[3,2,2]azine (**6**) and its dehydrogenation either with DDQ

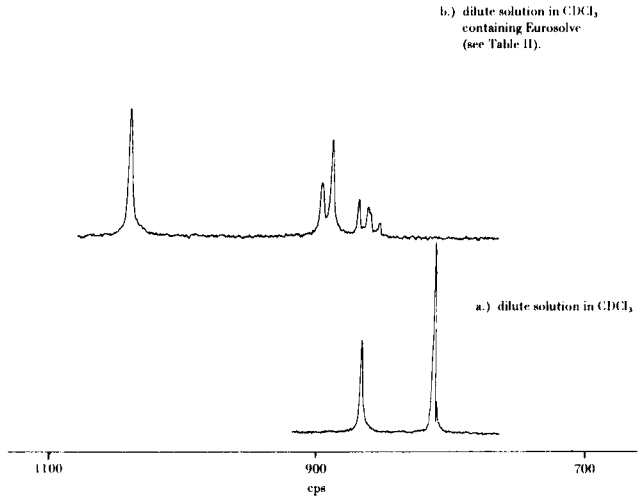
SCHEME I



or palladium-on-carbon affords a material which gives the correct elemental analysis and has the proper molecular weight expected for 1,4-diazacycl[3,2,2]azine (**7**).

However, to our surprise, the pmr spectrum of this compound (Figure 1) shows two apparent singlets in the ratio of 2:3. One would, of course, expect to see a two-proton singlet (due to H-2 and H-3) and an AB_2 system (due to H-5, 6 and 7).

FIGURE 1
100 MHz Spectra of 1,4-Diazacyclo[3,2,2]azine



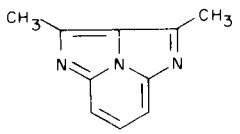
The advent of the development of "Eurosolve" (4) and related compounds afforded a means to decipher this fortuitously simple pmr spectrum. Upon addition of Eurosolve to a deuteriochloroform solution of 1,4-diazacycl[3,2,2]azine (**7**) one obtains the spectrum "expected" for this compound (Figure 1). The complexing agent affects the chemical shifts of the various protons in such a manner that H-5, 6 and 7 now appear as a second order AB_2 pattern (J_{AB} = 8.0 cps) (5). Thus, this technique dramatically confirms the structure of compound **7**.

The pmr spectrum (Table II) of the 1,4-diazacycl[3,2,2]-azine (**7**) in aqueous acid is not in agreement with that expected for this ring system since it is composed of two one-proton singlets and a three-proton ABX pattern. Furthermore, basification of the acidic solution and re-isolation of the organic material affords a compound whose molecular weight differs from that of compound **7** by the elements of water. This change in elemental composition is also supported by an elemental analysis of this material.

That we are dealing with 5-amino-imidazo[1,2-*a*]-pyridine-3-carboxaldehyde (**9**) is confirmed by its mass spectrum (loss of CO), infrared spectrum (ν C=O 1650 cm^{-1}), and a comparison of its pmr spectrum with that of compound **4**. All attempts to observe the probable intermediate, the carbinolamine **8** by means of pmr spectroscopy have, so far, failed. As soon as a catalytic amount of acid is added to a deuterium oxide solution of 1,4-diazacycl[3,2,2]azine (**7**), one obtains the spectrum typical of the amino-aldehyde **9**.

The great facility with which the 1,4-diazacycl[3,2,2]-azine is hydrolyzed by trace amounts of acid is in direct contrast to the reported stability of cycl[3,2,2]azine (**1**).

The only derivative of 1,4-diazacycl[3,2,2]azine which has been described in the literature is the 2,3-dimethyl derivative **10**, with no comment regarding its stability



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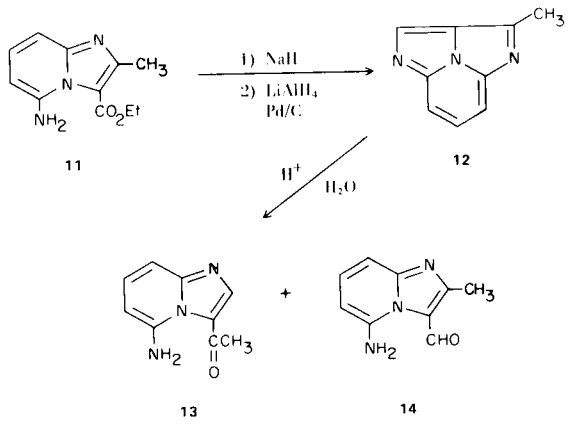
being offered (6). Since the presence of the methyl groups could conceivably decrease the ease of covalent hydration we decided to prepare 2-methyl-1,4-diazacycl[3,2,2]azine (**12**) in an attempt to examine the ease of hydrolysis on this compound. The mode of its formation (Scheme II) parallels the method described for the synthesis of the parent compound. The pmr parameters for this compound are listed in Table II.

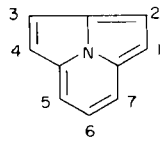
SCHEME II

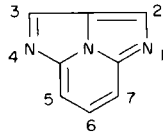


The 2-methyl-1,4-diazacycl[3,2,2]azine can, depending upon which of the 5-membered rings in structure **12** is more readily covalently hydrated, yield either compound **13**, **14** or both. Again, as in the case of the parent material, addition of a trace of acid to a deuterium oxide solution of 2-methyl-1,4-diazacycl[3,2,2]azine (**12**) results in destruction of the cyclazine skeleton. An analysis of the pmr spectrum of the hydrolysis product(s) showed that both 5-membered rings are subject to covalent hydration and that both of the possible hydrolysis products are formed. The relative proportions of compounds **13** to **14** are approximately 40:60 as determined by an

TABLE I

The Total and π-Electron Densities of
Cycl[3,2,2]azine and 1,4-Diazacycl[3,2,2]azine

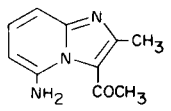




Position	Cycl[3,2,2]azine (1) Jackman (2) HMO	Cycl[3,2,2]azine (1) Boekelheide (1) HMO	This work CNDO/II	1,4-Diazacycl[3,2,2]azine (7) This work CNDO/II
1	1.096	1.168	4.089	5.226
2	1.008	1.062	3.979	3.887
3	1.008	1.062	3.979	3.887
4	1.096	1.168	4.089	5.226
5	1.000	0.997	4.043	4.062
6	1.016	1.043	3.945	3.928
7	1.000	0.997	4.043	4.062
8		1.196	5.078	5.117

analysis of the pmr spectrum. Consequently there is little reactivity difference between the alkylated and non-alkylated 5-membered rings.

This observation prompted us to examine the behavior of 2,3-dimethyl-1,4-diazacycl[3,2,2]azine (**10**) under acidic conditions. Again, we find that this material is hydrolyzed and yields compound **15**. However, in order to accomplish this, it is necessary to warm the acid solution. Consequently, the presence or absence of methyl substituents does not alter the acid stability of this ring system very seriously.



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Further studies which will, hopefully, delineate these stability factors in various aza analogs of cycl[3,2,2]azine are in progress.

EXPERIMENTAL (7)

5-Amino-3-carbethoxyimidazo[1,2-*a*]pyridine (**4**).

To a solution of ethyl α-chloroformylacetate (8) (**3**) (3 g., 20 mmoles) in 100 ml. of dioxane was added 2,6-diaminopyridine (2.2 g., 20.2 mmoles). The resulting mixture was stirred for 5 hours and the oily solid which separated was collected. This material was recrystallized from 95% ethyl alcohol to yield a crystalline material which was dissolved in water (200 ml.). The solution was then made basic with solid potassium hydroxide and the precipitate was collected. Recrystallization from 95% ethyl alcohol yielded needles (3.7 g., 90%; m.p. 147-149°) of 5-amino-3-carbethoxyimidazo[1,2-*a*]pyridine (**4**).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.54; H, 5.36; N, 20.48. Found: C, 58.84; H, 5.19; N, 20.73.

2-Oxo-1,2-dihydro-1,4-diazacycl[3,2,2]azine (**5**).

5-Amino-3-carbethoxyimidazo[1,2-*a*]pyridine (3 g., 14.6 mmoles) dissolved in 10 ml. of dried dimethylformamide was treated with sodium hydride (2 g., 50% oily dispersion). After the vigorously foaming and exothermic reaction had subsided, the reaction mixture was heated on a steam bath for 1 hour. Water (5 ml.) was then slowly added to this reaction mixture to decompose the excess sodium hydride and the resulting solution was washed with chloroform and the aqueous layer was acidified with concentrated hydrochloric acid. Finally, sodium bicarbonate was added to the acidic solution until a precipitate formed. The collected precipitate was recrystallized from absolute methanol to yield light tan crystals (1.2 g., 52%, m.p. 287°) of 2-oxo-1,2-dihydro-1,4-diazacycl[3,2,2]azine (**5**).

Anal. Calcd. for $C_8H_5N_3O$: C, 60.37; N, 26.42; H, 3.14. Found: C, 60.36; N, 26.26; H, 3.21.

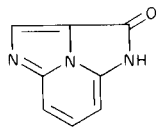
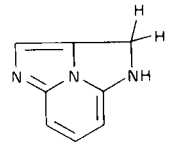
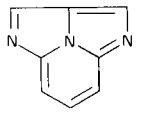
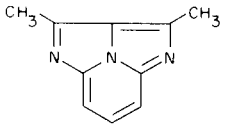
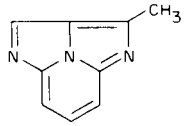
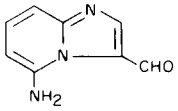
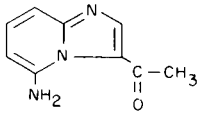
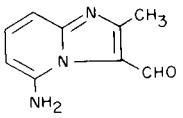
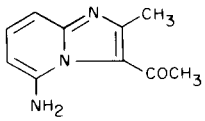
1,2-Dihydro-1,4-diazacycl[3,2,2]azine (**6**).

Two molar equivalents of lithium aluminum hydride (0.120 g., 3.3 mmoles) was added to 2-oxo-1,2-dihydro-1,4-diazacycl[3,2,2]-azine (0.25 g., 1.6 mmoles) dissolved in 200 ml. of dry tetrahydrofuran. The mixture was refluxed for 5 hours and ice was added very slowly. The inorganic material was removed by filtration and the filtrate was extracted with chloroform. The chloroform extracts were dried over anhydrous sodium carbonate, filtered and evaporated to dryness to yield yellow crystals (0.0928 g., 40%, m.p. 168°) of 1,2-dihydro-1,4-diazacycl[3,2,2]azine (**6**).

Anal. Calcd. for $C_8H_7N_3$: C, 66.21; H, 4.81; N, 28.96. Found: C, 65.98; H, 5.03; N, 28.67.

TABLE II

Pmr Parameters of Some 1,4-Diazacycl[3,2,2]azines and Related Compounds

Compound	Number	Chemical Shifts (τ) H_2	H_3	H_5	H_6	H_7	Substituent		Coupling Constant
	**5**	--	1.59	2.2	2.2	2.95	---	---	J_{56} = 8.0 cps J_{67} = 7.0 cps
	**6**	4.82	2.99	3.36	---	4.44	---	---	J_{56} = 8.0 cps J_{67} = 6.0 cps
	**7**	1.3	1.3	1.88	1.88	1.88	---	---	-----
Eurosolve Complex of **7** (a)		-0.05	-0.05	1.04	1.37	1.04	---	---	$J_{5,6}$ (7) 8.0 cps
	**10**	--	--	2.22	2.00	2.22	$-CH_3$	7.08	$J_{5,6}$ (7) 8.0 cps
	**12**	--	1.44	2.12	1.98	2.12	$-CH_3$	7.17	$J_{5,6}$ (7) 8.0 cps
	**9**	1.29	--	3.16	2.88	2.08	-CHO	0.4	J_{67} = 8.0 cps J_{78} = 8.0 cps
	**13** (b)	2.25	--	3.55	3.02	3.55	$-CH_3$	7.26	J_{78} = 8 cps J_{67} = 8 cps
	**14** (b)	--	--	3.55	3.02	2.41	$-CH_3$ -CHO	7.34 0.49	J_{78} = 8 cps J_{67} = 8 cps
	**15**	--	--	2.21	1.46	1.72	$-CH_3$ $-COCH_3$	7.12 7.04	J_{78} = 8 cps J_{67} = 8 cps

(a) Sample is made by dissolving 20 mg. of **7** in 0.5 ml. of chloroform and adding 20 mg. of Europium(III)-2,2,6,6-tetramethyl-heptanedionate. (b) Since both compounds were present in the same sample, chemical shift values for H_8, H_7, and H_6 are the averages between the two values.

1,4-Diazacycl[3,2,2]azine (**7**).

Procedure (a).

To 1,2-dihydro-1,4-diazacycl[3,2,2]azine (**6**) (2 g., 14 mmoles) in toluene, which had been dried by distillation from magnesium ethoxide, was added two molar equivalents of 2,3-dichloro-5,6-dicyanabenzoquinone (DDQ) (7.01 g., 27 mmoles) and the resulting suspension was refluxed for 1 hour. The precipitate was collected, dissolved in water and the solution was made basic with solid sodium hydroxide. This solution was then extracted with chloroform and evaporated to dryness to yield yellow crystals of 1,4-diazacycl[3,2,2]azine (**7**) (1.58 g., 75%, m.p. 217-218°).

Anal. Calcd. for $C_8H_5N_3$: C, 67.13; H, 3.50; N, 29.37. Found: C, 67.10; H, 3.39; N, 28.73.

Procedure (b).

To a solution of 1,2-dihydro-1,4-diazacycl[3,2,2]azine (**6**) (2 g.) in 100 ml. of dry toluene was added 2 g. of 10% Pd/C. The resulting suspension was refluxed under a nitrogen atmosphere for 2 hours, cooled, and filtered. The filtrate was evaporated to dryness to yield yellow crystals of 1,4-diazacycl[3,2,2]azine (**7**) (1.96 g., 96%, m.p. 217-218°).

5-Amino-3-carbethoxy-2-methylimidazo[1,2-*a*]pyridine (**11**).

To a solution of ethyl α-chloroacetoacetate (3.2 g., 20 mmoles) in 50 ml. of absolute ethanol was added 2,6-diaminopyridine (2.2 g., 20.2 mmoles). The resulting mixture was stirred for 12 hours and then refluxed for 4 hours. The solvent was evaporated until only a thick slurry remained. To this slurry was then added 31 ml. of a 30:1 mixture of chloroform and ethanol and the mixture was filtered. The collected solid was washed with a 30:1 chloroform-ethanol solution and recrystallized from 95% ethanol to yield a crystalline solid. This material was dissolved in 200 ml. of water and made basic with potassium hydroxide pellets and the precipitate was collected. Recrystallization from 95% ethanol yielded light tan crystals (3.18 g., 73%, m.p. 129-130°) of 5-amino-3-carbethoxy-2-methylimidazo[1,2-*a*]pyridine (**11**).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.27; H, 5.94; N, 19.17. Found: C, 60.74; H, 5.21; N, 19.34.

2-Oxo-1,2-dihydro-3-methyl-1,4-diazacycl[3,2,2]azine (**16**).

5-Amino-3-carbethoxy-2-methylimidazo[1,2-*a*]pyridine (**11**) (3.2 g., 14.6 mmoles) dissolved in 10 ml. of dried dimethylformamide was treated with sodium hydride (2 g., 50% oily dispersion). After the vigorously foaming and exothermic reaction had subsided, the reaction mixture was heated on a steam bath for 1 hour. Water (5 ml.) was then added slowly to this mixture to decompose the excess sodium hydride and the resulting solution was washed with chloroform. The aqueous layer was acidified with concentrated hydrochloric acid and sodium bicarbonate was added to the acidic solution until a precipitate formed. The collected precipitate was recrystallized from absolute methanol to yield light tan crystals (1.1 g., 43%, m.p. 300-301°) of 2-oxo-1,2-dihydro-3-methyl-1,4-diazacycl[3,2,2]azine (**16**).

Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.05; N, 24.28. Found: C, 62.23; H, 4.18; N, 24.19.

1,2-Dihydro-3-methyl-1,4-diazacycl[3,2,2]azine (**17**).

Lithium aluminum hydride (0.120 g., 3.3 mmoles) was added to 2-oxo-1,2-dihydro-3-methyl-1,4-diazacycl[3,2,2]azine (**16**) (0.28 g., 1.6 mmoles) in 200 ml. of dry tetrahydrofuran. The mixture was refluxed for 7 hours and ice was slowly added. The inorganic material was removed by filtration and the filtrate was extracted with chloroform (13 x 100 ml.). The combined chloroform extracts were dried over anhydrous sodium carbonate, filtered and evaporated to dryness to yield yellow crystals (0.089 g., 35%, m.p. 174-175°) of 1,2-dihydro-3-methyl-1,4-diazacycl[3,2,2]azine (**17**).

Anal. Calcd. for $C_9H_9N_3$: C, 67.92; H, 5.66; N, 26.42. Found: C, 68.07; H, 5.53; N, 26.49.

2-Methyl-1,4-diazacycl[3,2,2]azine (**12**).

To a solution of 1,2-dihydro-3-methyl-1,4-diazacycl[3,2,2]-azine (**17**) (2 g., 12.6 mmoles) in 100 ml. of dry toluene was added 2 g. of palladium-on-carbon. The resulting suspension was refluxed under a nitrogen atmosphere for 2 hours, cooled, and filtered. The filtrate was evaporated to dryness to yield yellow crystals of 2-methyl-1,4-diazacycl[3,2,2]azine (**12**) (1.62 g., 82%, m.p. 86-87°).

Anal. Calcd. for $C_9H_7N_3$: C, 68.79; H, 4.46; N, 26.75. Found: C, 68.84; H, 4.51; N, 26.65.

5-Amino-3-formylimidazo[1,2-*a*]pyridine (**9**).

To 1,4-diazacycl[3,2,2]azine (**7**) (0.25 g., 1.7 mmoles) dissolved in methanol (25 ml.) was added 3 ml. of concentrated hydrochloric acid and the solution was stirred overnight. The solvent was evaporated and the resulting solid was dissolved in water, made basic with 10% sodium hydroxide and extracted with chloroform (300 ml.). The chloroform solution was evaporated to dryness and the residue was sublimed to yield yellow crystals of 5-amino-3-formylimidazo[1,2-*a*]pyridine (0.261 g., 95%, m.p. 158-160°).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.34; N, 26.07. Found: C, 59.89; H, 4.62; N, 26.08.

REFERENCES

(1a) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 452 (1961), and earlier papers in this series. (b) The proper name for this compound is pyrrolo[2,1,5-*cd*]indolizine. However, we will utilize the cycl[3,2,2]azine system of nomenclature for the sake of more facile comparisons.

(2) L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Aust. J. Chem.*, 18, 1221 (1965).

(3) The proper name for this ring system is 1,4,7b-triazacyclopent[*cd*]idene, with the numbering of positions as indicated in structure **7**. For the sake of pointing out the similarity of this system with cycl[3,2,2]azine (**1**), we will refer to it as 1,4-diazacycl[3,2,2]azine (**7**).

(4a) J. K. M. Sanders and D. H. Williams, *J. Am. Chem. Soc.*, 93, 641 (1971). (b) "Eurosolve", is the trade name for Europium(III)-2,2,6,6-tetramethylheptanedionate.

(5) A note of caution should be inserted regarding the interpretation of coupling constants obtained in this fashion. These values may not be the same as those obtained for a non-complexed sample. Consequently, this coupling constant is only correct for this combination of compound to "resolving agent".

(6) K. Valentin and A. Taurins, *Tetrahedron Letters*, 3621 (1966).

(7) The nmr spectra were obtained with a Varian HA-100 spectrometer. Elemental analyses were done by Mrs. Victoria Gindlesperger of this department. Melting points were determined on a Thomas-Hoover Capillary Melting Point apparatus and are corrected.

(8) A. S. Elina and O. Yu. Magidson, *Zh. Obshch. Khim.*, 21, 780 (1951).

(9) D. B. Wyman, P. R. Kaufman, and W. R. Freeman, *J. Org. Chem.*, 29, 2706 (1964).