Synthesis of 2-Azacycl[3.2.2]azine

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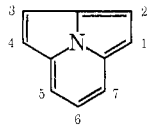
The synthesis of the aromatic 2-azacycl[3.2.2]azine is described. The results of CNDO/2 calculations point to the conclusion that the C_3–C_4 bond in this molecule seems to be only minimally involved in bond delocalizaiion with the remainder of the periphery.

Some years ago, Boekelheide and coworkers[1] prepared and studied the 10-π periphery aromatic cycl[3.2.2]azine (**1**).



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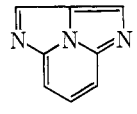
In view of the fact that resonance theory, as well as various LCAO approximations, place a substantial negative charge at positions 1 and 4 in the ground state of this molecule, we prepared the 1,4-diazacycl[3.2.2]azine (**2**) in order



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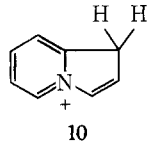
to examine its chemistry. To our surprise, we found this molecule to be readily hydrolyzed under rather mild acidic conditions.[2]

This result leads us to prepare 2-azacycl[3.2.2]azine (**8**) in an attempt to examine the effect that an sp^2 nitrogen has when it is in the 2 position of the cycl[3.2.2]azine (**1**) ring system rather than in the 1 position, as is the case in the 1,4-diazacycl[3.2.2]azine (**2**).

Since attempts at a cycloaddition of various dienophiles to imidazo[1,5-*a*]pyridine failed to produce the desired ring system, it was necessary to develop an alternate synthesis of 2-azacycl[3.2.2]azine (**8**). The sequence employed, and found useful, is delineated in Scheme I. The identities of the new compounds (**6**, **7**, and **8**) were established by means of elemental analyses, ^{1}H NMR and ir spectral identifications, as well as mass spectroscopy.

Compound **6** could be, in principle, either the 3- or 4-substituted compound (**9** or **6**). This substance can be envisioned to be formed by cyclization of the possible intermediate **13** or by formylation of the primary product (**8**) ex-



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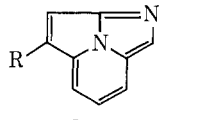
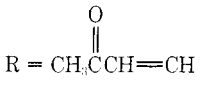
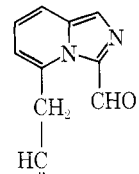


11, R = HC(=O)–C(C$_3$H$_7$)=CH–



12, R = CH$_3$C(=O)CH=CH



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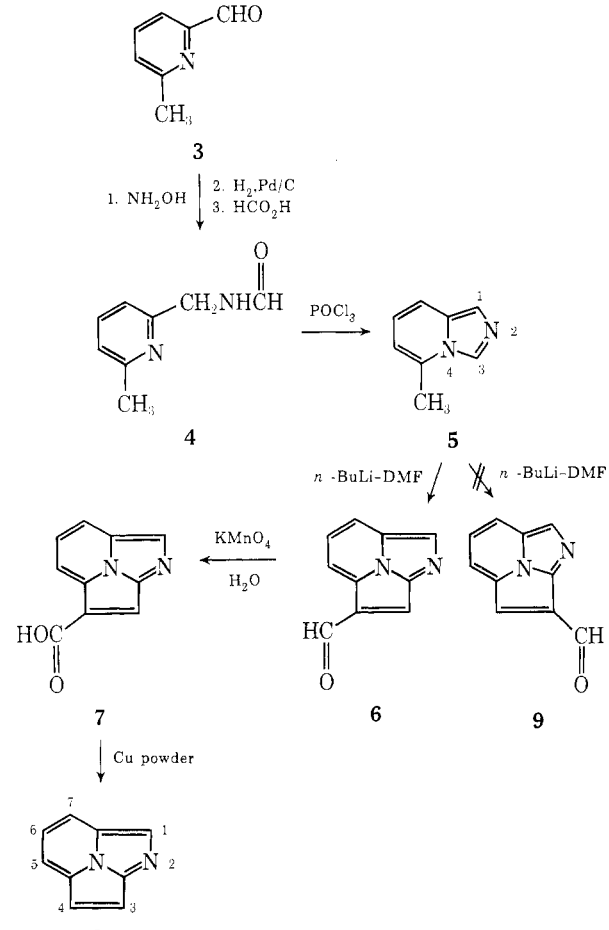
Scheme I[a]



[a] DMF = dimethylformamide.

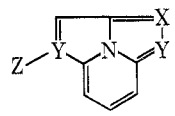
pected from the reaction of 5-methylimidazo[1,5-*a*]pyridine (**5**) with dimethylformamide in the presence of butyllithium.

In order to establish the structure of this formyl derivative (**6** or **9**), the ^{1}H NMR spectrum of the compound was compared with those of compounds **11** and **12**.

If the substituents in these compounds were at position **3**, we would not expect any changes in the chemical shift of H-5. However, if the substituents are at C_4, the chemical shifts of H-5 in the three compounds would differ. As the tabulation of the spectral parameters (see Table I) shows, H-5 differs significantly in the formyl derivative from the chemical shifts of H-5 in the derivatives **11** and **12**. Thus, we are dealing with the 4-formyl derivative **6**.

This information is of great help in identifying the chemical shift of H-5 in the parent compound, since we can obtain $J_{5,6}$ in the formyl derivative (8.0 Hz) and thus, anticipating no change in this coupling constant in going from **6** to **8**, we can analyze the ^{1}H NMR spectrum of the parent (**8**) keeping this in mind.

Table I
^{3}H NMR PMR Spectral Parameters of Some Cycl[3.2.2]azines[a]



1, X = Y = C; Z = H
2, X = C; Y = N; Z = H
8, X = N; Y = C; Z = H
6, X = N; Y = C; Z = CHO
11, X = N; Y = C; Z = CH=C[$(CH_2)_2CH_3$](CHO)
12, X = N; Y = C; Z = HC=CH($COCH_3$)

	Chemical shifts, ppm						
Compd	H_1	H_2	H_3	H_4	H_5	H_6	H_7
1	2.81	2.50	2.50	2.81	2.14	2.14	2.14
2		1.30	1.30		1.88	1.88	1.88
8	1.55		2.35	2.70	2.04	2.49	2.18
6	1.28		1.86		1.45	2.02	1.74
11	1.38		2.04		1.78	2.13	1.78
12	1.40		2.11		1.72	2.13	1.76

	Coupling constants, hz			
1	$J_{5,6} = 8.0$,	$J_{1,2} = 4.2$		
2	$J_{5,6} = 8.0$			
8	$J_{5,6} = 7.8$,	$J_{6,7} = 7.0$,	$J_{3,4} = 4.7$,	$J_{1,4} = 1.0$
6	$J_{5,6} = 8.0$,	$J_{6,7} = 7.5$		
11	$J_{5,6} = 8.0$,	$J_{6,7} = 7.5$		
12	$J_{5,6} = 8.0$,	$J_{6,7} = 7.5$		

[a] Dilute solutions in $CDCl_3$.

Unfortunately, the ^{1}H NMR spectrum of the parent 2-azacycl[3.2.2]azine 8 cannot be analyzed by first-order principles. Consequently, it was necessary to compute a matching theoretical spectrum. The chemical shifts and coupling constants so obtained are listed in Table I, while Figure 1 shows the experimental, as well as theoretical, spectrum of the compound.

The ^{1}H NMR parameters of 2-azacycl[3.2.2]azine (8), in comparison with those of cycl[3.2.2]azine (1) and of the 1,4-diaza analog 2, allow some intriguing speculations.

If it is assumed that the ring current contribution in these three compounds is very similar, we can suggest that any differences in the chemical shifts of H_5, H_6, and H_7 between these compounds will, by and large, be a reflection of differences in the electron densities of C_5, C_6, and C_7.

A comparison of the ^{1}H NMR spectra of cycl[3.2.2]azine (1) with those of the 2-aza analog reveals their great similarity except for the expected greater deshielding of H-1 ($\Delta\delta$ 1.26) observed in the aza derivative 8, a value which is typical for the anisotropic contribution of sp^2 nitrogens to the chemical shift of protons on adjacent carbon atoms. The other difference is the chemical shift of H_3 in compound 8 as compared to H_3 (H_2) in cycl[3.2.2]azine (1). This proton is more deshielded by 0.15 ppm in the aza derivative 8. This is, of course due to the anisotropic effect of the lone pair of electrons on N_2 in compound 8 upon the peri-situated H-3. This peri effect has been previously described to be of this magnitude. It is of interest that H_5, H_6, and H_7 in 1,4-diazacycl[3.2.2]azine (2) are all more deshielded, implying a lower electron density at C_5, C_6, and C_7, than the similar protons in compounds 1 and 8. Thus, the presence of the two nitrogen atoms at positions 1 and 4 accommodate the negative charges more effectively than the corresponding carbon atoms in compounds 1 and 8.

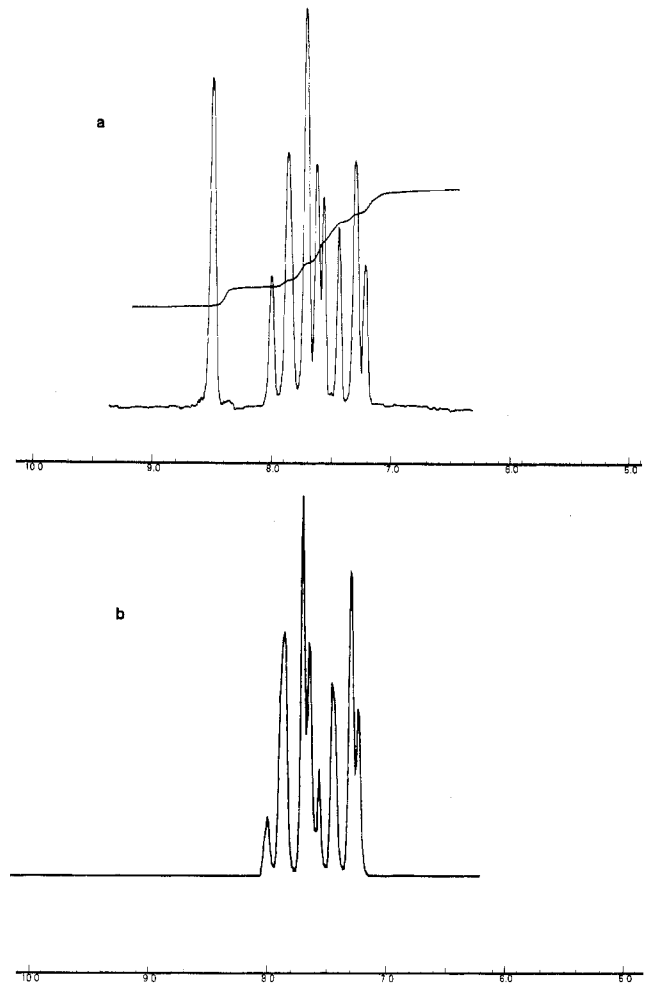
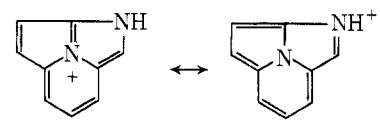


Figure 1. ^{1}H NMR spectra of 2-azacycl[3.2.2]azine: a, experimental spectrum, dilute solution in $CDCl_3$; b, computer-simulated spectrum without H-1.

The ^{1}H NMR spectrum of 2-azacycl[3.2.2]azine (8) in deuteriotrifluoroacetic acid (DTFAA) is instructive in determining the site of protonation to be N_2 rather than C_3 as is the case in the related pyrrocoline (10), since, upon basification of the DTFAA solution with sodium carbonate, the ^{1}H NMR spectrum in $CDCl_3$ of the recovered 2-azacycl[3.2.2]azine (8) is unchanged from the original spectrum.

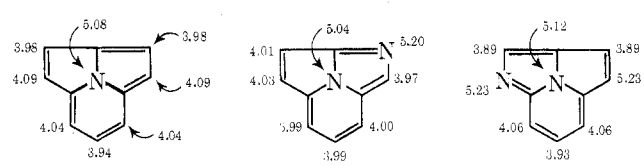
Thus, the protonated species of compound 8 is probably best represented by a resonance hybrid of **8a** and **8b.**



8a 8b

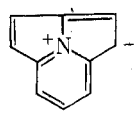
CNDO/2 Calculations. It is instructive to compare the results of CNDO/2 calculations on the three cyclazines, **1, 2,** and **8,** in an attempt to examine the effects that the various nitrogen atoms in the periphery have upon the electron densities and other properties.[3]

The total electron densities at the various position for these compounds are indicated in the following structures.



1 8 2

In none of these compounds is there an electron withdrawal from the central nitrogen atom, thus resonance-contributing structures such as

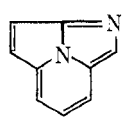


need not be considered for ground-state arguments. Quite to the contrary, there is a slight electron drift toward the central nitrogen atom, with the least pronounced one being in compound 8 and the most pronounced one in compound 2.

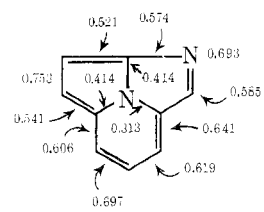
As expected, the peripheral nitrogens in compounds 2 and 8 have a substantial excess electron density. This excess density clearly derives largely from electron depletion from the carbon atoms adjacent to the periphery nitrogens.

The electron densities at the remaining carbon atoms are, not surprisingly, the same for the three cyclazines (1, 2, and 8). The great similarity of these ground-state electron densities precludes any possible predictions in terms of the expected patterns of electrophilic substitution, other than to suggest that position 1 might well be the most susceptible one toward this type of reaction.

2-Azacycl[3.2.2]azine (8), in contrast to compounds 1 and 2, has two different resonance-contributing structures, 8a and 8b.



8a

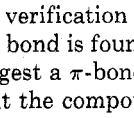


CNDO / 2 Bond orders are given

8b

An examination of the CNDO/2 bond orders given on structure 8b reveals that the size of the C_3–C_4 values is "unusually" large (indicating a "strong" double bond), and that the bond orders of the bonds emanating from the central nitrogen are rather small. This clearly displaces any thought that these bonds have any double-bond character.

Some experimental verification for the existence of a rather localized double bond is found in the size of $J_{3,4}$ (4.7 Hz), a value which suggest a π-bond order of 0.8.[5,6] Consequently, it appears that the compound should probably be written as follows (the dotted lines indicate π–π overlap of significant extent).



Thus, in terms of resonance theory, structure 8a is the more appropriate representation for this new cycl[3.2.2]-azine.

Experimental Section[4]

2-Formaldoximo-6-methylpyridine. To 6-methyl-2-pyridine carboxaldehyde (6.05 g, 0.05 mol) dissolved in 10 ml of water was added a solution of hydroxylamine hydrochloride (7.0 g, 0.1 mol) in 20 ml of water. The solution was made basic with K_2CO_3 and heated gently for 3 hr. After cooling, the brown solid was separated by filtration, washed with water, and recrystallized from EtOH–H_2O to afford 6.10 g (90%) of the pure formaldoxime: mp 170–171°; NMR (DMSO) δ 8.32 (s, 1 H), 7.92–7.7 (m, 2 H), 7.40 (d, 1 H, J = 6 Hz), 2.72 (s, 3 H, CH_3); mass spectrum m/e 136 (M^+), 118 ($M^+ - 18$), 106 ($M^+ - 30$), 92 ($M^+ - 44$).

Anal. Calcd for $C_7H_8N_2O$: C, 61.76; H, 5.89; N, 20.06. Found: C, 61.37; H, 5.86; N, 20.49.

6-Methyl-2-aminomethylpyridine. 2-Formaldoximo-6-methylpridine (6.8 g, 0.05 mol) was dissolved in 200 ml of absolute methanol and 10% Pd/C (0.7 g) was added to the solution. The mixture was hydrogenated in a Parr hydrogenation apparatus at room temperature and at 40 psi for 3 hr. Most of the hydrogen was taken up after 1 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure in order to remove the solvent. The remaining liquid was distilled under vacuum to afford a colorless liquid boiling at 55–57° (0.1 mm) (5.7 g, 94%) which rapidly turns yellow: NMR (D_2O) δ 7.71 (t, 1 H, J = 8 Hz), 7.26 (d, 1 H, J = 8 Hz), 7.07 (d, 1 H, J = 8 Hz), 3.91 (s, 2 H, $-CH_2-$), 2.54 (s, 3 H, CH_3), 5.13 (s, 2 H, $-NH_2$); mass spectrum (70 eV) m/e 122 (M^+), 121 ($M^+ - 1$), 107 ($M^+ - 15$), 93 ($M^+ - 29$).

6-Methyl-2-formamidomethylpyridine (4). To 6-methyl-2-aminomethylpyridine (6.8 g, 0.0557 mol) was added slowly with stirring 12 ml of 88% formic acid. The mixture was refluxed for 12 hr. Removal of the excess formic acid and fractional distillation in vacuo of the remaining liquid gave a yellow oil boiling at 118° (0.1 mm), which solidifies upon standing (7.0 g, 89.6%): ^1H NMR ($CDCl_3$), δ 8.26 (s, 1 H, –CHO), 7.50 (t, 1 H, J = 8 Hz), 7.02 (d, 2 H, J = 8 Hz), 4.51 (d, 2 H, J = 5 Hz), 2.47 (s, 1 H); mass spectrum (70 eV) m/e 150 (M^+), 120 ($M^+ - 30$), 106 ($M^+ - 44$).

Anal. Calcd for $C_8H_{10}N_2O$: C, 64.00; H, 6.68; N, 18.64. Found: C, 64.12; H, 6.78; N, 18.65

5-Methylimidazo[1,5-*a*]pyridine (5). To a stirred solution of 6-methyl-2-formamidomethylpyridine (4, 35.0 g, 0.233 mol) in 200 ml of dried benzene (distilled from sodium) was added dropwise freshly distilled phosphorus oxychloride (72 ml). The mixture was refluxed for 7 hr, and the excess $POCl_3$ and solvent were removed by distillation under reduced pressure. The remaining liquid was hydrolyzed at 0° with ice–water followed by basification with concentrated ammonium hydroxide. The solid which is formed was solubilized by addition of water (25 ml). The oily layer was separated by decantation and the aqueous layer was extracted with chloroform (2 × 150 ml). The two fractions (oil and extract) were combined, dried over anhydrous sodium carbonate, and distilled in vacuo. The product (5) is thus obtained as a pale yellow liquid boiling at 95–98° (0.1 mm) (23.87 g, 78%): ^1H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.40 (s, 1 H), 7.20 (d, 1 H, J = 9 Hz), 6.46 (dd, 1 H, J = 9, 7 Hz), 6.13 (d, 1 H, J = 7 Hz); mass spectrum (70 eV) m/e 132 (M^+), 131 ($M^+ - 1$), 104 ($M^+ - 28$), 92 ($M^+ - 40$).

Anal. Calcd for $C_8H_8N_2$: C, 72.72; H, 6.06; N, 21.21. Found: C, 72.78; H, 6.11, N, 21.07.

4-Formyl-2-azacycl[3.2.2]azine (6). To a stirred solution of 45 ml of 2 *M* BuLi (0.0908 mol) in 20 ml of sodium-dried tetrahydrofuran (THF) was added tetramethylethylenediamine (TMEDA, 10.53 g, 0.0908 mol) under a N_2 atmosphere and at −15°. Then 5-methylimidazo[1,5-*a*]pyridine (5 g, 0.0379 mol) in 20 ml of dried THF was added to the solution. After 1 min, a solution of dried dimethylformamide (DMF, 5.52 g, 0.0758 mol) in 20 ml of THF was added at once. The resulting dark blue solution was warmed to room temperature and stirred for an additional 15 min. Water (100 ml) was then added and the mixture was extracted with chloroform (3 × 150 ml). The combined extracts were dried over anhydrous Na_2CO_3 and filtered and the solvent was removed under reduced pressure. The resulting brown solid was chromatographed over Al_2O_3 (grade III) and eluted with a 25:75 mixture of *n*-hexane–benzene. The third fraction gave a yellow solid (0.950 g, 14.6%): mp 156–157°; ^1H NMR, see Table I; mass spectrum (70 eV) m/e 170 (M^+), 169 ($M^+ - 1$),141 ($M^+ - 29$), 115 ($M^+ - 55$); ir (Nujol) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.52; N, 16.47. Found: C, 70.52; H, 3.42; N, 16.39.

2-Azacycl[3.2.2]azine-4-carboxylic Acid (7). To 4-formyl-4-azacycl[3.2.2]azine (0.1 g, 0.588 mmol) dissolved in 10 ml of pure acetone (distilled over $KMnO_4$) was added 5 ml of water. Solid $KMnO_4$ (220 mg, 1.4 mmol) was then added in five approximately equal portions with stirring until the purple color remained. The mixture was the treated with a small amount of solid sodium bisulfite to eliminate the excess $KMnO_4$. The mixture was filtered by suction through a pad of Celite and the brown cake was washed with several portions of acetone and hot water. The reddish solution was decolorized with activated charcoal and concentrated to a small volume. Aqueous HCl (5%) was then added carefully until no more yellow solid precipitated (pH ~5). The yellow solid was separated by filtration and washed with a small amount of saturated aqueous NaCl solution. Recrystallizations from DMSO–H_2O gave a yellow solid (80 mg, 73%) which decomposes at its melting point

(274–275°): mass spectrum (70 eV) *m/e* 186 (M^+), 169 ($M^+ - 17$), 141 ($M^+ - 45$), 114 ($M^+ - 72$); ir (KBr) 2530 (OH), 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.51; H, 3.23; N, 15.05. Found: C, 64.32; H, 3.25; N, 14.98.

2-Azacycl[3.2.2]azine (Imidazo[2,1,5-*cd*]indolizine, 8). In a 25-ml distillation flask, fitted with a short-path condenser, was placed a mixture of 2-azacycl[3.2.2]azine-4-carboxylic acid (520 mg, 2.79 mmol) and copper powder (600 mg). The flask with its content was cautiously heated with a flame; a reddish liquid was collected on the walls of the flask and the condenser. This liquid was recovered by dissolving it in anhydrous ethyl ether. The liquid was chromatographed over alumina (grade III) and eluted with petroleum ether to give a fluorescing yellow liquid (340 mg, 85.5%), bp 116–118° (0.2 Torr), which darkens eventually: ^1H NMR, see Table I; mass spectrum (70 eV) *m/e* 142 (M^+), 115 ($M^+ - 27$).

Anal. Calcd for $C_9H_6N_2$: C, 76.05; H, 4.22; N, 19.73. Found: C, 74.91; H, 4.58; N, 19.24.

Preparation of Compound 12.[8] To a stirred solution of 4-formyl-2-azacycl[3.2.2]azine (0.102 g, 0.72 mmol) in 20 ml of pure acetone was added a basic solution of Ag_2O (prepared from 270 mg of $AgNO_3$ in 4 ml of water and 127 mg of NaOH in 4 ml of water). The mixture was stirred at room temperature for 1.5 hr, and the filtrate was concentrated under reduced pressure. Acidification with 5% HCl to pH 5 and evaporation of the solution to dryness gave a dark red solid, which was further purified by sublimation to afford a fluorescing red-brick solid (110 mg, 88%): mp 159–161°; ^1H NMR, see Table I; mass spectrum (70 eV) *m/e* 210 (M^+), 195 ($M^+ - 15$), 167 ($M^+ - 43$), 140 ($M^+ - 70$); ir (Nujol) 1650 [M^{-1} (>C=O)], 1605 cm^{-1} (>C=C<), enhanced absorption.

Anal. Calcd for $C_{13}H_{10}N_2O$:C, 74.29; H, 4.76; N, 13.33. Found: C, 74.15; H, 4.80; N, 13.37.

Preparation of Compound 11.[7] To a stirred solution of 20.7 ml of 2 *M* BuLi (in hexane) and 20 ml of anhydrous ethyl ether was added imidazo[1,5-*a*]pyridine (1.085 g, 8.22 mmol) in 20 ml of THF and under a N_2 atmosphere at 0°. Then DMF (2.4 g, 32.9 mmol) in ether was added at once and the mixture was stirred for an additional 15 min. The reaction mixture was treated with 10 ml of water, acidified with 5% HCl, and washed with ethyl ether. The aqueous layer was made basic with anhydrous Na_2CO_3 and extracted with chloroform. Evaporation of the solvent under reduced pressure gave a dark solid which was chromatographed (neutral Al_2O_3 grade III) and eluted with a 27:75 mixture of hexane–benzene. The second fraction afforded a highly fluorescing reddish solid (55 mg, 3.5%): mp 162–163°; ^1H NMR, see Table I; mass spectrum (70 eV) *m/e* 238 (M^+), 239 ($M^+ - 1$), 209 ($M^+ - 29$), 181 ($M^+ - 57$), 155 ($M^+ - 83$), 142 ($M^+ - 96$); ir (Nujol) 1655 (>C=O), 1605 cm^{-1} (>C=C<).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.88; N, 11.75. Found: C, 75.56; H, 6.11; N, 11.47.

Registry No.—**1**, 209-81-4; **2**, 10558-77-7; **3**, 1122-72-1; **3** oxime, 1195-40-0; **4**, 54384-88-2; **5**, 6558-64-1; **6**, 54446-41-2; **7**, 54384-89-3; **8**, 54384-90-6; **11**, 54384-91-7; **12**, 54384-92-8; hydroxylamine hydrochloride, 5470-11-1; 6-methyl-2-aminomethylpyridine, 6627-60-7.

References and Notes

(1) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 452 (1961), and earlier papers in this series.
(2) W. W. Paudler, R. A. VanDahm, and Y. N. Park, *J. Heterocycl. Chem.*, **9**, 81 (1972).
(3) The CNDO/2 calculations were done on the University of Alabama Univac 1110. The bond lengths used were those determined for 1,4-dibromocycl[3.2.2]azine: A. W. Hanson, *Acta Crystallogr.*, **14**, 124 (1961).
(4) The ^1H NMR spectra were obtained with a Varian HA-100 spectrometer. Elemental analyses were done by the Analytical Services Laboratory of the University of Alabama chemistry department.
(5) We wish to thank a referee for bringing this to our attention.
(6) W. B. Smith, W. H. Watson, and S. Chirangeevi, *J. Am. Chem. Soc.*, **89**, 1438 (1967).
(7) Compound **11** was obtained during the course of our investigation on the reaction of 5-methylimidazo[1,5-*a*]pyridine with BuLi and DMF. It was found that by using a 1:5:1 ratio of the reactants the main product was compound **11**. No attempt was made to improve the yield.
(8) Compound **12** was obtained during one attempt to oxidize the 4-formyl derivative (**6**) with basic silver oxide when acetone was used as solvent.

Hydrazinolysis of 1-Phenylethane Diazotate. A New Synthesis of 1-Phenylethylhydrazine (Mebanazine)[1]

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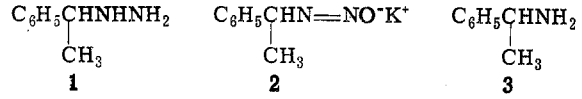
Conversion of 1-phenylethylamine to 1-phenylethane diazotate, followed by treatment of the diazotate with hydrazinium sulfate in anhydrous hydrazine, afforded 40% 1-phenylethylhydrazine (isolated as the oxalate), 35% styrene, and 15% 1-phenylethanol. Starting with optically active 1-phenylethylamine, optically active 1-phenylethylhydrazine was obtained with 54% net inversion of configuration and optically active 1-phenylethanol was obtained with 66% net retention of configuration. In peripheral experiments, optically active 1-phenylethylhydrazine and 1-phenylethylamine were catalytically reduced to optically active 1-cyclohexylethylamine.

Although the synthesis of monoalkylhydrazines is problematical,[3] a number of practical methods exist. These include the direct alkylation of hydrazine or hydrazine hydrate,[4] reaction of azines with Grignard reagents,[5] conversion of alkylamines to sydnones and thence to alkylhydrazines,[6] amination of alkylamines with chloramine[7] or hydroxylamine-*O*-sulfonic acid,[8] and syntheses of *N*-alkyldiaziridines (which may be cleaved to monoalkylhydrazines).[9,10]

For another project, we required substantial quantities of (optically active) 1-phenylethylhydrazine (**1**).[11] *Racemic*



1 **2** **3**

1 has been prepared from *N*-1-phenylethyl-*N,N'*-dicarboethoxyhydrazine,[12] and also by the direct alkylation of hydrazine or its hydrate with 1-phenylethyl halides,[13] by the catalytic reduction of acetophenone azine,[14] and by reaction of acetaldehyde azine with phenylmagnesium bromide, followed by hydrolysis of the resulting acetaldehyde 1-phenylethylhydrazone.[5] However, the only reported preparation of optically active **1** appears to be that of Kopecky and Gillan, who prepared (*S*)-(−)-**1** from (*S*)-(−)-1-phenylethylamine in 8% yield via amination with hydroxylamine-*O*-sulfonic acid.[15]

The poor yield afforded by this procedure led us to develop an alternative synthesis. Because ammonolysis of optically active 1-phenylethane diazotate (**2**) affords 1-phenylethylamine (**3**) with 46% net inversion,[16] we anticipated