

Table I. Decomposition of *t*-Butylperoxy Formate by 2,6-Lutidine in Frozen *p*-Xylene Solutions

Run	Concn. TBF, $M \times 10^2$	Concn. base, $M \times 10^2$	Temp., °C.	$k_{\text{obsd.}} \times 10^6$ sec. ⁻¹
1 ^a	2.92	1.12	0.0	46.2
2 ^b	2.92	1.12	0.0	50.2
3 ^c	2.57	0.0386	0.0	2.69
4 ^d	2.88	0.0773	0.0	4.82
5	3.08	1.16	11.0	8.56
6	3.08	1.19	6.0	33.5
7	3.08	1.19	2.0	52.4
8	3.05	1.16	-10.0	36.1
9	3.09	1.25	-20.0	19.3
10	3.05	1.16	-30.0	7.61
11 ^e	3.0	1.2	0.0	0.23
12	3.05	2.06	0.0	62.4
13	3.05	4.98	0.0	77.0
14	2.82	7.50	0.0	85.7
15	2.93	1.63	0.0	60.8
16	29.2	1.49	0.0	9.09
17	3.02	1.19	0.0	45.3
18 ^f	3.02	1.19	0.0	24.1
19 ^g	3.01	1.19	0.0	10.3
20 ^h	3.05	1.19	0.0	11.1
21 ⁱ	3.05	1.19	0.0	10.2

^a Samples, ca. 2 ml., frozen slowly by seeding at +8°. ^b Samples, ca. 0.5 ml., frozen at -195°. ^c Followed to 60% decomposition. ^d Followed to 87% decomposition. ^e Calculated for reaction at the given concentration of 2,6-lutidine in *p*-xylene from $\Delta H^* = 12.3$ kcal., $\Delta S^* = -30.5$ e.u., obtained for second-order rate constants measured at 90, 70, and 50°. ^f Solution contains 0.0149 *M* benzene. ^g 0.0571 *M* benzene. ^h 0.0473 *M* carbon tetrachloride. ⁱ 0.0368 *M* heptane.

(relative concentration) against time, followed usually to 90% decomposition. (B) Observed rate constants were independent of the method of freezing samples (see runs 1 and 2). (C) Even 2.6% 2,6-lutidine relative to the initial TBF concentration resulted in complete loss of the peroxide (runs 3 and 4). (D) The rate of reaction in frozen *p*-xylene solutions is a maximum at ca. +2° but reaction occurs at +12° and at -30° (however not at -70°) at greater rates than those calculated for the reaction in liquid at the given lutidine concentrations (see runs 5-10). (E) For constant initial peroxide concentration and low 2,6-lutidine concentrations the observed rate constants at 0° are approximately proportional to the lutidine concentration; however, at high concentrations of lutidine the observed rate constants reach a maximum (runs 3, 4, 2, 12-14). (F) Although the decomposition is first order in TBF, the observed first-order rate constants decrease with greater initial concentrations of TBF (runs 15 and 16). (G) At low concentrations of TBF and 2,6-lutidine the observed first-order rate constants are greatly sensitive to the presence of "inert" impurities (e.g., 0.16 mole % benzene in *p*-xylene decreases the observed rate by one-half; see runs 17 and 18). Within certain limits⁴ the nature of the impurity is unimportant; similar concentrations of different substances decrease the rate to the same extent (runs 19-21).

These results indicate that the reaction proceeds in liquid⁵ holes, present among the crystalline solid, which

(4) Anthracene, 0.015 *M*, has no effect on the rate while *t*-butyl alcohol, 0.033 *M*, is less than half as effective in decreasing the rate as benzene, carbon tetrachloride, or heptane at the same concentration.

(5) The deuterium isotope effect for reaction of *t*-butylperoxy formate-*d* with pyridine in frozen *p*-xylene at 0° is $k_H/k_D = \text{ca. } 9$,

contain high concentrations of the reactants.⁶ If ideal behavior for the solutes is assumed then the following relationship is expected

$$k_{\text{obsd}} = k_2 C \frac{M_b}{M_b + M_p + M_i}$$

where k_{obsd} is the observed first-order rate constant, k_2 is the second-order rate constant for liquid phase reaction, C is the total constant concentration of solutes in the liquid holes, and M_b , M_p , and M_i are the initial concentrations of base, peroxide, and impurities, respectively. This relationship reproduces, from experimental measurements of C for 2,6-lutidine in *p*-xylene (i.e., from the freezing point-composition phase diagram) and from the calculated k_2 extrapolated from higher temperatures, the form of the observed temperature dependence of k_{obsd} (see D above). For low and high concentrations of 2,6-lutidine or of pyridine the experimentally observed change in k_{obsd} with base concentration is correctly predicted (see E above). At high TBF concentrations or in the presence of impurities which follow ideal behavior at 0° in *p*-xylene the predicted decrease in rate constant is experimentally found (see F and G above). These variations in k_{obsd} , which are related by the above equation to measurable solution concentrations, may be visualized in terms of changes in the total volume and in the relative reactant concentrations of the liquid regions.

Many of the features reported here for the TBF-base reactions in frozen organic solutions are similar to results reported by Bruce and Butler⁷ for several bimolecular reactions in ice. It may be generally expected that, if the reactants of a bimolecular reaction are sufficiently soluble at temperatures below the freezing point of the solvent, and the reaction has a low activation energy, an acceleration due to the concentration effect will be observed when the system is frozen. Experiments on the reaction of methyl iodide with triethylamine in benzene and the Diels-Alder reaction of cyclopentadiene with methyl acrylate in *p*-xylene at 0° show that freezing accelerates the formation of products.

close to the expected ratio for liquid phase reaction as estimated from the known isotope effects at 90°.³

(6) A concentration of 2.35 *M* 2,6-lutidine in *p*-xylene is required to prevent freezing at 0°. From this the maximum total volume of "holes" for most of the runs of Table I may be estimated to be ca. 2% of the volume of the original solution before freezing.

(7) T. C. Bruce and A. R. Butler, *J. Am. Chem. Soc.*, **86**, 313, 4104 (1964).

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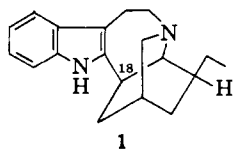
The Total Synthesis of (±)-Ibogamine and of (±)-Epiibogamine

Sir:

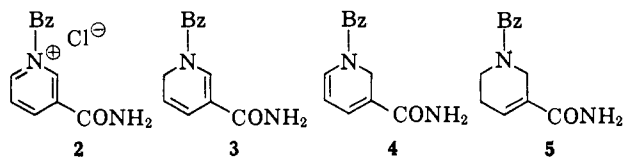
Ibogamine (1)^{1,2} is the least substituted member of a large group of natural bases structurally characterized by the presence of an isoquinuclidine ring and a seven-membered ring C. We have now completed the first total synthesis of an iboga alkaloid.

(1) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958).

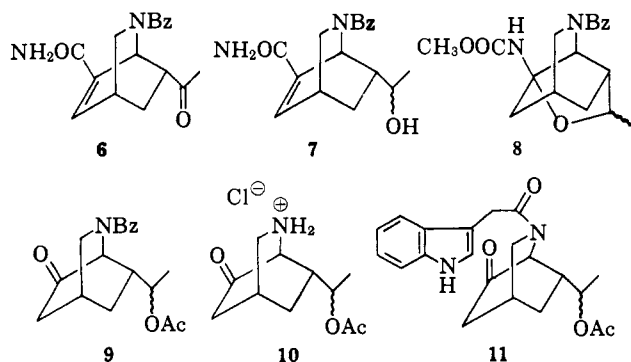
(2) G. A. Jeffrey, G. Arai, and J. Coppola, *Acta Cryst.*, **13**, 553 (1960).



3-Carboxamido-N-benzylpyridinium chloride (**2**) was reduced in aqueous sodium carbonate solution with 3 molar equiv. of sodium borohydride (-5° , 2 min.) to afford a mixture of the 1,6-dihydropyridine **3**, the 1,2-dihydropyridine **4**, and minor amounts of the tetrahydropyridine **5**, m.p. $118-120^{\circ}$. Only one

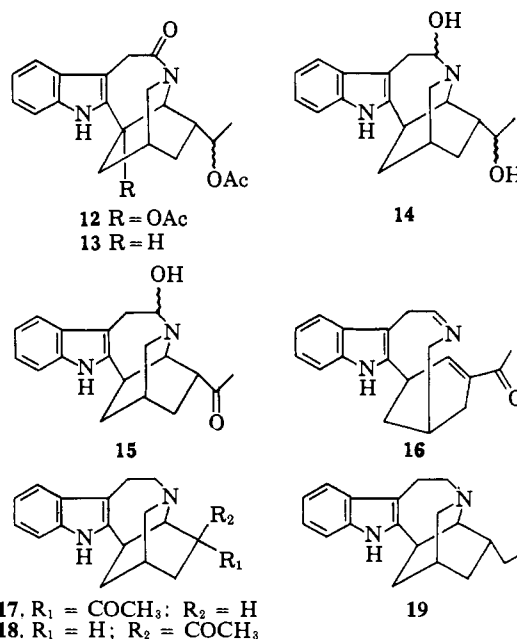


(**3**) of the two dihydropyridines (**3** and **4**) is capable of undergoing Diels-Alder condensations, and when a crude mixture of reduced pyridines was condensed with methyl vinyl ketone in hot chloroform the desired isoquinuclidine **6**, m.p. $173.5-175.5^{\circ}$, was formed (13% yield from **2**).³ This was transformed to a mixture of epimeric alcohols by reduction with sodium borohydride in methanol. The major component (**7**), m.p. $157-162^{\circ}$, $\nu_{\max}^{\text{Nujol}}$ 3400, 3200, 1675, 1645, and 1600 cm^{-1} , on oxidation with sodium hypochlorite in methanolic potassium hydroxide (50° , 1 hr.) yielded the tricyclic urethan **8**, m.p. $147.5-149^{\circ}$, $\nu_{\max}^{\text{Nujol}}$ 3300, 1750, and 1550 cm^{-1} ; n.m.r. (CDCl_3) δ 1.2 (doublet, $J = 7$ c.p.s., 3 H), 3.65 (singlet, 3 H), 3.75 (singlet, 2 H), and 7.3 (singlet, 5 H) (42% from **6**). Hydrolysis with 6 *N* aqueous sulfuric acid at 100° for 18 hr. followed by exposure to acetic anhydride in pyridine furnished the acetoxyketone **9**, m.p. $111.5-112.5^{\circ}$; $\nu_{\max}^{\text{Nujol}}$ 1740 and 1715 cm^{-1} ; n.m.r. (CDCl_3) δ 1.25 (doublet, $J = 7$ c.p.s., 3 H), 2.05 (singlet, 3 H), 3.75 (AB quartet), and 4.8 (quintet, $J = 7$ c.p.s., 1 H) (94% from **8**). Debenzylation was effected by hydrogenation of **9** in methanolic hydrochloric acid over a palladium-charcoal catalyst. The resulting hydrochloride **10**, m.p. $207-212^{\circ}$, $\nu_{\max}^{\text{Nujol}}$ 2750, 2500, and 1750 cm^{-1} , combined with β -indolylacetyl chloride in methylene chloride containing triethylamine (25° , 30 min.) to give the amorphous amide **11**, $\nu_{\max}^{\text{Nujol}}$ 3400, 1750, and 1650 cm^{-1} .



(3) A Diels-Alder type condensation with a dihydropyridine was described previously by K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960, 1971 (1959).

To complete the construction of the molecular framework present in ibogamine (**1**) the seven-membered ring had to be closed by an internal cyclization reaction which was brought about smoothly by the action of *p*-toluenesulfonic acid in acetic acid (reflux, 1 hr.). The resulting diacetate **12**, which incidentally did not have to be isolated, was reduced with zinc in acetic acid (reflux, 1 hr.) to the pentacyclic acetoxy lactam **13**, m.p. $268-275^{\circ}$, $\nu_{\max}^{\text{Nujol}}$ 3400, 1720, and 1620 cm^{-1} ; n.m.r. ($\text{DMSO}-d_6$) δ 1.1 (doublet, $J = 7$ c.p.s., 3 H), 1.8 (singlet, 3 H); 7.2 (multiplet, 4 H), and 11.4 (broad, 1 H; 68% from **9**). When this lactam (**13**) in tetrahydrofuran was subjected to the action of lithium aluminum hydride at room temperature the carbinolamine **14**, m.p. $122-128^{\circ}$, $\nu_{\max}^{\text{Nujol}}$ 3500, 1100, 995, and 955 cm^{-1} , was formed in 74% yield, but the anticipated amino alcohol was not detected. Attempts to reduce the carbinolamine **14** with formic acid, with zinc in acetic acid, and with combinations of aluminum chloride and lithium aluminum hydride all failed, and we attribute this behavior to the highly strained nature of the hypothetical imine. Oxidation of the alcohol **14** to the ketone **15**, m.p. $167-172^{\circ}$, $\nu_{\max}^{\text{Nujol}}$ 3500 and 1710 cm^{-1} , was eventually accomplished using dicyclohexylcarbodiimide and dimethyl sulfoxide⁴ (50%). Exposure of the β -aminoketone **15** to sodium methoxide in methanol led to the tetracyclic ketone **16**, $\nu_{\max}^{\text{Nujol}}$ 3600, 1670, and 1640 cm^{-1} , in essentially quantitative yield. The imine function in this latter compound was now smoothly reduced with zinc in acetic acid, and the resulting tetracyclic intermediate underwent cyclization to a mixture of pentacyclic ketones **17** and **18**; $\nu_{\max}^{\text{Nujol}}$ 3400 and 1710 cm^{-1} . The synthesis was completed by Wolff-Kishner reduction of this crude mixture which yielded (\pm)-ibogamine (**1**), m.p. $128.5-130.5^{\circ}$, and (\pm)-epibiogamine (**19**), m.p. $193-197^{\circ}$.



Identity of synthetic ibogamine (**1**) with material of natural origin was established by comparison of infrared and mass spectra and by thin layer chromatography. Identical criteria were used to ascertain

(4) K. E. Pfitzner and J. G. Moffat, *J. Am. Chem. Soc.*, **85**, 3027 (1963); S. McLean, University of Toronto, kindly called our attention to this method.

the identity of synthetic epiibogamine (19) with a sample prepared from catharanthine.⁵ We have previously described a method for the introduction of a carbomethoxy group at C-18, which is present in the voacanga alkaloids.⁶

Acknowledgment. This work was supported by grants from the National Institutes of Health and from the Hoffmann-LaRoche Anniversary Foundation.

(5) M. Gorman, N. Neuss, and N. J. Cone, *J. Am. Chem. Soc.*, **87**, 93 (1965). We are grateful to Dr. N. Neuss, Eli Lilly and Co., for sending us an authentic sample of epiibogamine.

(6) G. Büchi and R. E. Manning, *Pure Appl. Chem.*, **9**, 21 (1964).

(7) Woodrow Wilson Fellow 1961-1962.

(8) National Institutes of Health Postdoctoral Fellow 1963-1964.

(9) National Science Foundation Postdoctoral Fellow 1964-1965.

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The Electron Paramagnetic Resonance of Triplet CNN, NCN, and NCCCN

Sir:

We wish to report the observation, by electron paramagnetic resonance, of the ground-state triplets diazomethylene, $:C=N^+=N^-$ (I); cyanonitrene, $N\equiv C-\dot{N}$ (II); and dicyanomethylene, $N\equiv C-\dot{C}-C\equiv N$ (III). Of particular interest is the previously unknown CNN which is prepared from cyanogen azide, NCN_3 (IV), using ultraviolet light of wave length below 3000 Å. If CNN inserted into existing bonds, it could yield a diazomethane derivative directly. Unlike the aromatic methylenes and nitrenes in which one electron is largely localized at the divalent carbon or univalent nitrogen,¹ I-III have extensive delocalization of both unpaired electrons. As such, they are similar to monocyanomethylene which has been observed by Bernheim, *et al.*²

The precursors^{3,4} were photolyzed with an Osram HBO-200 mercury lamp in fluorolube, perfluorodimethylhexane, or hexafluorobenzene matrices at 77 or 4°K. The spectra were obtained with a Varian V-4500 spectrometer with 100-kc. modulation. A single line in the region of 6500-8000 gauss was observed. The shape was characteristic of approximately linear molecules.⁵ We were observing those molecules in the randomly oriented sample in which the external magnetic field was perpendicular to the molecular axis. The parameters characteristic of the triplet state were obtained⁵ assuming $g = 2.0023$.

Photolysis of IV for 30 min. with $\lambda > 3000$ Å., gave NCN with $D_{II} = 1.544$ and $E_I < 0.002$ cm.⁻¹. Subsequent irradiation including $\lambda < 3000$ Å. for 3 min.

(1) E. Wasserman, A. M. Trozzolo, W. A. Yager, and R. W. Murray, *J. Chem. Phys.*, **40**, 2408 (1964), and references cited therein; G. Smolin-sky, L. C. Snyder, and E. Wasserman, *Rev. Mod. Phys.*, **35**, 576 (1963).

(2) R. A. Bernheim, R. J. Kempf, P. W. Humer, and P. S. Skell, *J. Chem. Phys.*, **41**, 1156 (1964). These workers have also observed derivatives of propargylene and diethynylmethylene which are iso- π -electronic with I-III: *ibid.*, to be published. We thank Dr. Bernheim for making their results available prior to publication.

(3) F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.*, **86**, 4506 (1964).

(4) E. Ciganek, *ibid.*, **87**, 652 (1965). Dr. Ciganek kindly supplied the hydrazone precursor for the diazomalononitrile.

(5) E. Wasserman, L. C. Snyder, and W. A. Yager, *J. Chem. Phys.*, **41**, 1763 (1964). A weak $H_{\alpha 1}$ line was also visible with I.

gave CNN,⁶ $D_I = 1.153$ and $E_I < 0.002$ cm.⁻¹, more intense than the NCN but with no observable diminution of the NCN. Thus the ground state of NCN does not seem to be a precursor of CNN. The production of the CNN by the above procedure appears to be more efficient than irradiation of a fresh sample of IV with unfiltered radiation for 3 min. Perhaps the >3000 -Å. irradiation produces an intermediate, which could be a linear or cyclic isomer of IV, which readily photolyzes to CNN with $\lambda < 3000$ Å.

We would expect the light of lower energy to cause the least structural change, so that the assignment of NCN to the first triplet is reasonable. However, the main support comes from the close agreement of D_{II} with the equivalent spin-spin coupling, 2λ , obtained by Herzberg and Travis from the ultraviolet spectrum of II in the gas phase, 1.567 cm.⁻¹.⁷ The $<2\%$ change is similar to the differences which have been observed with other triplets on varying the rigid matrix in e.s.r. experiments.⁸ The close correspondence of the gas phase and rigid matrix results indicates that D is largely independent of environment, uniquely so for a quantity which is a measure of the distribution of the highest energy electrons in the molecule.

NCN may be viewed as composed of two $N=C-N$ radials occupying orthogonal orbitals on the same nuclei. Then the main contribution to D , which measures the magnetic dipole interaction of the unpaired electrons and is roughly proportional to $1/r^3$, is the interaction of the unpaired electrons on the same atom,⁹ $\sum_i \rho_i^2 D_i$. Here ρ_i is the spin density in one

orbital of the i th atom and D_i is $D_{NH} = 1.86$ cm.⁻¹ ¹⁰ if $i = N$, and $D_{linearCH_2} = 0.74$ cm.⁻¹ ¹¹ if $i = C$. Assuming spin densities of $\rho_1 = \rho_3 = \rho_N = 0.62$, $\rho_2 = \rho_C = -0.24$, somewhat larger in absolute value than those of the allyl radical,¹² and including the two-center interactions⁹ ($\sim +0.05$ cm.⁻¹), we find $D_{II} = 1.52$ cm.⁻¹. A negative spin density at the central atom is necessary to avoid a much lower computed value.

The assignment of the low wave length triplet to CNN is based on several factors. The formation occurs in dilute glassy samples so that it appears to be first order in IV. If photolysis removes a nitrogen molecule from IV, a CN_2 fragment remains. Since E measures the deviation from cylindrical symmetry, a zero value indicates that the species is linear and eliminates $N=N-\dot{C}$. With NCN not a possibility, CNN is the

remaining choice. Assuming that the spin densities of the outer and inner atoms of CNN are the same as NCN, we have $D = 1.16$ cm.⁻¹. Although the close agreement with experiment must be partly fortuitous, it does give additional support for the assignment of CNN.

(6) Dr. D. E. Milligan has made parallel observations in the ultraviolet and infrared spectra resulting from the photolysis of IV in an argon matrix at 4°K. The structural assignments are the same as those given here: D. E. Milligan, private communication.

(7) G. Herzberg and D. N. Travis, *Can. J. Phys.*, **42**, 1658 (1964).

(8) A. M. Trozzolo, E. Wasserman, and W. A. Yager, *J. chim. phys.*, **61**, 1663 (1964).

(9) E. Wasserman, *J. Chem. Phys.*, in press. The examples considered in detail in this reference are the systems discussed in ref. 2.

(10) R. N. Dixon, *Can. J. Phys.*, **37**, 1171 (1959).

(11) Extrapolated value from CF_3CH , to be published; see also ref. 9.

(12) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).