measurements on $C_7H_7\cdot$. A positive temperature coefficient has also been recently found in the related case of nitrogen-14 splittings for the N,N'-dihydro-1,4-diazine cation and similar radicals.[18]

Further work in progress includes calculation of the enthalpy of cleavage of bitropenyl from the temperature dependence of the e.s.r. intensity, investigations of alkyl- and aryl-substituted tropenyl radicals, and studies of the chemical and physical properties of the tropenyl radical.

Acknowledgment. We wish to thank Professor Ernest R. Davidson for many helpful discussions.

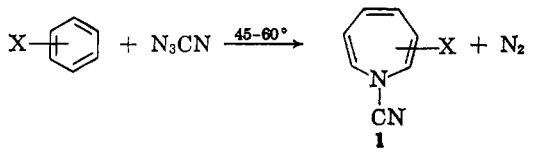
(18) M. R. Das and G. K. Fraenkel, *J. Chem. Phys.*, **42**, 792 (1965).
(19) Alfred P. Sloan Foundation Research Fellow.

Gershon Vincow,[19] M. Lee Morrell, Walter V. Volland
Hyp J. Dauben, Jr., Frank R. Hunter
Department of Chemistry, University of Washington
Seattle, Washington
Received June 5, 1965

N-Cyanoazepines from Cyanonitrene and Aromatic Compounds

Sir:

Cyanonitrene,[1,2] formed by thermolysis of cyanogen azide at 45–60°, reacts with aromatic compounds to give N-cyanoazepines (**1**)[3] (X = H, CH_3, *p*-$(CH_3)_2$, CO_2CH_3, Cl, F, 6F, CF_3, CCl_3) in high yield. The physical properties of the parent compound **1** (X = H, 70% yield) are similar to those of N-carboethoxyazepine,[4–8] but some of its chemical properties are significantly different. N-Cyanoazepine (**1**, X = H) is a mobile, red oil (b.p. 48° (0.2 μ); $n^{25}D$ 1.5520; $\lambda_{max}^{CCl_4}$ 2.27 (=CH), 4.50 (C≡N), and 6.03, 6.13 μ (–CH=CH–); $\lambda_{max}^{isooctane}$ 330 (ϵ 437) and 202 mμ (ϵ 25,500); H n.m.r. complex pattern at τ 3.83–3.93 (2 H) and multilined pattern at τ 4.40–4.49 (4 H)). *Anal.* Found: C, 71.14; H, 5.25; N, 23.66; mol. wt. 118 (mass spectrometric).

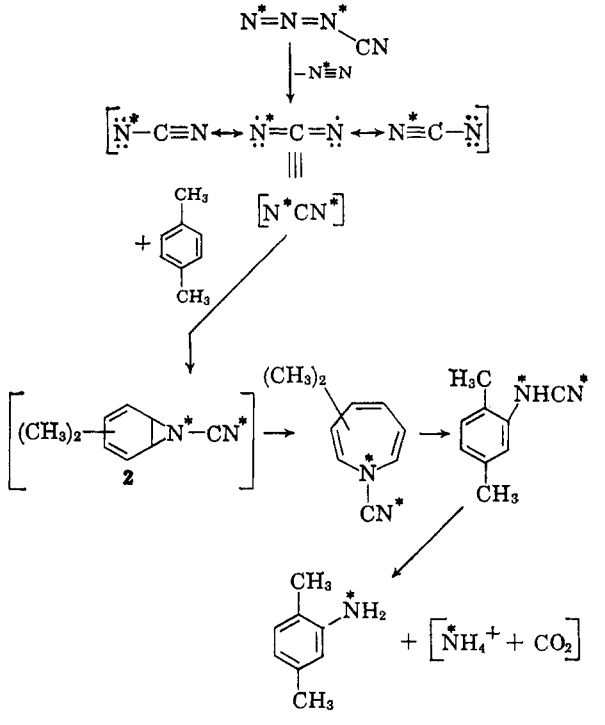


1

At room temperature **1** (X = H) spontaneously dimerizes to a white crystalline solid (m.p. 220–221°) but is stable when sealed in glass and stored at −78°. In dilute acid it is rearranged to phenylcyanamide and hydrolyzed to phenylurea in quantitative yield. In basic hydrogen peroxide it is hydrolyzed without rearrangement to give yellow crystalline N-carbamylazepine (m.p. 118.5–119.5°).

(1) F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.*, **87**, 1819 (1965).
(2) A. Anastassiou, H. E. Simmons, and F. D. Marsh, *ibid.*, **87**, 2296 (1965).
(3) *Chemical Abstracts* nomenclature for the parent compound 1 (X = H) is 1H-azepine-1-carbonitrile.
(4) K. Hafner and C. König, *Angew. Chem.*, **75**, 89 (1963).
(5) K. Hafner, *ibid.*, **75**, 1049 (1963).
(6) K. Hafner, D. Zinser, and K. L. Moritz, *Tetrahedron Letters*, **26**, 1733 (1964).
(7) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).
(8) W. Lwowski, T. J. Maricich, and T. W. Mattingly, Jr., *J. Am. Chem. Soc.*, **85**, 1200 (1963).

N-Cyanoazepine appears to be formed from a symmetrical intermediate believed to be cyanonitrene as illustrated by the following experiment. Cyanogen azide with azido nitrogens 1 and 3 labeled (N^{15}) was allowed to react with *p*-xylene to give two isomeric dimethyl-N-cyanoazepines (84%), which rearranged subsequently to 2,5-dimethylphenylcyanamide (100%) containing 51.5% of the original N^{15}. Hydrolysis of the cyanamide gave 2,5-dimethylaniline (70%) containing 25.5% of the original N^{15}. Scrambling of nitrogen atoms in the intermediate cyanonitrene can account for this observation. Presumably, the 7-azanorcaradiene (**2**) is an intermediate. An alternative mechanism, involving an unstable N-cyanotriazoline intermediate,[9] is eliminated since addition of labeled cyanogen azide to olefins occurs without scrambling of the label.[2] Although the ground state of NCN is $^3\Sigma_g^-$,[10] the species produced in the low temperature thermolysis of cyanogen azide may be an excited singlet state because of spin conservation. Experiments to test this point are in progress (A. G. Anastassiou).

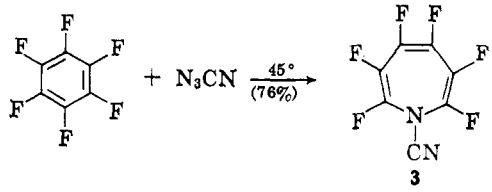


Monosubstituted benzenes react with cyanogen azide to give three isomeric N-cyanoazepines. Substituents have a marked influence on the stability and reactions of the products. Electron-withdrawing substituents such as F, CCl_3, or CF_3 stabilize the seven-membered ring, and these products show less tendency to rearrange to cyanamides but dimerize when heated. Mixtures of the three isomeric methyl-N-cyanoazepines rearrange at room temperature to *ortho*- and *para*-substituted phenylcyanamides in 2:1 ratio. The isomeric chloro-N-cyanoazepines gave comparable results. Acid-catalyzed hydrolysis of the mixture of isomeric fluoro-N-cyanoazepines from fluorobenzene gave *o*- and *p*-fluorophenylureas in 1:1 ratio containing less than 0.5% *meta* isomer. The absence of *meta*

(9) F. D. Marsh and M. E. Hermes, *ibid.*, **86**, 4506 (1964).
(10) G. Herzberg and D. N. Travis, *Can. J. Phys.*, **42**, 1658 (1964); G. J. Pontrelli and A. G. Anastassiou, *J. Chem. Phys.*, **42**, 3735 (1965).

isomer in the cyanamides or ureas may be explained by assuming that N-cyanoazepines on acid hydrolysis revert to mixtures of isomeric N-cyano-7-azanorcaradienes which undergo highly selective azirane ring opening to the observed products.

A striking example of the reactivity of cyanogen azide with highly substituted benzenes is provided by



3

hexafluorobenzene. Hexafluoro-N-cyanoazepine (**3**) is a colorless, crystalline solid, m.p. 51–52°, which is stable to subsequent rearrangement.

To prepare N-cyanoazepine (**1**), an acetonitrile solution of cyanogen azide (2 *M*) (caution! potentially explosive) is diluted with a 10–15-fold *M* excess of benzene, and the solution is heated at 45–60° until nitrogen evolution is complete. The mixture is filtered and the solvent removed under reduced pressure to give essentially pure product. The parent compound and the more stable substituted N-cyanoazepines can be obtained analytically pure by passing a methylene chloride solution through Florisil and distilling the eluent in a molecular still.

A full account of the chemistry of N-cyanoazepine is in preparation.

F. D. Marsh, H. E. Simmons

Contribution No. 1082, Central Research Department Experimental Station, E. I. du Pont de Nemours and Company Wilmington, Delaware 19898

Received June 11, 1965

Pyrroles from Azaindoles. A Synthesis of Porphobilinogen

Sir:

Porphobilinogen, the only monopyrrolic precursor in the biosynthesis of porphyrins, has been the subject of previous chemical syntheses which were undertaken to confirm its structure[1,2] and to obtain it in preparative amounts.[3,4] All these syntheses made use of the classical Knorr pyrrole synthesis and resulted in very poor over-all yields, the best[4] being around 1%. The only practical method of obtaining porphobilinogen remained its isolation from porphyric urines.

We wish to report a facile new and practical synthesis of porphobilinogen (XI) which proceeds *via* a 6-azaindole. It is based on the fact that porphobilinogen lactam (X)[3,5] can be easily and reversibly transformed to porphobilinogen, and on the observation that the lactam may be considered as the α-piperidone form of a suitable substituted pyrrolo[2,3-*c*]pyridine (6-azaindole).

Azaindoles form a relatively little studied heterocyclic system for which the best ring syntheses require such drastic reaction conditions that the synthesis of substituted azaindoles is highly restricted.[6] As an alternative, we have developed a synthesis based on the cyclization of *o*-nitropyridinepyruvates, a reaction which we have found to proceed well and under mild conditions, although previous failures to effect this type of ring closure have been reported.[7]

For the particular case of porphobilinogen synthesis, 2-methoxy-4-methyl-5-nitropyridine (I,[8] m.p. 81°; lit.[9] m.p. 82–84°; λ_{max} 289 mμ (ϵ 6800); prepared by the action of methanolic sodium methoxide on 2-chloro-4-methyl-5-nitropyridine[9]) was condensed with diethyl oxalate in the presence of potassium ethoxide, and ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (II), isolated as the potassium enolate and liberated from its salt at pH 3, was obtained in 93% yield; m.p. 97–98° from ethanol; λ_{max} 287 mμ (ϵ 10,100); ν_{max} 3350 (enolic OH) and 1710 cm.$^{-1}$; δ 7.8 (H-3), 9.1 (H-6), and 7.2 (*CH*=*C*(OH)COOR). Although the pyridinepyruvate II exists predominantly as the enol, nevertheless after hydrogenation in ethanol over palladium on carbon it cyclized readily to give ethyl 5-methoxy-6-azaindole-2-carboxylate (IV) in 85% yield after sublimation at 90° (0.1 mm.); m.p. 103–106°; λ_{max} 278 mμ (ϵ 15,000), 287 (17,000), and 344 (3600); δ 7.1, 7.2 (H-3, H-4), and 8.7 (H-7). When the hydrogenation was carried out over platinum oxide, an appreciable quantity of 1,2,3,4-tetrahydro-3-oxy-6-methoxy-1,7-naphthyridin-2-one (III) [m.p. 215° from ethanol; λ_{max} 248 mμ (ϵ 14,070); ν_{max} 1650 and 1600 cm.$^{-1}$; δ (in CF_3COOH) 3.1 (H-4, 2 protons), 4.5 (H-3), 7.0 (H-5), and 8.5 (H-8)] was isolated as a by-product.

A Mannich base (V) could be prepared easily in 75% yield by the reaction of the azaindole IV with dimethylamine hydrochloride and paraformaldehyde and was isolated as V·2HCl; m.p. 162°; λ_{max} 283 mμ (ϵ 12,100), 292 (13,800), and 347 (3700); δ (in D_2O) 8.2 (H-7). By treating V with diethyl sodiomalonate, the corresponding 6-azaindolylmethylmalonate (VI) was obtained as the hydrochloride in 80% yield; m.p. 188°; λ_{max} 284 mμ (ϵ 18,600), 294 (20,400), and 350 (4600). When the malonate VI was boiled in concentrated hydrochloric acid and the pH then adjusted to 4, a 95% yield of the propionic acid VII [m.p. 210–215°; λ_{max} 283 mμ (ϵ 13,000), 292 (15,700), and 350 (4400)] resulted. This propionic acid VII was heated at 150° in 48% hydrobromic acid, cleaving the methyl ether and giving 2-carboxy-5-oxo-5,6-dihydro-1H-pyrrolo[2,3-*c*]pyridine-3-propionic acid (VIII); 70%

(1) J. J. Scott, *Biochem. J.*, **62**, 6P (1956).
(2) C. Rimington and S. Krol, *Nature*, **175**, 630 (1955).
(3) A. H. Jackson and S. F. MacDonald, *Can. J. Chem.*, **35**, 715 (1957).
(4) G. P. Arsenault and S. F. MacDonald, *ibid.*, **39**, 2043 (1961).
(5) G. H. Cookson and C. Rimington, *Biochem. J.*, **57**, 476 (1954).

(6) For a brief evaluation of various syntheses of azaindoles prior to 1960 see T. K. Adler and A. Albert, *J. Chem. Soc.*, 1794 (1960). Recent azaindole ring syntheses are: (a) Madelung type: W. Hertz and D. R. K. Murty, *J. Org. Chem.*, **25**, 2242 (1960); J. Reisch, *Ber.*, **97**, 2717 (1964); A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964); (b) *via* hydrazones: G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 3202 (1959), 584 (1961); A. H. Kelly, D. H. McLeod, and J. Parrick, *Can. J. Chem.*, **43**, 296 (1965); (c) *via* haloalkylpyridines: L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubstov, *Zh. Obshch. Khim.*, **34**, 1449, 1456 (1964); L. N. Yakhantov and M. V. Rubstov, *ibid.*, **32**, 432 (1962).
(7) W. Herz and D. R. K. Murty, *J. Org. Chem.*, **26**, 122 (1961); G. M. Badger and R. P. Rao, *Australian J. Chem.*, **17**, 1399 (1964).
(8) Satisfactory elemental analyses and molecular weights have been found for all compounds reported; unless otherwise noted, ultraviolet absorptions were measured in ethanol, infrared spectra were obtained on potassium bromide wafers, and nuclear magnetic resonance spectra were taken in deuteriochloroform with internal TMS (δ 0). Professor J. Comin (Department of Organic Chemistry, Faculty of Sciences, University of Buenos Aires) took several of the n.m.r. spectra, for which we thank him.
(9) D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 2448 (1954).