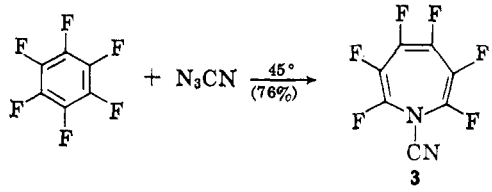
isomer in the cyanamides or ureas may be explained by assuming that N-cyanoazepines on acid hydrolysis revert to mixtures of isomeric N-cyano-7-azanorcaradienes which undergo highly selective azirane ring opening to the observed products.

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.

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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]

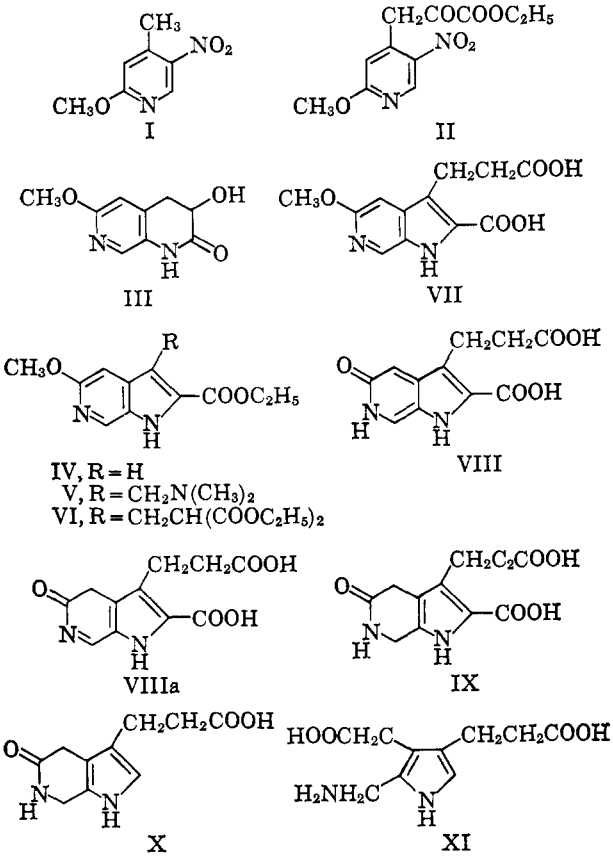
For the particular case of porphobilinogen synthesis, 2-methoxy-4-methyl-5-nitropyridine (I,[8] m.p. 81°; lit.[9] m.p. 82–84°; λ_{max} 289 mμ (ϵ 6800); prepared by the action of methanolic sodium methoxide on 2-chloro-4-methyl-5-nitropyridine[9]) was condensed with diethyl oxalate in the presence of 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).

yield; m.p. 280° dec.; λ_{max} 292 mμ (ε 4200) and 302 (4400); ν_{max} 3250, 1630, and 1600 cm.$^{-1}$. The structure VIII rather than VIIIa was assigned on the basis of the amide II band.



The pyridonepropionic acid VIII was hydrogenated in aqueous solution at pH 7 and 50 p.s.i. over palladium on carbon and, after adjustment of the pH to 4, 2-carboxyporphobilinogen lactam (IX) was obtained in 90% yield; m.p. 295° (lit.[3] m.p. 325°); λ_{max} 276 mμ (ε 12,600). In boiling water, the carboxylactam IX was smoothly decarboxylated (80% yield) to porphobilinogen lactam (X), m.p. 295° dec. (lit.[3] m.p. 280–283°), which was then treated at 20° with 2 *N* potassium hydroxide for 72 hr. When the pH was adjusted to 4, porphobilinogen (XI) was obtained as the monohydrate in 85% yield, m.p. 167° (lit.[3] m.p. 170–174°). It was identical with an authentic sample of porphobilinogen (from urine)[10] by paper chromatography, electrophoresis, and infrared absorption, and both gave identical lactams. Polymerization of our synthetic porphobilinogen, catalyzed by enzyme preparations from spinach and wheat germ,[11] gave quantitative yields of uroporphyrins.

The over-all yield of porphobilinogen (XI) starting from 2-methoxy-4-methyl-5-nitropyridine (I) is 19%, and an analogous series of compounds has been prepared from the 2-benzyloxy analog. By introducing different substituents at C-3 of the 6-azaindole IV, a series of azaindoles and pyrroles related to porphobilinogen has been obtained. These compounds and the application of this synthesis to isomeric azaindoles will be described in our future publications.

(10) We are indebted to Professor M. Grinstein (Buenos Aires) for samples of authentic porphobilinogen.

(11) L. Bogorad, *J. Biol Chem.*, **233**, 501, 510 (1958).

(12) Career investigator of the Consejo Nacional de Investigaciones de la Republica Argentina. This research was supported in part by the Consejo Nacional de Investigaciones de la Rep. Argentina (Grant 1646) and by the National Institutes of Health (Grant GM-11973).

(13) Fellow of the Consejo Nacional de Investigaciones de la Rep. Argentina, 1964–1965.

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Spontaneous Free-Radical Formation in the Pyrolysis of Nitroaromatic Compounds

Sir:

Nitroanilines, nitrotoluenes, nitrobenzaldehydes, nitrophenols, nitrophenyl disulfides, and numerous nitrobenzyl derivatives readily produce free radicals when heated above their melting points. This report gives our preliminary results on the effect of structure and temperature on this reaction.[1]

All nitroanilines studied gave free radicals upon heating (Table I), the *meta* derivatives giving rise to radicals at lower temperatures than the *ortho* or *para* derivatives. From a study of the concentration of radicals produced as a function of temperature, N,N-dimethyl-*m*-nitroaniline was found to behave very much like *m*-nitroaniline. These observations suggest that the radical formation in the case of the nitroanilines is the result of an electron-transfer reaction, since the ease of removal of an electron from the nitrogen unshared electron pair and the ease of reducing the substituted nitrobenzene would be expected to follow the order *meta* > *ortho* ≃ *para*.[2]

$$2NO_2C_6H_4\ddot{N}R_2 \longrightarrow NO_2C_6H_4\dot{N}^+R_2 + NR_2C_6H_4NO_2^-$$

A hydrogen transfer mechanism seems unlikely since the ease of removal of hydrogen from *m*-nitroaniline would have to equal the ease of removal of an N-methyl hydrogen from N,N-dimethyl-*m*-nitroaniline.

The radicals indicated in the above reaction are considered the primary products of pyrolysis but not necessarily the radicals giving the e.s.r. spectrum observed. Heated nitroanilines gave broad triplets with relative intensities 1:1:1 (*e.g.*, *m*-nitroaniline) or quintets (*e.g.*, *o*- and *p*-nitroaniline) with splitting constants in reasonable agreement with expected values for nitrobenzene[3] or nitrosobenzene[4] radical anion derivatives. The broadness of the lines is probably due to rapid electron transfer with solvent (nitroaniline).

Although *p*-nitrotoluene did not give free radicals and *o*- and *m*-nitrotoluene only a trace at temperatures

(1) A Varian 4502 e.p.r. spectrometer was used to detect and monitor the formation of free radicals. Samples were heated in a flat quartz tube with preheated nitrogen inside a quartz dewar in the cavity of the spectrometer.

(2) Similar reactions are known to occur with carbanions: G. A. Russell and E. G. Janzen, *J. Am. Chem. Soc.*, **84**, 4153 (1962); G. A. Russell, E. G. Janzen, and E. T. Strom, *ibid.*, **86**, 1807 (1964).

(3) D. H. Geske, J. L. Ragle, M. A. Bambenek, and A. L. Balch, *ibid.*, **86**, 987 (1964).

(4) G. A. Russell and E. J. Geels, *ibid.*, **87**, 122 (1965).