[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

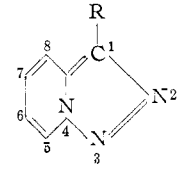
The Azomethine Linkage of Pyridine in Ring-closure Isomerizations[1]

BY J. H. BOYER, R. BORGERS[2] AND L. T. WOLFORD

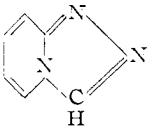
RECEIVED JULY 20, 1956

Pyridotriazole (Ia), 1-phenylpyridotriazole (Ib), 5,6-benzopyridotriazole (VIII) and 1,1′-dipyridotriazole (IX) were obtained from the facile silver oxide oxidation of the corresponding hydrazones. Presumably diazoalkyl compounds were intermediates which underwent spontaneous ring-closure isomerization. Pyridotriazole was not detected as a product from the diazotization of α-aminomethylpyridine. Cyclization of 3-diazomethylisoquinoline was not detected; instead nitrogen elimination with formation of the azine of isoquinoline-3-aldehyde was observed upon oxidation of the hydrazone of isoquinoline-3-aldehyde. Apparently the azido group does not cyclize to a quaternary azomethine nitrogen. In contrast α-pyridyl isocyanate-N-oxide upon formation underwent cyclization with the formation of pyridoöxadiazolone (XII).

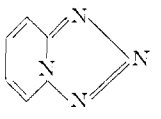
An interest in pyridotriazoles[3] and, in particular, the previously unreported 2,3,4-pyridotriazole (Ia) developed from certain investigations on pyridotetrazole (III). Of the three isomers, 1,2,4-pyridotriazole (II) has been reported,[4] but the third isomer, 1,3,4-pyridotriazole, remains unknown.



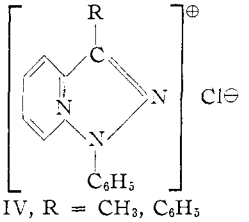
Ia, R = H
Ib, R = C_6H_5



II



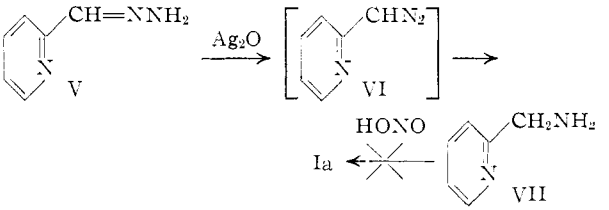
III



IV, R = CH_3, C_6H_5

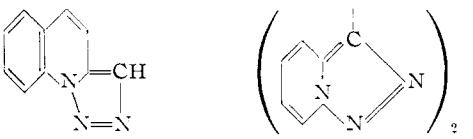
Upon formation, α-azidopyridine underwent irreversible ring-closure isomerization into pyridotetrazole.[4,5] The present synthesis of *vic*-pyridotriazole (Ia) required a similar isomerization of α-diazomethylpyridine (VI) upon formation from the hydrazone (V) of α-pyridylaldehyde by oxidation with silver oxide. A somewhat similar ring closure occurred upon the oxidation of the phenylhydrazones of 2-acylpyridines with lead tetraacetate followed by treatment with hydrogen chloride. In this case 8-azaindazolium salts (IV) were obtained.[6] The spontaneous transformation (VI → I) is reminiscent of Dimroth's classical studies on the tautomeric rearrangement of certain hydroxytriazoles into α-diazo derivatives of acid amides.[7]

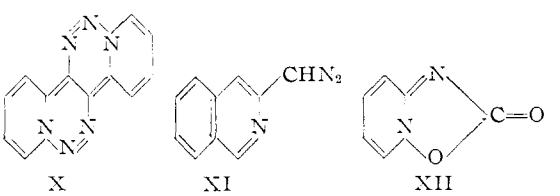
Curiously enough carbamyl azide and hydroxytetrazole did not interchange,[8a] consistent with the greater facility for unsaturated groups to undergo addition reactions with diazoalkanes than with the corresponding azides.[8b]



An attempted transformation of α-aminomethylpyridine (VII) into *vic*-pyridotriazole was suggested by Dimroth's preparation of α-diazo derivatives of acid amides. That pyridotriazole was not detected as a product of the diazotization of the amine demonstrated that the intermediate diazonium cation underwent the loss of molecular nitrogen more rapidly than the loss of a proton.[9] An unidentified product was analyzed as its picrate derivative.

Silver oxide oxidation of the hydrazone of α-quinolinealdehyde, α-benzoylpyridine and the dihydrazone of α-pyridil was realized only at higher temperatures. The products have been assigned the structures of 5,6-benzopyridotriazole (VIII), 1-phenylpyridotriazole (Ib) and 1,1′-dipyridotriazole (IX), respectively.

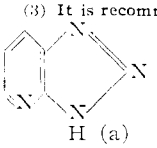




(1) A National Science Foundation Grant and a Louisiana Heart Association Grant in support of this work are gratefully acknowledged. Presented at the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(2) Research Assistant from the University of Leiden, Leiden, Holland, 1955–1956.

(3) It is recommended that the term pyridotriazole be used to describe that fused ring system in which a nitrogen atom is common to the pyridine and triazole rings. This allows the term triazolopyridine to describe those molecules in which a nitrogen is not common to the two fused rings, *e.g.* (a).



H (a)

(4) R. G. Fargher and R. Furness, *J. Chem. Soc.*, **107**, 688 (1915).

(5) J. v. Braun and W. Rudolph, *Ber.*, **74**, 284 (1941).

(6) R. Kuhn and W. Münzing, *ibid.*, **85**, 29 (1952).

(7) O. Dimroth, *Ann.*, **373**, 349 (1910); **377**, 131 (1910); J. E. Leffler and S. K. Kiu, THIS JOURNAL, **78**, 1949 (1956).

(8) (a) J. Thiele and O. Stange, *Ann.*, **283**, 37 (1894); R. Stolle, E. Schick, F. Henke-Stark and L. Krauss, *Ber.*, **62**, 1118 (1929); (b) T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," New Edition, Oxford University Press, London, 1945 (corrected) p. 372.

(9) C. Niemann, R. N. Lewis and J. T. Hays, THIS JOURNAL, **64**, 1679 (1942), reported the diazotization of α-pyridylmethylamine in the presence of hydrochloric acid. Presumably the unisolated initial product was the corresponding carbinol.

The triazoles I, VIII and IX resembled pyridotetrazole in resistance to attack by cold dilute mineral acid and in pyrolysis with the release of nitrogen. Pyridotriazole, in contrast with pyridotetrazole, was decomposed by concentrated sulfuric acid at room temperature and by acetic acid at 70°. The vicinal bicyclic triazoles, as well as 1,2,4-pyridotriazole[4] but not pyridotetrazole, reacted with aqueous silver nitrate with the formation of silver salt complexes.

Except for the region 750–1000 cm.$^{-1}$, infrared absorption data[10] supported similar structural assignments for pyridotetrazole and pyridotriazole. Absorption at 1626 cm.$^{-1}$ for pyridotetrazole possibly represented a composite of C=C and C=N stretching, whereas the absorption at 1631 cm.$^{-1}$ for pyridotriazole presumably represented C=C stretching only. It was assumed that absorption in this region which may have arisen from the N=N linkage was relatively unimportant.[11] The structural assignment for 1,1′-dipyridotriazole (IX) was based, to a certain extent, upon the agreement of infrared absorption data for this compound with that for pyridotriazole and pyridotetrazole. Nevertheless, the alternate assignment, 5,6,11,12,13,-16-hexaaza-13,16-dihydroxychrysene (X), was not eliminated.

Attempts to prepare 3-diazomethylisoquinoline (XI) by oxidation of the corresponding hydrazone were unsuccessful. A low yield of the azine of isoquinoline-3-aldehyde was obtained instead.[12]

Samples of impure α-azidopyridine-N-oxide were obtained from the interaction of α-bromopyridine-N-oxide and sodium azide,[13] and also from the treatment of diazotized α-aminopyridine-N-oxide with sodium azide. An attempt to purify the liquid product by distillation led to an explosion.[13] Presence of an azido group in the unstable and impure product which contained no inorganic azide was indicated by absorption in the infrared at 2138 cm.$^{-1}$. These results suggested that quaternary azomethine nitrogen atoms and a vicinal azido group have little, if any, tendency to interact.

A similar investigation on α-pyridylisocyanate-N-oxide was undertaken with the recognition that in this case ring-closure with the formation of pyridoöxadiazolone (XII) was possible. Curiously enough, α-bromopyridine-N-oxide failed to react with either sodium or silver cyanate. Upon treating α-aminopyridine-N-oxide with phosgene the solid product XII was obtained. Pyridoöxadiazolone was not hygroscopic, did not react with cold water and alcohols and absorbed in the infrared at 1773 cm.$^{-1}$, indicative of a carbonyl group in a five-membered ring and at 1613 cm.$^{-1}$, indicative of the azomethine linkage. There was no absorption in the 1950 cm.$^{-1}$ region, in agreement with the absence of the isocyanate group. This new ring system resembles sydnones, but does not require consideration of a non-classical mesoionic structure.

(10) Infrared absorption data for Ia, III, VIII, IX and XII from KBr disks has been deposited as Document number 4992 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints, or $1.25 for 35 mm. microfilm payable to Chief, Photoduplication Service, Library of Congress.

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 229.

(12) The observation by Th. Curtius and A. Lublin, *Ber.*, **33**, 2463 (1900), that the azine of *o*-nitrobenzaldehyde was formed upon oxidation of the corresponding hydrazone by mercuric oxide was confirmed.

(13) This experiment was carried out by Dr. J. H. Stocker.

Experimental[14]

Preparation of the Carbonyl Compounds.—α-Pyridylaldehyde, quinoline-2-aldehyde, α-pyridil and α-benzoylpyridine were commercially available. Isoquinoline-3-aldehyde was prepared previously.[15] α-Pyridylaldehyde was redistilled, b.p. 79° (18 mm.); oxime derivative, m.p. 112–113° (lit.[16] m.p. 113.5°). A picrate of the oxime of α-pyridylaldehyde was prepared and recrystallized from aqueous ethanol from which it separated as yellow needles, m.p. 169–171°.

Anal. Calcd. for $C_6H_6N_2O \cdot C_6H_3N_3O_7$: C, 41.03; H, 2.58; N, 19.94. Found: C, 41.10; H, 2.59; N, 19.76.

Preparation of the Hydrazones.—During the dropwise addition of 30.0 g. (0.28 mole) of redistilled α-pyridylaldehyde to 28.3 g. of a 65% solution (0.56 mole) of hydrazine in water, the mixture was stirred vigorously and maintained at 38–40°. After additional stirring for 45 minutes the slightly yellow solution was saturated with salt and thoroughly extracted with ether. The combined ether extractions were dried and concentrated *in vacuo*. The residual yellow oil distilled at 96–97° (0.45 mm.), 25.0 g. (74%). An analytical sample of the hydrazone of α-pyridylaldehyde was obtained upon redistillation at 89° (0.25 mm.), $n^{24.5}D$ 1.6397, $d^{24.5}$ 1.144.

Anal. Calcd. for $C_6H_7N_3$: C, 59.47; H, 5.84; N, 34.68; M_D 36.81. Found: C, 59.55; H, 5.75; N, 34.99; M_D, 38.18.

For the preparation of the hydrazone of quinoline-2-aldehyde a 20% solution of the aldehyde in pyridine was added to a 95% aqueous solution of hydrazine at 25–35°. The product was recrystallized from *n*-hexane and was obtained as colorless needles, m.p. 115–116°, 4.5 g. (80%).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.34; H, 5.27; N, 24.89.

The hydrazone of isoquinoline-3-aldehyde was also prepared in pyridine and was obtained in 71% yield. It was recrystallized from dichloromethane from which it separated as yellow needles, m.p. 144–145°.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 69.90; H, 5.97; N, 23.78.

The dihydrazone of α-pyridil was obtained by refluxing a mixture of 5.0 g. (0.024 mole) of α-pyridil and 3.0 g. of a 95% aqueous solution of hydrazine in 50 ml. of ethanol for 15 hours. The solvent was removed and the oily mass was recrystallized from a mixture of ethyl acetate and hexane from which it separated as slightly red crystals, m.p. 152–153°, 2.8 g. (55%).

Anal. Calcd. for $C_{12}H_{12}N_6$: C, 59.98; H, 5.04; N, 34.98. Found: C, 60.28; H, 5.23; N, 34.84.

In a similar manner the hydrazone of α-benzoylpyridine was obtained in 67% yield. It was recrystallized from ethyl acetate, from which it separated as long colorless needles, m.p. 106–108°.

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.09; H, 5.62; N, 21.30. Found: C, 73.16; H, 5.60; N, 21.17.

Oxidation of the Hydrazones.—A mixture of 20.0 g. (0.16 mole) of the hydrazone of α-pyridylaldehyde in 175 ml. of ether, 40 g. of silver oxide and 13 g. of magnesium sulfate hydrate was stirred for 1.5 hours according to a procedure of Schroeder and Katz.[17] The reaction was mildly exothermic and external cooling was required to keep the temperature below 30°. Ether extractions of the precipitate obtained from the reaction mixture were combined with the filtrate and concentrated *in vacuo* to an oil which solidified

(14) Melting points are corrected. Elemental analyses by Microtech Laboratory, Skokie, Ill. Infrared analyses through the courtesy of Dr. J. Picard, Picatinny Arsenal, Dover, N. J.

(15) J. H. Boyer and L. T. Wolford, unpublished data.

(16) G. Lenart, *Ber.*, **47**, 808 (1914).

(17) W. Schroeder and L. Katz, *J. Org. Chem.*, **19**, 718 (1954).

upon cooling in a Dry Ice and acetone bath. The oil distilled at 120–122° (0.25 mm.) and upon redistillation, b.p. 78° (0.09 mm.), 16.0 g. (80%) of the light yellow pyridotriazole, m.p. 34–35°, was obtained.

Anal. Calcd. for $C_6H_5N_3$: C, 60.49; H, 4.23; N, 35.28. Found: C, 59.93; H, 4.33; N, 34.99.

The azine of isoquinoline-3-aldehyde was isolated in 17% yield upon oxidation of the corresponding hydrazone with silver oxide. It was recrystallized from pyridine from which it separated as orange needles, m.p. 248–251°. The remainder of the product from the oxidation was an intractable tar.

Anal. Calcd. for $C_{10}H_{14}N_4$: C, 77.42; H, 4.55; N, 18.05. Found: C, 77.43; H, 4.88; N, 17.54.

In a similar oxidation of the hydrazone of quinoline-2-aldehyde it was necessary to heat the reaction mixture at reflux temperature for 18 hours. The solid product, 5,6-benzopyridotriazole, was obtained in 65% yield and was recrystallized from *n*-hexane from which it separated as colorless leaflets, m.p. 81°.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.23; H, 4.29; N, 24.73.

The oxidation of the hydrazone of α-benzoylpyridine with silver oxide also was carried out in refluxing ether for 15 hours. The product, 1-phenylpyridotriazole, was obtained in 83% yield and recrystallized from *n*-hexane as long silky colorless needles, m.p. 113–115°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.73; H, 4.99; N, 21.46.

The oxidation of the dihydrazone of α-pyridil was carried out in pyridine for one hour at 70°. The product, 1,1′-dipyridotriazole was obtained in 57% yield and was recrystallized from ethyl acetate from which it separated as colorless needles, m.p. 272–274° dec.

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.60. Found: C, 61.09; H, 3.61; N, 35.96.

α-Pyridylmethylamine.—Apparatus and procedure for reduction with lithium aluminum hydride by normal addition was followed.[18] A solution of 20 g. (0.19 mole) of α-cyanopyridine in 75 ml. of anhydrous ether was added slowly to a vigorously stirred suspension of 10 g. of lithium aluminum hydride in 25 ml. of anhydrous ether at such a rate that reflux was maintained. The reaction mixture was held at reflux temperature for an additional three hours, cooled, cautiously diluted with 45 ml. of aqueous ethanol, treated with 75 ml. of 40% sodium hydroxide solution and separated by filtration. Ether extracts of both the precipitate and filtrate were combined, dried and concentrated *in vacuo*. Distillation of the brown oil residue afforded a light yellow oil, b.p. 96–98° (14 mm.). Upon redistillation, b.p. 81°[19] (12 mm.) and 70–72° (11 mm.), 10.5 g. (55%) of α-pyridylmethylamine was obtained; picrate m.p. 159–160° dec. (lit.[19] 162), oxalate m.p. 166–167° (lit.[19] 167°).

Upon diazotization of the amine under either normal conditions, in which sodium nitrite and aqueous hydrochloric acid were used, or under anhydrous conditions in which isoamyl nitrite and absolute alcohol were used, a brown oil was obtained which gave a picrate from ethanol. Upon recrystallization from ethanol the picrate, m.p. 178–181° dec. after turning green at about 175°, was obtained as an unidentified yellow powder.

Anal. Calcd. for $C_6H_8N_2O_2 \cdot C_6H_3N_3O_7$: C, 39.03; H, 3.00; N, 18.97. Found: C, 38.81; H, 2.91; N, 18.50.

Preparation of Pyridoöxadiazolone.—The reaction between phosgene and 2-aminopyridine-N-oxide[20] was carried out in an apparatus described by Shriner, Horne and Cox.[21] To 50 ml. of chloroform saturated with phosgene, 0.400 g. (0.0036 mole) of 2-aminopyridine-N-oxide in 25 ml. of chloroform was added dropwise. An oil separated which gradually crystallized. Excess solvent was removed *in vacuo* and the solid residue was recrystallized from a mixture of ethyl acetate and hexane from which the product separated as light yellow needles, m.p. 185–187° dec.

Anal. Calcd. for $C_6H_4N_2O_2$: C, 52.94; H, 2.96; N, 20.59. Found: C, 52.46; H, 3.39; N, 20.32.

A small amount of residue insoluble in ethyl acetate and hexane was not identified.

(18) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947); **70**, 3738 (1948).

(19) R. Graf, G. Parathoner and M. Tatzel, *J. prakt. Chem.*, **146**, 88 (1936); L. C. Craig and R. M. Hixon, THIS JOURNAL, **53**, 436 (1931).

(20) R. Adams and S. Miyano, *ibid.*, **76**, 2785 (1954).

(21) R. L. Shriner, W. H. Horne and R. F. B. Cox, *Org. Syntheses*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 453.

NEW ORLEANS, LOUISIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Nucleophilic Displacements on Difunctional Pyrazines

BY GEORGE KARMAS[1] AND PAUL E. SPOERRI

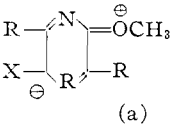
RECEIVED SEPTEMBER 13, 1956

The action of sodium alkoxides and cuprous cyanide on dihalopyrazines and halopyrazyl ethers has been studied with particular attention to the effect of ether groups on the halogen reactivity. Cleavage of pyrazine diethers by sodium methoxide has been developed as a method of preparing *o*- and *p*-dihydroxypyrazines and hydroxypyrazyl ethers.

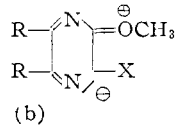
In a previous publication[2] we described the synthesis of *o*- and *p*-dihalopyrazines and now we wish to report on some novel aspects of the chemistry of these dihalides and their simple derivatives, the halopyrazyl ethers and the diethers.

Spring and co-workers reported that only one chlorine atom is readily displaced when a *p*-dichloropyrazine is refluxed in excess ethanolic sodium ethoxide and that temperatures of 120–130° are required for displacement of the second halogen by this very strong base.[3] Other examples of this diminished second halogen reactivity have been described by us,[2] and it seems to be a general property of this class of compounds. It seems likely that this is due to the substantial contribution of a resonance form such as (a) in which a second nucleophilic attack is discouraged by electrostatic repulsion.

We have observed that *o*-dihalopyrazines give high yields of diethers when refluxed in excess methanolic sodium methoxide. Apparently the



(a)



(b)

(1) Ortho Pharmaceutical Corporation, Raritan, N. J.

(2) G. Karmas and P. E. Spoerri, THIS JOURNAL, **78**, 4071 (1956).

(3) R. A. Baxter, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1859 (1948).