# Furazan*,[1,2]

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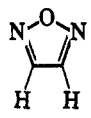
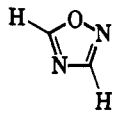
The synthesis of the unsubstituted heterocycle furazan (I), a stable liquid of b.p. 98°, is reported. The kinetics of the base-induced ring scission of I to the sodium salt of α-oximinoacetonitrile (IV) has been studied. This facile reaction has a half-life of only 4.3 min. at 25.0° in aqueous sodium hydroxide at pH 11.97. That ionization of the C–H bond is involved in the rate-determining step is indicated by a primary isotope effect, $k_H/k_D = 2.9$ (*vs.* dideuteriofurazan). It was also shown that hot acetic anhydride is a strong enough base to promote ring cleavage of phenylfurazan (XI).

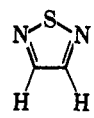
Though mono- and disubstituted 1,2,5-oxadiazoles have long been known,[4,5] furazan (I) itself has resisted the synthetic efforts of organic chemists for 80 years.



I



II



III

We were interested in preparing this unsubstituted heterocycle because we believed its N-alkyl salt would undergo a base-induced ring scission similar to that of the synthetically useful 3-unsubstituted isoxazolium salts.[6,7] The synthesis and reactions of furazanium and other oxadiazolium salts are discussed in a future communication.[8] In this paper we wish to record the preparation and some reactions of furazan itself.

Furazan is only the second of the four possible unsubstituted oxadiazoles to be prepared; the first, 1,2,4-oxadiazole (II), an unstable compound, was made by Eloy and his co-workers[9] in 1962. All of the possible unsubstituted thiadiazoles, however, have been synthesized,[10] including the stable sulfur analog of furazan, 1,2,5-thiadiazole (III).

Furazans are most often prepared by heating the corresponding glyoximes in water, aqueous ammonia, or aqueous sodium hydroxide,[5] but no product from the reaction of glyoxime itself in aqueous neutral or basic solutions has been reported. Hantzsch[11] attempted to dehydrate glyoxime with hydrogen chloride and with phosphorus pentachloride but only obtained cyanogen. Lach[12] achieved the same result by heating the diacetate of glyoxime, a procedure which has been used successfully to convert other glyoxime diesters to the corresponding furazans.[13,14] The most imaginative published proposal for the synthesis of furazan was outlined by Wieland and his students[15] who undertook a four-step synthesis from diethyl furoxandicarboxylate but were unsuccessful in their endeavors to decarboxylate furoxanmonocarboxylic acid.

Like many of our predecessors, we believed that a simple dehydration of the readily available glyoxime would constitute the easiest and most straightforward synthesis of the elusive furazan molecule. The problem was to choose the proper dehydration conditions. We felt that any attempts to dehydrate glyoxime in alkaline media would be doomed to failure, since furazan could not be expected to survive if formed; it is known that monosubstituted furazans undergo immediate ring opening in basic solution[13] as do the related 3-unsubstituted isoxazoles.[16] Also dehydration in strongly acidic media did not look promising since salt formation with the weakly basic heterocycle would complicate isolation procedures. Further, oximes are known to maintain their stereochemical integrity at room temperature,[17] and a study of the n.m.r. spectrum of glyoxime itself suggested that our sample is one of the symmetrical isomers, species which would be much less likely to undergo cyclization to furazan than a derivative of the *amphi* isomer. It should be possible to circumvent this problem of geometrical isomerism by carrying out the dehydration at a temperature at which the oxime is configurationally mobile. This would, however, introduce the possibility of thermal decomposition of any product heterocycle formed. After careful consideration of all these factors, one would expect the most practical synthesis of furazan should involve a high-temperature dehydration of glyoxime in a mildly acidic medium under conditions in which furazan is removed from the reaction mixture as it is generated.

* To Professor Louis F. Fieser.

(1) A preliminary account of a portion of this work has appeared: R. A. Olofson and J. S. Michelman, *J. Am. Chem. Soc.*, **86**, 1863 (1964).

(2) This research was supported by grants from the U. S. Public Health Service (GM-09317) and the Milton Fund of Harvard University.

(3) National Institutes of Health Predoctoral Fellow, 1962–1964.

(4) In 1883, H. Goldschmidt [*Chem. Ber.*, **16**, 2176 (1883)] synthesized the first "glyoxime anhydride," phenanthro[9,10]furazan. In the years that followed, so much attention was devoted to these compounds by German and Italian chemists that L. Wolff [*Ann.*, **260**, 79 (1890)] felt compelled to shorten the name to "furazan" arguing from an analogy with furan. The name furazan has become so entrenched in the chemical literature that the more systematic name, 1,2,5-oxadiazole, is only rarely used.

(5) J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 462 ff; L. C. Behr in "Five and Six Membered Compounds with Nitrogen and Oxygen," R. H. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p. 283 ff (in the series "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed.).

(6) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

(7) R. B. Woodward, R. A. Olofson, and H. Mayer, *ibid.*, **83**, 1010 (1961).

(8) See ref. 1 for partial preliminary discussion; this work will be published in conjunction with the work on isoxazolium salts (communication is ref. 6).

(9) C. Moussebois, R. Lenaers, and F. Eloy, *Helv. Chim. Acta*, **45**, 446 (1962).

(10) 1,2,3-Thiadiazole: L. Wolff, *Ann.*, **333**, 1 (1904); 1,2,4-thiadiazole and 1,3,4-thiadiazole: J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956); 1,2,5-thiadiazole: L. M. Weinstock, Thesis, Indiana University, 1958; M. Carmack, L. M. Weinstock, and D. Shew, Abstracts of Papers, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1959, p. 37-P.

(11) von A. Hantzsch, *Chem. Ber.*, **25**, 705 (1892).

(12) B. Lach, *ibid.*, **17**, 1571 (1884).

(13) A. Russanow, *ibid.*, **24**, 3497 (1891).

(14) K. Auwers and V. Meyer, *ibid.*, **22**, 705 (1889); G. Malagnini, *Gazz. chim. ital.*, [2] **24**, 1 (1894).

(15) H. Wieland, L. Semper, and E. Gmelin, *Ann.*, **367**, 52 (1909); L. Semper, Thesis, Munich, 1907; E. Gmelin, Thesis, Munich, 1909.

(16) L. Claisen, *Chem. Ber.*, **36**, 3664 (1903).

(17) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958); E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961); G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 2327 (1963).

The method described for the preparation of dimethylfurazan by Behr and Brent[18] seemed tailor-made to fit our requirements. They melted dimethylglyoxime with succinic anhydride and encouraged the product to distil from the reaction mixture as formed. When we adapted essentially the same procedure to the dehydration of glyoxime itself, the furazan generated needed little encouragement in its endeavors to escape from the reaction vessel. However, after suitable modification of the apparatus and procedure, we were able to prepare furazan in moderate batches in 51% yield by this method.

Furazan is a stable liquid of m.p. −28° and b.p. 98° at 760 mm. A comparison of its properties with those of the closely related 1,2,5-thiadiazole (III)[19] is summarized in Table I. As would be expected, furazan exhibits a single peak at very low field in its n.m.r. spectrum, a peak which moves from $\tau$ 1.34 in the neat liquid to 1.81 at infinite dilution in carbon tetrachloride; the peak is relatively broad (2.2 c.p.s. at one-half peak height) which implies a spin interaction of the proton with the $\alpha$-nitrogen atom. The $C^{13}$-H coupling constant is a remarkably high 199 c.p.s.

TABLE I

| | Furazan | 1,2,5-Thiadiazole[a,b] |
|---|---|---|
| B.p. (760 mm.), °C. | 98 | 94 |
| M.p., °C. | −28 | −50.1 |
| $\rho_{20}$, g./ml. | 1.168 | 1.268 |
| $n^{20}D$ | 1.4077 | 1.5150 |
| $\lambda^{H_2O}$, m$\mu$ ($\epsilon$) | Only end absorption | 255 (7800) |
| N.m.r., $\tau$ | | |
| Neat | 1.34 | 1.24 |
| $CCl_4$ (inf. dil.) | 1.81 | 1.42 |
| $J_{C^{13}-H}$, c.p.s. | 199 | 192 |
| Microwave spectrum,[c,d] Å. | | |
| X–N length | 1.380 | 1.631 |
| N–C length | 1.300 | 1.328 |
| C–C length | 1.421 | 1.420 |
| C–H length | 1.076 | 1.079 |
| N–X–N angle | 110° 24′ | 99° 33′ |
| X–N–C angle | 105° 49′ | 106° 27′ |
| C–C–H angle | 130° 10′ | 126° 14′ |
| N–C–H angle | 120° 51′ | 120° 0′ |
| Dipole moment, D. | 3.38 | 1.57 |

[a] See ref. 10. [b] See ref. 19. [c] See ref. 20. [d] See ref. 21.

An accurate determination of the structure of furazan has been completed by Wilson and Saegebarth[20] at Harvard. The molecule is planar and the bond angles and bond lengths are compared with the related values for 1,2,5-thiadiazole[21] in Table I. Of particular interest is the abnormal size of the N–O–N angle of furazan and the fact that the H–C–N angle is much smaller than the H–C–C angle; the significance of these results is discussed by Wilson and Saegebarth.[20]

The mass spectra of furazan and dideuteriofurazan (*vide infra*, see Figure 1) are in agreement with the respective molecular weights and indicate at least two general modes of fragmentation (Scheme I) under ionizing radiation. The weakness of the N–O bond in furazan, suggested by an analysis of its mass spectrum, is the most important factor in the chemistry of this ring system.

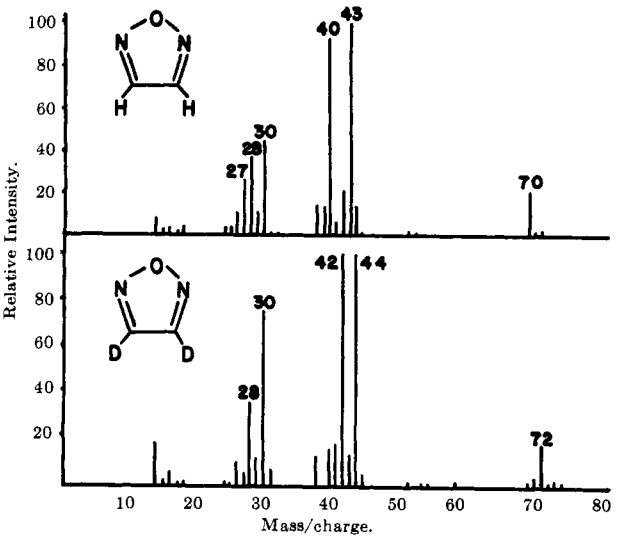
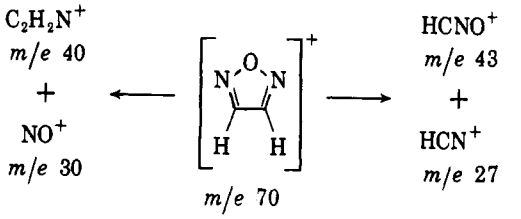


Figure 1.

SCHEME I[22]




Furazan reacts with sodium hydroxide in methanol to yield a crystalline, pyrophoric, and otherwise unstable sodium salt (IV). The free oxime (V) is even less stable and was never isolated. Though IV could not be analyzed satisfactorily, spectroscopic properties are in accord with the structure proposed: infrared, 4.55 $\mu$ in Nujol; ultraviolet, $\lambda_{max}$ 261 m$\mu$ ($\epsilon$ 6300) in water; n.m.r., singlet at $\tau$ 2.50 in deuterium oxide.

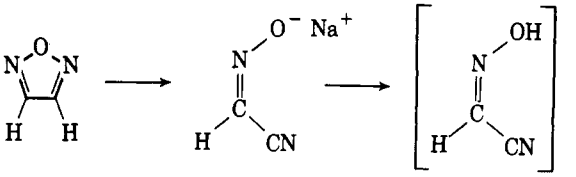



Table II outlines the kinetics of ring scission of furazan in aqueous base. The reaction is so facile that furazan has a half-life of only 4.3 min. at 25.0° in sodium hydroxide solution at pH 11.97. The reaction is first order in substrate and first order in hydroxide ion. There is a small effect of added anions; for example, $HPO_4^{-2}$ seems to accelerate the rate (Table II, runs 10–18).

Pino and co-workers[23] have studied the kinetics of a similar base-induced ring cleavage of 3-unsubstituted

(18) L. C. Behr and J. T. Brent, *Org. Syn.*, **34**, 40 (1954).

(19) We wish to thank Dr. L. M. Weinstock of Merck Sharp and Dohme Research Laboratories for a sample of 1,2,5-thiadiazole.

(20) E. Saegebarth, Symposium on Molecular Structure and Spectroscopy, Ohio State University, Columbus, Ohio, June 1963, paper C7; E. B. Wilson and E. Saegebarth, unpublished results.

(21) V. Dobyns and L. Pierce, *J. Am. Chem. Soc.*, **85**, 3553 (1963).

(22) For dideuteriofurazan the related ions would be $C_2D_2N^+$ (42), $NO^+$ (30), $DCNO^+$ (44), and $DCN^+$ (28). Part of the peak at *m/e* 28 in both spectra is caused by nitrogen gas.

(23) P. Pino, A. Scartabelli, and E. Lombardi, *Rend. Ist. Lombardo Sci. Lettere*, **87**, 229 (1954).

TABLE II

FURAZAN CLEAVAGE KINETICS (25.0°)

| Run | pH | $k_1 \times 10^4$, sec.$^{-1}$ | $T_{1/2}$, sec. | $k_2$, l./mole sec. |
|---|---|---|---|---|
| | | Dilute NaOH | | |
| 1 | 11.98 | 2.76 | 251 | 0.288 |
| 2 | 11.96 | 2.69 | 258 | 0.298 |
| 3 | 11.96 | 2.59 | 268 | 0.282 |
| | | | Av. | 0.289 |
| 4 | 11.66 | 1.34 | 517 | 0.293 |
| 5 | 11.66 | 1.35 | 513 | 0.297 |
| 6 | 11.69 | 1.35 | 513 | 0.278 |
| | | | Av. | 0.289 |
| 7[a] | 11.95 | 0.924 | 750 | 0.103 |
| 8[a] | 11.97 | 0.923 | 751 | 0.099 |
| 9[a] | 11.96 | 0.923 | 751 | 0.101 |
| | | | Av. | 0.101 |
| | | $10^{-2}$ *M* $Na_2HPO_4$, $10^{-2}$ *M* NaOH | | |
| 10 | 11.83 | 2.00 | 347 | 0.294 |
| 11 | 11.83 | 2.05 | 338 | 0.302 |
| 12 | 11.83 | 2.13 | 325 | 0.315 |
| | | | Av. | 0.304 |
| | | $10^{-2}$ *M* $Na_2HPO_4$, $7 \times 10^{-3}$ *M* NaOH | | |
| 13 | 11.63 | 1.43 | 485 | 0.338 |
| 14 | 11.62 | 1.37 | 506 | 0.328 |
| 15 | 11.62 | 1.37 | 506 | 0.329 |
| | | | Av. | 0.332 |
| | | $10^{-2}$ *M* $Na_2HPO_4$, $4.5 \times 10^{-3}$ *M* NaOH | | |
| 16 | 11.33 | 0.898 | 772 | 0.420 |
| 17 | 11.29 | 0.841 | 824 | 0.432 |
| 18 | 11.30 | 0.806 | 860 | 0.405 |
| | | | Av. | 0.419 |

[a] Reaction of dideuteriofurazan.

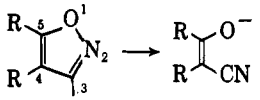
TABLE III

BASE CLEAVAGE OF ISOXAZOLES AND FURAZAN

| Compd. | Temp., °C. | $k_2$, l./mole sec. | Rel. rate |
|---|---|---|---|
| 5-Methylisoxazole[a] | 25.5 | $1.46 \times 10^{-4}$ | 1 |
| 5-Phenylisoxazole[a] | 25.5 | $4.40 \times 10^{-4}$ | 3.0 |
| 4,5-Dimethylisoxazole[a] | 25.5 | $5.67 \times 10^{-5}$ | 0.39 |
| Furazan | 25.0 | 0.283 | 2000 |

[a] See ref. 23.

isoxazoles (VI) to the nitrile enolates (VII). The rates of isoxazole and furazan ring opening are compared in Table III and it is seen that furazan undergoes this reaction 2000 times faster than 5-methylisoxazole.



VI VII

Before these data are analyzed it is necessary to include one more result. Ionization of the C–H bond is involved in the rate-determining step of the ring cleavage of furazan as indicated by a primary isotope effect, $k_H/k_D = 2.9$ (*vs.* dideuteriofurazan. This was prepared from dideuterioglyoxal which was synthesized by decarboxylation of diketosuccinic acid[24,25] in heavy water).

(24) A. Lachman, *J. Am. Chem. Soc.*, **43**, 577, 2091 (1921).
(25) O. Hinsberg, *Chem. Ber.*, **24**, 3235 (1891).

Only two conclusions can be drawn from a primary isotope effect of 2.9. Either (1) both C–H and N–O bonds are broken in a single concerted *trans* elimination step, or (2) ring opening of the carbanion generated on deprotonation of furazan is much faster than the rate of its creation. If the former is true, the rate factor of 2000 between the reactivity of furazan and 5-methylisoxazole reflects mainly the expected greater stability of the oxime anion (IV) *vs.* the enolate anion (VII). If, on the other hand, the second conclusion is correct, the 2000 rate difference is mainly a measure of an intrinsic greater stability of a furazan carbanion *vs.* an isoxazole 3-carbanion. We have recently reported a similar rate-enhancing effect of added electronegative atoms in the base-induced deuterium exchange of five-membered, heterocyclic nitrogen salts (tetrazolium salts undergo exchange faster than imidazolium salts which in turn exchange more rapidly than pyrazolium salts[26]), and we have also observed a parallel rate-enhancing effect in the base-catalyzed deuterium exchange reactions of free heterocyclic bases.[27]

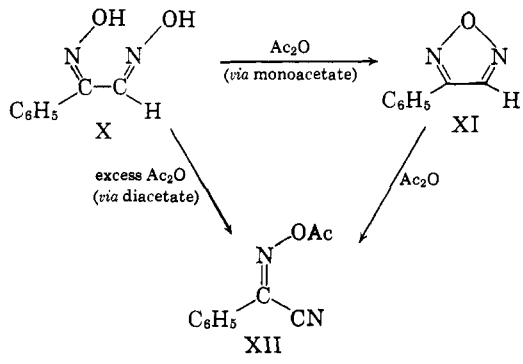
Though it is not yet possible to prove conclusively whether the base-induced ring scission of furazan is a one- or two-step process ($k_2 > k_1$), it is hoped that our studies on the exchange and cleavage rates of other heterocyclic bases will provide the necessary data. One preliminary observation[27] might be noted here. In furazan (I), 5-phenylisoxazole (VIII, A = C–H), and 5-phenyl-1,2,4-oxadiazole (VIII, A = N), the ioniza-

VIII IX

tion of the C–H bond is involved in the rate-determining step for ring cleavage. In 3-phenylisoxazole (IX, A = C–H) and 3-phenyl-1,2,4-oxadiazole (IX, A = N), base-catalyzed deuterium exchange occurs faster than ring cleavage. Compounds I, VIII, and IX, however, all undergo base-catalyzed ring opening by the same mechanism.[16,28]

The final topic covered in this paper is a short and relevant discussion of the synthesis and reactions of phenylfurazan (XI). Russanow[13] first synthesized phenylfurazan by steam distillation of phenylglyoxime (X) and Ponzio[29] later accomplished the dehydration in sulfuric acid but the yield by both methods was poor. Russanow reported that, when phenylglyoxime is heated with acetic anhydride, the product is not phenylfurazan, as might be expected, but O-acetyl-$\alpha$-oximinophenylacetonitrile (XII). In fact, when phenylglyoxime is heated with 1 equiv. of acetic anhydride, the product in 87% yield is phenylfurazan. However, when phenylglyoxime is heated with 4 equiv. of acetic anhydride, the product mixture contains 27% phenylfurazan and 58% of the oxime acetate (XII). Though phenylfurazan does decompose to XII under the reaction conditions, this reaction is too slow to allow one to postulate phenylfurazan as an intermediate in Russa-

(26) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Am. Chem. Soc.*, **86**, 1865 (1964).
(27) R. A. Olofson, J. M. Landesberg, J. S. Michelman, W. R. Thompson, A. C. Rochat, and K. N. Houk, unpublished results.
(28) C. Mousseboix and F. Eloy, *Helv. Chim. Acta*, **47**, 838 (1964).
(29) G. Ponzio and L. Avogadro, *Gazz. chim. ital.*, **53**, 311 (1923).




now's procedure. In the presence of excess acetic anhydride the dioxime diacetate is undoubtedly formed before the monoacetate can undergo cyclization. This species then eliminates acetic acid to yield XII.

The most remarkable observation from this series of reactions is the fact that phenylfurazan undergoes ring cleavage in the presence of acetic anhydride. When 4 equiv. of acetic anhydride are heated with 1 equiv. of XI at 151° for 4 hr., the reaction mixture contains 71% XI and 29% of the oxime acetate (XII). When XI is heated with acetic anhydride and 1 equiv. of acetic acid for 4 hr. at 151°, the product mixture contains 90% XI and only 10% XII. The reaction is then base catalyzed; either acetic anhydride or XI itself would seem to be a strong enough base to deprotonate phenylfurazan at high temperature. Another possibility would involve a deprotonation by acetate as base on an O- or N-acyliumfurazan. If this latter mechanism has any validity, a number of interesting synthetic consequences can be imagined.

## Experimental[30]

**Glyoxime.**—Many procedures have been published, none very practical,[31,32] and earlier authors have had difficulty isolating glyoxime from the reaction of hydroxylamine and glyoxal in aqueous solution. We have found it necessary to work with concentrated and slightly acidic reaction solutions in order to minimize loss of glyoxime due to its solubility. The following is our simplest and most economical procedure.

Hydroxylamine hydrochloride (Eastman practical), 139 g. (2.0 moles), was dissolved in an ice-cold solution of 55 g. (1.37 moles) of sodium hydroxide in 150 ml. of water, and 193 g. (1.0 mole) of 30% aqueous glyoxal (Eastman technical) was added slowly with stirring and cooling in ice. The mixture was allowed to stand at this temperature for 15 min. and then at room temperature overnight after which the flask and contents were cooled to 0° and the precipitated glyoxime was filtered, washed with a small amount of cold water, and dried *in vacuo*. The crude yield was 54.6 g. or 62%, m.p. 170–173°. The tan solid was then dissolved in the minimum amount of hot methanol, clarified with Norit, and allowed to crystallize at 0°. Upon concentration of the mother liquor, a second crop of crystals was obtained. A second crystallization from methanol yielded 44.3 g. or 50% of white crystalline product: m.p. 176–178° (lit.[32] m.p. 178°); n.m.r., broad singlet $\tau$ −0.16 (1), singlet $\tau$ 2.26 (1) in *p*-dioxane.

*Anal.* Calcd. for $C_2H_4N_2O$: C, 27.27; H, 4.58; N, 31.81. Found: C, 27.32; H, 4.66; N, 31.54.

(30) All melting points were taken in soft-glass capillary tubes using a calibrated thermometer. Infrared spectra were measured on either a Perkin-Elmer, Model 137 or Model 21, recording spectrophotometer. A Varian A-60 n.m.r. spectrometer was used to record the n.m.r. spectra; the chemical shifts are expressed in $\tau$ units using an external tetramethylsilane (TMS) standard unless otherwise specified. To obtain mass spectral data, a Consolidated Engineering Co., Type 21-103C, mass spectrograph was used. Vapor phase chromatography was carried out on an F and M Model 609 flame ionization gas chromatograph.

(31) M. Wittenberg and V. Meyer, *Chem. Ber.*, **16**, 500 (1883); C. Ulpiani and A. DeDominicis, *Gazz. chim. ital*, [I] **42**, 250 (1912).

(32) von A. Hantzsch and W. Wild, *Ann.*, **289**, 285 (1896).

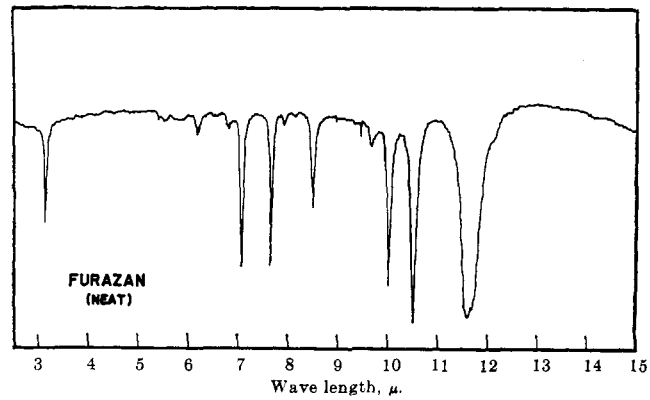



Figure 2.

Hantzsch[32] has reported that glyoxime crystallizes as a hemihydrate; we have no evidence for such a species.

**Furazan.**—The formation of furazan from glyoxime is exothermic and takes place with the copious evolution of noxious gases. Therefore, the preparation of this material should be carried out in a hood and behind a glass shield. The preparation of furazan in larger batches than that described below is not suggested.

A 500-ml. three-necked flask was fitted with a slipseal stirrer, a thermometer extending almost to the bottom of the flask, and an alembic in turn fitted with an efficient reflux condenser. A 125-ml. receiver, suspended in an ice bath, was used to collect the distillate. The reaction flask was charged with a pulverized mixture of 44.0 g. (0.5 mole) of glyoxime and 62.5 g. (0.63 mole) of succinic anhydride. The mixture was heated slowly until dense fumes appeared in the flask (*ca.* 150°), and the mixture began to melt. The heating mantle was then rapidly removed and the reaction was controlled by intermittent use of an ice bath. For best yields the reaction should be allowed to proceed as fast as possible without flooding the condensing system. Once the frothing subsided, heat was reapplied for 30 min. at 150–170° with stirring. The distillate, composed of furazan, water, succinic acid, and its anhydride, was treated with 20 ml. of dichloromethane and enough sodium sulfate to remove the water and obtain a clear supernatant solution. This solution was decanted and distilled at atmospheric pressure; all distillate in the 95–100° range was collected except for approximately 2 ml. of pot residue. The yield averaged 18 g. or 51%.

Analytically pure furazan[33] was prepared by drying the above distillate with a small amount of sodium sulfate and redistilling the liquid through an 18-in. spinning-band column with a reflux ratio of 10:1. Only that material boiling at 98° at 760 mm. was collected: m.p. −28°, $\rho_{20}$ 1.168 g./ml. (specific gravity bottle), $n^{20}D$ 1.4077 (Abbe refractometer). The ultraviolet spectrum showed only end absorption (methanol). The mass and infrared spectra are reproduced in Figures 1 and 2. The n.m.r. spectrum[34] showed only one peak $\tau$ 1.34 in the neat liquid (internal standard, TMS), $\tau$ 1.96 in a 2.3% furazan in TMS solution, $\tau$ 1.81 at infinite dilution in $CCl_4$ (internal standard, TMS).

*Anal.* Calcd. for $C_2H_2N_2O$: C, 34.29; H, 2.88; N, 39.99. Found: C, 34.18; H, 2.96; N, 40.09.

A number of other anhydrides were tested for their utility as dehydrating agents in the furazan synthesis: *n*-butyric anhydride (57%), phthalic anhydride (52%), glutaric anhydride (36%), and maleic anhydride (20%), $P_2O_5$ (0%). The conditions varied only slightly from those described in the preceding discussion.

**Perdeuterioglyoxal Bisulfite.**[25]—$NaDSO_3$ was prepared by exchanging 59.3 g. of sodium bisulfite in 75 ml. of 99.8% $D_2O$. The tightly stoppered solution was allowed to stand for 3 hr. before removal of the heavy water *in vacuo*.

The $NaDSO_3$, 44 g. (0.42 mole), dissolved in 102 ml. of $D_2O$, was added to 28.0 g. (0.15 mole) of the disodium salt of diketosuccinic acid (prepared as described by Lachman[24]) in a predried 1-l. flask fitted with a condenser and calcium chloride tube. When the foaming had subsided, the mixture was heated on a steam bath until an almost clear solution was obtained. After

(33) The furazan is essentially pure prior to this last distillation.

(34) The spectra were calibrated with sidebands (from an internal TMS standard) generated by an audiooscillator monitored by a frequency counter. With this apparatus the chemical shifts are accurate to $\tau$ 0.01. Each $\tau$ value was determined twice sweeping upfield and twice sweeping downfield.

2 days in the refrigerator, 8.39 g. or 21% of perdeuterioglyoxal bisulfite had precipitated. The filtered material was dried (m.p. 175–178° dec.) and used without further purification.

**Dideuterioglyoxime.**—Glyoxal-$d_2$ was formed *in situ* by treating 20.2 g. (0.075 mole) of perdeuterioglyoxal bisulfite with 20.5 ml. of concentrated hydrochloric acid in 52.5 ml. of water. The mixture was heated on the steam bath for 15 min. to remove sulfur dioxide and after cooling, 13.9 g. (0.20 mole) of hydroxylamine hydrochloride and 80.5 ml. of 10% sodium hydroxide in water were added. The solution was filtered to remove insoluble impurities and allowed to stand overnight in the refrigerator; the precipitate was collected and dried. The mother liquor was extracted six times with ether, the ether extracts were dried with sodium sulfate and evaporated *in vacuo*, and the residue was added to the initial precipitate. In total, 4.52 g. or 67% was collected and one recrystallization from methanol yielded white, crystalline glyoxime-$d_2$, m.p. 173–176°.

The n.m.r. spectrum showed a broad singlet at $\tau$ −0.06 in *p*-dioxane. A small peak was present at $\tau$ 2.32 and integration of the spectrum led to the estimate that 90% of the aldehydic protons had been exchanged for deuterium assuming no O–D species present.

**Dideuteriofurazan.**—The procedure used for the synthesis of diprotiofurazan was followed as closely as possible. Glyoxime-$d_2$, 7.66 g. (0.085 mole), was pulverized with 10.8 g. (0.108 mole) of succinic anhydride. The mixture was placed in a 50-ml. round-bottomed flask fitted with a system arranged for downward distillation. The reaction mixture was heated for 4 hr. (the reaction seemed to proceed at a much slower rate than the formation of the diprotio analog). During this period approximately 3 ml. of liquid was collected. The distilling head and condenser were washed with a small amount of ether and the washings were added to the distillate. The resulting solution was dried with sodium sulfate and distilled; the material boiling between 50 and 100° was collected. This distillate was then refractionated from a small apparatus equipped with a 4-cm. Vigreux column. Only that product boiling at 98° was collected: yield 3.64 g. or 59%, infrared C–D stretch at 4.35 $\mu$ in $CS_2$. The redistilled deuteriofurazan was 99.5% pure by v.p.c. (retention time 7.4 min. at column temperature 65° on an 8-ft. column of silicone rubber on Chromosorb P); the other component was ether.

The mass spectrum of the deuterated furazan (Figure 1) was the only experimental source of its per cent composition. The spectrum shows the parent peak at 72 mass units, monodeuteriofurazan at 71, and a peak at 70 attributed to diprotiofurazan. A rigorous calculation, taking into account the relative intensities of peaks at masses 71 and 72 in diprotiofurazan, gives values of 81% dideuterio-, 16.6% monodeuterio-, and 2.4% diprotiofurazan.

*Anal.* Calcd. for $C_2(H + D)_2N_2O$: C, 33.44; H+D, 5.28; N, 39.00. Found: C, 33.38; H+D, 3.24; N, 38.88.

**Mass Spectra of Furazan and Deuteriofurazan.**—These are reproduced in Figure 1 and Table IV. The spectra were scanned from 3250 to 365 v. using a sweep speed of 1 and an ionizing current of 10.5 $\mu$a.

**Phenylglyoxime.**—The sodium salt of $\alpha$-isonitrosoacetophenone[35] was converted to phenylglyoxime (m.p. 173°, lit.[13] m.p. 168°) by treatment with hydroxylamine hydrochloride.[36]

**Phenylfurazan.**—Acetic anhydride, 31.2 g. (0.306 mole), was added to 50.2 g. (0.306 mole) of phenylglyoxime and the mixture was heated at 100° for 1 hr. The acetic acid formed in the reaction was evaporated at aspirator pressure and the residual oil was distilled under vacuum, b.p. 68–72° at 0.3 mm. The yield of solid phenylfurazan by this method was 39 g. (87%) and the product was identical with the compound prepared by steam distillation of phenylglyoxime[13] or by heating phenylglyoxime with sulfuric acid.[29] Translucent needles (m.p. 36–36.5°, lit.[29] m.p. 35–36°) were obtained when the material was recrystallized from methanol: ultraviolet, $\lambda_{max}$ 251 m$\mu$ ($\epsilon$ 7600) in $CH_2Cl_2$; n.m.r., complex multiplet $\tau$ 1.86–2.50 (5), singlet $\tau$ 1.36 (1) in $CCl_4$.

**Reaction of Phenylglyoxime with Excess Acetic Anhydride.**—Phenylglyoxime, 3.28 g. (0.02 mole), was treated with 8.16 g. (0.08 mole) of acetic anhydride and the mixture was heated for 2 hr. at 130°. The acetic acid and anhydride were removed *in vacuo*, and the residual oil, 2.93 g., was dissolved in carbon tetrachloride. Integration of the n.m.r. spectrum of this solution showed that the reaction mixture was composed of 70 mole % O-acetyloxime of benzoyl cyanide[13] and 30 mole % phenylfurazan. The yields were 58 and 27%, respectively.

TABLE IV

| Mass/charge | Relative intensity: Furazan | Deuteriofurazan |
|---|---|---|
| 14 | 7.5 | 18.8 |
| 15 | 2.7 | 1.8 |
| 16 | 3.2 | 6.8 |
| 17 | 1.0 | 0.5 |
| 18 | 3.2 | 1.5 |
| 24 | 3.1 | 2.1 |
| 25 | 3.3 | ... |
| 26 | 9.7 | 9.9 |
| 27 | 25.3 | 6.0 |
| 28 | 36.9 | 34.9 |
| 29 | 9.9 | 11.1 |
| 30 | 44.5 | 72.4 |
| 31 | ... | 7.1 |
| 38 | 13.4 | 11.7 |
| 39 | 13.1 | 1.7 |
| 40 | 93.9 | 14.1 |
| 41 | 5.4 | 19.0 |
| 42 | 20.1 | 100.0 |
| 43 | 100.0 | 13.6 |
| 44 | 12.7 | 99.2 |
| 45 | ... | 4.0 |
| 59 | ... | 3.0 |
| 70 | 20.4 | 0.7 |
| 71 | 1.0 | 3.6 |
| 72 | 1.9 | 17.6 |
| 73 | ... | 0.7 |
| 74 | ... | 1.8 |

**Reaction of Phenylfurazan with Acetic Anhydride.**—Phenylfurazan, 1.46 g. (0.01 mole), was heated at 151° for 4 hr. with 4.08 g. (0.04 mole) of acetic anhydride and the anhydride then was removed *in vacuo*. Integration of the n.m.r. spectrum of a carbon tetrachloride solution of the residual oil showed the reaction mixture was composed of 71 mole % phenylfurazan and 29 mole % O-acetyloxime of benzoyl cyanide.[13]

Phenylfurazan, 1.46 g. (0.01 mole), was refluxed at 151° for 4 hr. with 4.08 g. (0.04 mole) of acetic anhydride and 0.60 g. (0.01 mole) of acetic acid. The reaction mixture was processed as above: 90 mole % phenylfurazan and 10 mole % of the oximino acetate.

**Reaction of Furazan with Base.**—Furazan, 3.55 g. (0.507 mole), was dissolved in 15 ml. of methanol and 101 ml. of a 0.495 *N* solution of sodium hydroxide in methanol was added dropwise with cooling and stirring. The yellow solution was then evaporated at reduced pressure, and the yellow crystalline sodium salt of $\alpha$-oximinoacetonitrile (monohydrate?), 5.50 g., was collected. The material is pyrophoric; so special precautions were taken in its purification. The salt was precipitated from methanol with ether yielding a white flocculent solid. Most of the solvent was decanted, and the material was dried *in vacuo* and packaged under nitrogen. The initially white sample was always a deep brown by the time it reached the analyst so no analysis could be obtained. Even in solution the material decomposed slowly, *vide infra:* ultraviolet, $\lambda_{max}$ 266 m$\mu$ in methanol, 261 m$\mu$ ($\epsilon$ 6300)[37] in water; infrared, 4.55 $\mu$ in Nujol; n.m.r., singlet $\tau$ 2.50, also a water peak (in $D_2O$).

We were unable to identify the decomposition products of the sodium salt or to isolate the free oxime on acidification. It was shown, however, by ultraviolet spectroscopy that the salt could be converted to the free oxime ($\lambda_{max}$ 220 m$\mu$ in water) in acid solution and then back to the salt in base.

**$\alpha$-Oximinophenylacetonitrile.**—Phenylfurazan, 1.46 g. (0.01 mole), was dissolved in 10 ml. of methanol and titrated with 20.7 ml. of 0.483 *N* methanolic sodium hydroxide solution. The methanol was evaporated *in vacuo*, and the yellow crystalline sodium salt (1.58 g., 94%) which remained was dissolved in water and acidified with 1.0 *N* HCl to pH 5. The precipitate of

(35) L. Claisen, *Chem. Ber.*, **20**, 655 (1887).

(36) H. Wieland and L. Semper, *Ann.*, **358**, 36 (1908).

(37) In order to obtain $\epsilon$, a standard solution of furazan was cleaved in aqueous base and the optical density was measured.

$\alpha$-oximinophenylacetonitrile was filtered and dried *in vacuo*, m.p. 127–129° (lit.[13] m.p. 128–129°).

**Kinetic Investigation of the Base-Induced Ring Scission of Furazan and Dideuteriofurazan.**—All glassware was pretreated with chromic acid in sulfuric acid, washed with distilled water, and dried at 120°. The reaction kinetics were measured in 1-cm. quartz cells and were followed on a Cary recording spectrophotometer, Model 14. The sample compartment was thermostated at 25.0 ± 0.1°.

Carbonate-free sodium hydroxide solution was used. To obtain the desired pH, aliquots of this solution were diluted with $CO_2$-free distilled water. Analytically pure $Na_2HPO_4$ was used.

Approximately 25 ml. of the base solution was thermostated at 25.0° for at least 1 hr. prior to use. A very small amount of freshly distilled furazan or furazan-$d_2$ was then added, and the timer was started. This solution was shaken well and the cell was filled and placed in the spectrophotometer. The kinetics were followed continuously to approximately 10 half-lives at 261 m$\mu$ ($\lambda_{max}$ of product). At the end of each kinetic run the pH of the reaction solution was taken. This pH differed by no more than 0.03 pH units from the pH of the initial base solution.

It was possible to show that the product, the anion from $\alpha$-oximinoacetonitrile, obeys Beer's law even though this substance could not be isolated in the pure state. Standard solutions of furazan in base were allowed to react to 10 half-lives and the optical densities of the solutions were then measured. A straight line was obtained when optical density was plotted against concentration.

The pseudo-first-order rate constants were obtained from a plot of log (O.D. at $t_\infty$ − O.D. at $t$) *vs.* time. This plot gave a straight line for over 4 half-lives except in the reactions of dideuteriofurazan which shows a slightly faster initial rate as expected. The second-order rate constants were obtained from $k_1/(OH^-)$. The primary isotope effect $k_H/k_D$ is 2.9.

The results are found in Table II.

**Kinetics of the Decomposition of the Sodium Salt of $\alpha$-Oximinoacetonitrile.**—A solution of furazan in pH 12.08 sodium hydroxide solution was allowed to stand for 290 hr. at 25°. Ultraviolet spectra were taken about every 10 hr. The decomposition was followed at 261 m$\mu$ (substrate) and a crude calculation indicated a half life of about 35 hr., too slow to interfere with the furazan cleavage kinetics.

# A Free-Radical Oxidation of a Dihydropyridine*,[1a]

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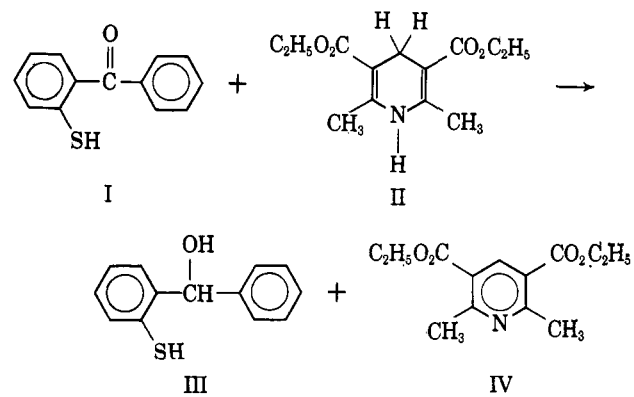
2-Mercaptobenzophenone (I) oxidizes 3,5-dimethyl-2,4-dicarboethoxy-1,4-dihydropyridine (II) to the corresponding pyridine; the ketone is reduced to 2-mercaptobenzhydrol. The oxidation–reduction requires the *o*-sulfhydryl group and fails with the corresponding *para* compound or with benzophenone substituted by *ortho* hydroxy, amino, or thiomethyl groups. The reaction between I and II occurs rapidly at room temperature in neutral aqueous alcoholic solution when promoted by peroxides and ferrous ion and thus has the characteristics of a free-radical process. During the oxidation–reduction, hydrogen is introduced from the solvent into the mercaptobenzhydrol formed; the reaction therefore does not involve direct hydrogen transfer and is not a model for the biochemical oxidation–reductions of dihydropyridines.

Enzymic reactions which involve diphosphopyridine nucleotide constitute one of the most important classes of biochemical oxidation–reduction processes. These reactions (such as the reduction of acetaldehyde to alcohol, the reduction of pyruvate to lactic acid, etc.) are characterized by the direct and stereospecific transfer of hydrogen from the dihydropyridine to the substrate.[2] Chemical models for the biochemical oxidation–reduction reaction which likewise involve direct hydrogen transfer include the reduction of pyruvate,[3] benzoyl formate,[3] thiobenzophenone,[4] 1-phenyl-4,4,4-trifluorobutene-2-one-1 (reduced at the double bond),[5] hexachloroacetone,[6] malchite green,[7] dipicrylhydrazyl[7] and (photochemically) bromotrichloromethane,[8] and diphenyl disulfide.[7] Of these oxidation–reduction reactions, the last three or four are free-radical processes, whereas the others presumably proceed by polar mechanisms. Other model reactions have been developed where the question of direct hydrogen transfer has not yet been investigated.[9] We have now found an example of a free-radical oxidation–reduction process involving the reduction of a carbonyl compound by 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (the "Hantzsch compound," I) which proceeds with hydrogen transfer from the solvent, *i.e.*, without direct transfer from the reducing agent to the substrate. The reaction follows.




I II III IV

The reaction is promoted by air or by hydrogen peroxide or other peroxides and by ferrous ion (Tables

* To Professor Louis F. Fieser.

(1) (a) This research was supported by the National Institutes of Health under Grant GM-04712. (b) National Institutes of Health Postdoctoral Fellow, 1960–1963.

(2) F. H. Westheimer, H. F. Fisher, E. E. Conn, and B. Vennesland, *J. Am. Chem. Soc.*, **73**, 2403 (1951); B. Vennesland and F. H. Westheimer, "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1954, p. 357; H. R. Levy and B. Vennesland, *J. Biol. Chem.*, **228**, 85 (1957).

(3) R. Abeles and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 459 (1958).

(4) R. Abeles, R. F. Hutton, and F. H. Westheimer, *ibid.*, **79**, 712 (1957).

(5) B. E. Norcross, P. E. Klindinst, and F. H. Westheimer, *ibid.*, **84**, 797 (1962).

(6) D. C. Dittmer, L. J. Steffa, J. R. Potoski, and R. A. Fouty, *Tetrahedron Letters*, 827 (1961).

(7) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955).

(8) J. L. Kurz, R. F. Hutton, and F. H. Westheimer, *ibid.*, **83**, 584 (1961).

(9) K. Wallenfels and H. Schuely, *Angew. Chem.*, **69**, 505 (1957); K. Wallenfels and M. Gellrich, *Ber.*, **92**, 1406 (1959); K. Wallenfels and D. Hofmann, *Tetrahedron Letters*, **No. 15**, 10 (1959); E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3249, 3257, 3268 (1960); B. Kadis, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959; M. J. Spiegel and G. R. Drysdale, *J. Biol. Chem.*, **236**, 436 (1961).