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Studies of the Synthesis of Furan Compounds. XXIII.[1] Cyclization Derivatives of 5-Nitro-2-furimidoylhydrazine[2]

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The reaction of 5-nitro-2-furimidoylhydrazine (I) with diacetyl or furil gave 3-(5-nitro-2-furyl)-5,6-disubstituted-1,2,4-triazine derivatives (IIa, b). Refluxing I in a large excess of ethyl orthoformate afforded 3-(5-nitro-2-furyl)-5-ethoxy-1,2,4-triazoline (III) and bis[3-(5-nitro-2-furyl)-1,2,4-triazolyl]methyl ethyl ether (IV). By heating with ethyl orthoformate, III was converted to IV. When III or IV was heated in diluted sulfuric acid, 3-(5-nitro-2-furyl)-1,2,4-triazole (V) was produced. The reactions of I with cyanogen bromide in refluxing methanol and with nitrous acid in diluted hydrochloric acid gave the corresponding 3-(5-nitro-2-furyl)-5-amino-1,2,4-triazole (VI) or -1,2,4,5-tetrazole (VIII) respectively. When heated in acetic anhydride, the VI afforded monoacetyl compound (VII), while the VIII yielded 5-(5-nitro-2-furyl)-2-methyl-1,3,4-oxadiazole (X). The structures of these compounds were discussed on the basis of their IR and NMR spectra.

In a previous paper[3] the present authors synthesized 5-nitro-2-furimidoylhydrazine (I) by treating 5-nitro-2-furonitrile with hydrazine hydrate. Since the structure of I is analogous to that of aminoguanidine, I is expected to show a reactivity similar to that of aminoguanidine toward various bifunctional compounds. This paper will deal with the preparation of several 5-nitro-2-furyl-heterocycles by the cyclization of I with bifunctional compounds.

Results and Discussion

Erickson[4] has prepared 3-amino-1,2,4-triazine derivatives by the reactions of aminoguanidine carbonate with glyoxal and diacetyl, but Thile *et al.* reported[5] that only bisguanylhydrazone was obtained instead of 1,2,4-triazine by the similar reaction of either aminoguanidine nitrate or the hydrochloride with glyoxal, and Polonovski[6] and Gianturco[7] have investigated this in detail. When I was treated with diacetyl in boiling methanol, an orange crystalline product, mp 212°C, was obtained. An elemental analysis of this product (Found: C, 46.54; H, 3.64; N, 25.42%) did not agree with the calculated value for the desired compound. The IR spectrum of this compound showed N–H absorption at 3250 cm^{-1}, but no C=O absorption was detected. No further determination of the structure of this compound has been undertaken. However, when treated with diacetyl in refluxing methanol containing *N,N*-dimethylformamide, I afforded the desired 3-(5-nitro-2-furyl)-5,6-dimethyl-1,2,4-triazine (IIa). The similar treatment of I with furil in refluxing methanol afforded the desired cyclization product, 3-(5-nitro-2-furyl)-5,6-bis(2-furyl)-1,2,4-triazine (IIb).

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[1] Part XXII of this series: Y. Kato, This Bulletin, **44**, 489 (1971).

[2] Presented at the 20th Annual Meeting of The Chemical Society of Japan, Tokyo, March, 1967.

[3] Y. Kato and I. Hirao, *Bull. Kyushu Inst. Tech.*, No. **15**, 57 (1965).

[4] J. G. Erickson, *J. Amer. Chem. Soc.*, **74**, 4706 (1952).

[5] J. Thile and E. Pralle, *Ann.*, **302**, 275 (1898).

[6] M. Polonovski and M. Pesson, *C. R. Acad. Sci., Paris*, **232**, 1260 (1951).

[7] M. Gianturco and A. Romeo, *Gazz. Chim. Ital.*, **82**, 429 (1953).

When I was refluxed in a large excess of ethyl orthoformate, two compounds, III (mp 131—132°C (32% yield)) and IV (mp 179—180°C (28.6%)), were produced. Judging from the results of the elemental analysis, III seems to be 3-(5-nitro-2-furyl)-5-ethoxy-1,2,4-triazoline, and IV, bis[3-(5-nitro-2-furyl)-1,2,4-triazolyl]methyl ethyl ether. The presence of a triazole structure in III and IV was supported by the characteristic IR absorption bands in the 3500—2800 cm^{-1} region.[8]

Table 1. Effects of reaction time on the yield and the compound ratio

Reaction time (hr)	Product Total yield (%)	Ratio III	 IV
0.25	78.3	92.2	7.8
1	60.6	52.8	47.2
5	58.6	0	100.0

The relation between the reaction time and the product ratio was investigated; the results are shown in Table 1. With an increase in the reaction time, the formation of III as well as the total yields decreased, but that of IV increased. This suggests that III was formed in the initial step and that IV may be produced by the existence of excess ethyl orthoformate.

Compound III was stable to heating in 2-methoxyethanol, but was unstable in diluted sulfuric acid, when it gave 3-(5-nitro-2-furyl)-1,2,4-triazole (V) by eliminating a molecule of ethanol. V was also obtained by heating IV in diluted sulfuric acid. It seems that IV reacts with water under the catalytic action of the acid to afford V by liberating ethyl formate. Compound V is obviously a 1,2,4-triazole derivative since, in the IR spectrum, characteristic absorptions of C–H in the triazole ring remained, but no more $-OC_2H_5$ was present. III was heated in ethyl orthoformate to give IV, but the V remained unchanged. When an equimolar mixture of ethyl orthoformate and I was heated in 2-methoxyethanol, no formation of IV was observed and the sole product was III. The NMR spectra (shown in Table 2) are compatible with the above structures, III, IV, and V.

Table 2. NMR data of III, IV, and V (at 60 MHz in DMSO-d_6)

	III δ	IV δ	V δ
Triazole ring C–H	8.28 (1H, sharp s)	9.35 (2H, sharp s)	8.82 (1H, sharp s)
Furan ring 4–H	7.78 (1H, sharp d, J=4.1 Hz)	7.86 (2H, sharp d, J=4.2 Hz)	7.85 (1H, sharp d, J=4.2 Hz)
Furan ring 3–H	7.29 (1H, sharp d, J=4.1 Hz)	7.43 (2H, sharp d, J=4.2 Hz)	7.34 (1H, sharp d, J=4.2 Hz)
Triazole ring N–H	6.62 (2H, broad s)		3.62 (1H, very broad s)
Methine ($-\overset{|}{\underset{|}{C}}-H$)		8.17 (1H, sharp s)	
Ethoxy CH_2	4.28 (2H, sharp q, J=7.2 Hz)	4.01 (2H, sharp q, J=7.2 Hz)	
Ethoxy CH_3	1.31 (3H, sharp t, J=7.2 Hz)	1.38 (3H, sharp t, J=7.2 Hz)	

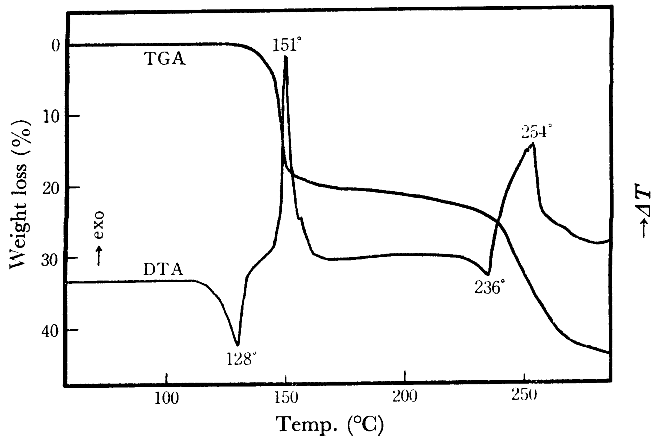

Fig. 1. Thermal analysis of III measured in an argon stream using 21.3 mg of sample at the heating rate of 3°C/min.

Furthermore, the thermostability of III was investigated by thermogravimetric analysis (TGA) and differencial thermal analysis (DTA). In Fig. 1, the DTA curve shows an endothermic peak at 128°C which coincides with the melting point of compound III. Two exothermic peaks, one at 151°C and the other at 254°C, correspond to the initial and the second stages (128—154°C and 236—270°C) respectively of the reduction in weight of the TGA curve. About 20% of the loss of weight occurs in the initial stage; this corresponds to the loss of a molecule of ethanol from III (theoretical 20.3%). The second stage of the reduction in weight agrees with the decomposition point of V during the pyrolysis.

These results show that the releasing of ethanol from III occurred at 128—154°C, but not under the refluxing temperature (110—120°C) in ethyl orthoformate or in 2-methoxyethanol. Therefore, it seems most resonable to conclude that the mechanism of the formation of IV is in the initial step, giving III from I and ethyl orthoformate, and in the following reaction of III with excess ethyl orthoformate, affording IV without the process: III→V→IV.

When acyl hydrazines are treated with cyanogen bromide, 5-substituted 2-amino-1,3,4-oxadiazole is formed.[9] Similarly, 3-(5-nitro-2-furyl)-5-amino-1,2,4-triazole (VI) was obtained by the treatment of I with cyanogen bromide in refluxing methanol. The IR spectrum of VI has characteristic absorptions at 3400, 3295 (νNH_2), 1646 (δNH_2), and 1320 cm^{-1} (νC–N), supporting the amino-triazole structure. A monoacetyl derivative (VII) was obtained by the treatment of VI with hot acetic anhydride, whereas it reverted to the

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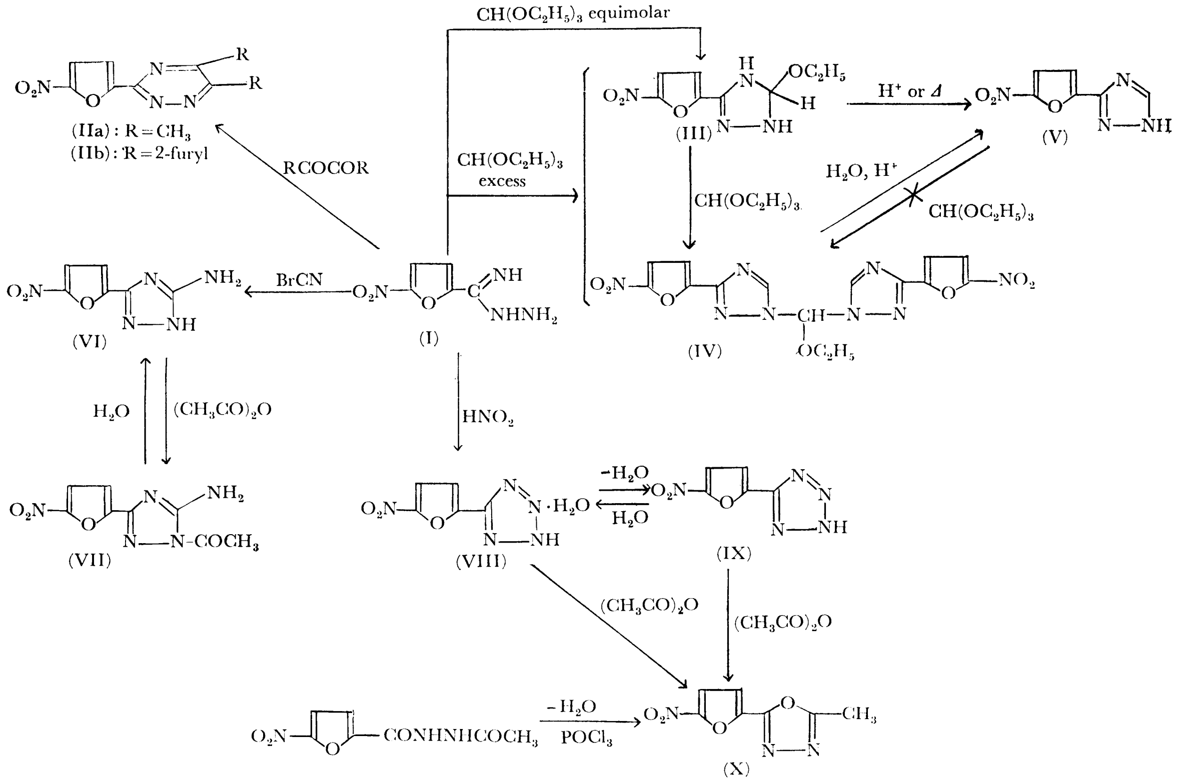
8) K. T. Potts, *J. Chem. Soc.*, **1954**, 3461.

9) A. Dornow and K. Brunken, *Ber.*, **82**, 121 (1949).



starting material VI upon heating with water. The presence of a carbonyl absorption at 1733 cm^{-1} in the IR spectrum of VII suggests that the acetylation had occurred at the ring imino nitrogen because of a shift to higher frequencies than with the usual amides. The lack of the production of di- or triacetyl derivative is attributable to the low solubility of VII in the given solvent.

In order to prepare the tetrazole derivative, I was treated with nitrous acid in diluted hydrochloric acid according to Pinner's procedure;[10] this afforded the product (VIII), mp 71—72°C. The IR spectrum has an O–H absorption at 3500—3200 cm^{-1}, perhaps due to the water of recrystallization. In fact, the elemental analysis is compatible with the value calculated for the monohydrate of 5-(5-nitro-2-furyl)tetrazole. Water was successfully removed when VIII was heated at 50—55°C *in vacuo* to give 5-(5-nitro-2-furyl)tetrazole (IX), mp 121—122°C, and IX was converted to VIII by heating it in water for several minutes. IX showed no O–H absorption in the infrared spectrum. In order to confirm the above facts, the thermal analysis of VIII was undertaken. As is shown in Fig. 2, two endothermic peaks are observed in the DTA curve, at 57 and 120°C. The initial peak and its shoulder (60°C) are in agreement with a stage of the reduction in weight at 30—70°C (about 8.9% of loss of weight), corresponding to the loss of a molecule of water (9.04%), and with the melting point of VIII of the TGA curve. The second endothermic peak is obviously in good accordance with the melting point of IX for the TGA curve.

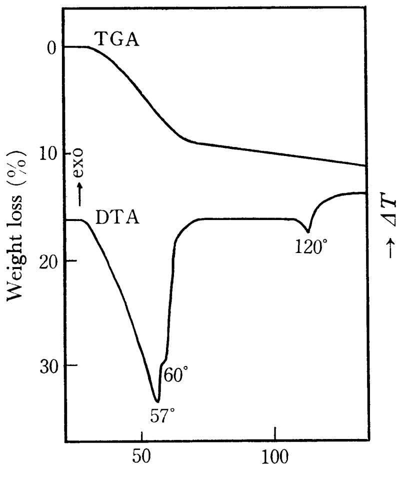


Fig. 2. Thermal analysis of VIII measured in an argon stream using 14.2 mg of sample at the heating rate of 3°C/min.

The IR spectra showed characteristic wide ammonium and immonium absorptions in the 2900—2100 and 2000—1800 cm^{-1} regions for VIII, and in the 3000—2300 cm^{-1} region for IX. These facts, as claimed by Otting,[11] suggest that both VIII and IX participate in an intermolecular association in which the hydrogen atom of the imino group protonates a nitrogen of an adjacent molecule, the two charged particles being stabilized by resonance. The difference between VIII and IX may be presumed to be that VIII can form the structural element $=\underset{|}{N}^{+}\text{–H}$ with greater facility than can IX because of the included water of recrystallization, the hydrogen transfer being thus made easier.

When VIII or IX was heated in acetic anhydride, the product (X) was not the desired *N*-acetyl-tetrazole but 5-(5-nitro-2-furyl)-2-methyl-1,3,4-oxadiazole, which was identified by means of an alternate method of pre-

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[10] A. Pinner, *Ber.*, **27**, 990 (1894).

[11] W. Otting, *Chem. Ber.*, **89**, 2887 (1956).

paration utilizing the dehydration of 1-(5-nitro-2-furoyl)-2-acetylhydrazine with phosphoryl chloride. This reaction might occur much as in the formation of 2,5-disubstituted 1,3,4-oxadiazole from 5-substituted tetrazole and acyl chlorides, as has been reported by Huisgen *et al.*,[12] though Pinner *et al.*[13] obtained a ring-opening *N*-acetyl-*p*-toluamidine on the treatment of 5-*p*-tolyltetrazole with hot acetic anhydride.

Experimental

All the melting and decomposing points are uncorrected. Microanalyses were carried out with a Yanagimoto C.H.N. Corder, MT-2 type. The infrared absorption spectra (IR) were obtained with a Shimadzu IR-27S spectrophotometer by the KBr method. The nuclear magnetic resonance spectra (NMR) were measured with a Nihon-Denshi NMR spectrometer, JNM C-60HL, in DMSO-d_6 and with tetramethylsilane as the internal standard; the peak positions are expressed in δ-values. The thermal analyses were carried out with a Rigaku Denki Thermoflex in an argon stream.

3-(5-Nitro-2-furyl)-5,6-dimethyl-1,2,4-triazine (IIa). A solution of I[3] (3 g, 17.6 mmol) and *N*,*N*-dimethylformamide (20 m*l*) in 200 m*l* of methanol was stirred slowly into a solution of diacetyl (1.6 g, 18.6 mmol) in 50 m*l* of methanol. The resulting solution was stirred for an additional 2 hr and then heated under reflux for 3 hr. Cooling provided 1.86 g of pale yellow needles (mp 160—161°C). When the mother liquor was concentrated *in vacuo*, a pale yellow powder was obtained, mp 160.5—161°C; weight, 1.61 g. The total yield was 3.47 g. Recrystallization from 30% aqueous methanol gave pale yellow needles, mp 160.5—161°C. The yield was 3.06 g (78.9%).

Found: C, 49.08%; H, 3.52; N, 25.29%. Calcd for $C_9H_8N_4O_5$: C, 49.09; H, 3.64; N, 25.45%.

3-(5-Nitro-2-furyl)-5,6-bis(2-furyl)-1,2,4-triazine (IIb). To a stirred solution of furil (0.19 g, 1 mmol) in 15 m*l* of methanol we added, drop by drop, a solution of I (0.17 g, 1 mmol) in 10 m*l* of methanol. After the addition was over, the resulting solution was refluxed for 3 hr and left to stand overnight; the product was then collected by filtration. Recrystallization from methanol gave yellow needles, mp 159—161°C. The yield was 0.15 g (51.3%).

Found: C, 55.43; H, 2.56; N, 17.53%. Calcd for $C_{15}H_8N_4O_5$: C, 55.56; H, 2.47; N, 17.28%.

3-(5-Nitro-2-furyl)-5-ethoxy-1,2,4-triazoline (III). A mixture of I (1.7 g, 10 mmol), ethyl orthoformate (1.48 g, 10 mmol), and 25 m*l* of 2-methoxyethanol was heated under reflux for 15 min. The resulting solution was concentrated to dryness *in vacuo* below 50°C. The residue was dissolved in hot benzene, and the insoluble material was filtered off. After the solution had been left standing, the precipitates were collected and crystallized from benzene to give 1.31 g (50%) of III as orange needles which melted at 131—132°C. IR: cm^{-1} 3409 and 3310 (N–H), 2980—2870 (CH_3, CH_2).

Found: C, 42.58; H, 4.49; N, 24.83%. Calcd for $C_8H_{10}N_4O_4$: C, 42.47; H, 4.42; N, 24.78%.

Bis[3-(5-nitro-2-furyl)-1,2,4-triazolyl]methyl Ethyl Ether (IV). From I and Ethyl Orthoformate: Compound I (3 g, 17.6 mmol) was suspended in ethyl orthoformate (30 m*l*) and heated under reflux for 5 hr. The solution was then cooled, and the precipitate was collected on a filter, washed with cold benzene, and dried to give a yellow powder. Recrystallization from dioxane-water provided yellow columns; mp 179—180°C. The yield was 2.15 g (58.6%). IR: cm^{-1} 3120 (C–H in triazole ring), 2960—2846 (CH_3, CH_2).

Found: C, 43.30; H, 3.00; N, 26.98%. Calcd for $C_{15}H_{12}N_8O_7$: C, 43.27; H, 2.88; N, 26.92%.

From III and Ethyl Orthoformate: A mixture of III (0.21 g, 1.2 mmol) and 2 m*l* of ethyl orthoformate was heated under reflux for 4 hr. The solution was concentrated *in vacuo* affording 0.23 g of brown crystals; mp 131—161°C. Work-up as above gave 0.11 g (45.5%) of yellow columns, mp 180—181°C. This product was found to be identical with IV by elemental analysis and by a mixed-melting-point determination.

Reaction of I with Excess Ethyl Orthoformate. A mixture of I (1 g, 5.8 mmol) and 10 m*l* of ethyl orthoformate was heated under reflux for a given time (*cf.* Table 1). The ethyl orthoformate was then removed *in vacuo*, and the residue was slurried in boiling benzene to give crude IV. Recrystallization from dioxane-water gave a pure product. The benzene liquor was worked-up as above in order to prepare III. The yields are shown in Table 1.

3-(5-Nitro-2-furyl)-1,2,4-triazole (V). From the Reaction of III in Diluted Sulfuric Acid: A solution of III (0.23 g, 1 mmol) in 15 m*l* of 5% sulfuric acid was heated on a steam bath for 7—10 min. After concentration, the separated product was collected on a filter, washed with ether, and dried. This weighed 0.11 g (61.1%) and melted at 249—251°C with decomposition. Crystallization from water gave pale yellow crystals; mp 254—255°C (dec.). IR: cm^{-1} 3080 (C–H in triazole ring).

Found: C, 40.11; H, 2.00; N, 31.15%. Calcd for $C_6H_4N_4O_3$: C, 40.00; H, 2.22; N, 31.11%.

Decomposition of IV with Sulfuric Acid: A mixture of IV (2.08 g, 5 mmol) and 30 m*l* of 25% sulfuric acid was heated to boiling for 1 hr. On the concentration of the solution to half of the initial volume, the product separated as yellow crystals; mp 249—253°C (dec.); weight, 0.7 g. An additional 1 g was obtained by neutralizing the sulfuric acid solution with solid sodium carbonate. The total yield was 1.7 g (94.4%). Recrystallization as above gave pale yellow crystals; mp 254—255°C (dec.). The melting point of this compound was not depressed upon admixture with an authentic sample.

3-(5-Nitro-2-furyl)-5-amino-1,2,4-triazole (VI). Cyanogen bromide (1.9 g, 17.6 mmol) and I (3 g, 17.6 mmol) were heated together under reflux in 200 m*l* of methanol for 1 hr. The solution was then taken to dryness *in vacuo*, affording a brown residue. Crystallization from water gave yellow plates; mp 273.5—274°C. The yield was 1.8 g (52.4%).

Found: C, 37.21; H, 2.71; N, 35.40%. Calcd for $C_6H_5N_5O_3$: C, 36.92; H, 2.56; N, 35.89%.

3-(5-Nitro-2-furyl)-1-acetyl-5-amino-1,2,4-triazole (VII). Compound VI (0.49 g, 2.5 mmol) was covered with acetic anhydride (5—10 m*l*) and heated on a steam bath for 15 min. Water (50 m*l*) was added to the resulting suspension in order to decompose the surplus acid anhydride. The product was filtered and then slurried in 50 m*l* of boiling methanol. In this way 0.57 g (95.8%) of pure VII was obtained as a fine yellow powder; mp>350°C.

Found: C, 40.88; H, 2.90; N, 29.28%. Calcd for $C_8H_7N_5O_4$: C, 40.51; H, 2.95; N, 29.54%.

Hydrolysis of VII. Acetyl compound VII (0.1 g, 0.36 mmol) was heated under reflux in 80 m*l* of water for 4.5 hr. Cooling provided 0.07 g (quantitative) of yellow plates of VI; mp 273°C (dec.) (water). This product was identical in its infrared spectrum with an authentic sample of VI.

5-(5-Nitoro-2-furyl)tetrazole Monohydrate (VIII). To a

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[12] R. Huisgen, J. Sauer, and H. J. Sturm, *Angew. Chem.*, **70**, 272 (1958).

[13] A. Pinner, *Ann.*, **298**, 7 (1897); A. Pinner and N. Caro, *Ber.*, **27**, 3278 (1894).

stirred, ice-cooled solution of I (5.0 g, 29.4 mmol) in a mixture of concentrated hydrochloric acid (5 g) and 50 m*l* of water, we added, portion by portion, 3.24 g (46.9 mmol) of sodium nitrite powder. Stirring was then continued for an additional 2 hr at 3—5°C. The product was filtered and washed with a small amount of water to give 5.1 g of a tan powder. Crystallization from water gave 4.7 g (80.2%) of VIII as yellow plates; mp 71—72°C.

Found: C, 30.67; H, 2.57; N, 35.48%. Calcd for $C_5H_3N_5O_3 \cdot H_2O$: C, 30.15; H, 2.51; N, 35.17%.

5-(5-Nitro-2-furyl)tetrazole (IX). Monohydrate VIII (314.4 mg, 1.58 mmol) was heated at 50—55°C in a vacuum flask for 6 hr. After the loss of 28.4 mg of water, 286 mg of IX were obtained as a pale yellow powder; mp 121—122°C.

Found: C, 33.20; H, 1.59; N, 38.72%. Calcd for $C_5H_3N_5O_3$: C, 33.14; H, 1.65; N, 38.67%.

Hydration of IX. A solution of IX (147 mg, 0.81 mmol) in 1 m*l* of water was heated on a steam bath for 5 min. Cooling gave 163 mg (quantative) of VIII as pale yellow needles; mp 70—71°C, undepressed on admixture with a sample prepared by the method described above for VIII.

5-(5-Nitro-2-furyl)-2-methyl-1,3,4-oxadiazole (X). From the Cyclization of 1-(5-Nitro-2-furoyl)-2-acetylhydrazine: A suspension of 2.13 g (10 mmol) of 1-(5-nitro-2-furoyl)-2-acetylhydrazine in 25 m*l* of phosphoryl chloride was heated on a steam bath for 3 hr. The resulting solution was taken to dryness *in vacuo*, and the residue was washed with water. Crystallization from methanol gave 0.8 g (41%) of X as yellow needles; mp 151—152°C.

Found: C, 42.93; H, 2.67; N, 21.85%. Calcd for $C_7H_5N_3O_4$: C, 43.08; H, 2.56; N, 21.55%.

From the Reacton of VIII or IX with Acetic Anhydride: A mixture of VIII (or IX) (1.5 mmol) and 5 m*l* of acetic anhydride was heated under reflux for 2 hr. The acetic anhydride was removed *in vacuo*, and the residue was dissolved in 30 m*l* of ethanol. Cooling provided pale yellow plates melting at 152—153°C in a 58—60% yield.

Found: C, 43.44; H, 2.58; N, 21.27%.

This product was identified as X by an admixture-test and by a comparison of the infrared spectrum with that of an authentic sample.