zinyl sulfones have moderately strong absorption bands in the 12.2-μ region. These are absent from the spectrum of 2-methylsulfonylphenothiazine, which instead shows a weak band in the 12.6-μ region. The absorption of the various sulfones in the 12.2 and 12.6-μ region is attributed to the two aromatic C—H bonds in series at the 1,2-positions for the 3-phenothiazinyl sulfones and the 3,4-positions of 2-methylsulfonylphenothiazine.

In addition, the normal 1,2,4-trisubstituted benzene absorption pattern is observed for all the 3-phenothiazinyl sulfones and not the 1,2,3-trisubstituted pattern which would be present if the sulfonylation products were 1- or 4-sulfonylphenothiazines.

Spectra of both 3-*p*-tolylsulfonylphenothiazine and its 2-isomer would be expected to show absorption at 12.2–12.3 μ as there are two isolated aromatic C—H bonds in series in the *p*-tolyl group itself. However, the spectrum of the 10-*p*-tolylsulfonyl derivative lacks the 11.2-μ absorption present in that of the corresponding sulfone and neither exhibits the absorption at 12.6 μ present in the spectrum of 2-methylsulfonylphenothiazine.

The presence of 10-sulfonylphenothiazines in chromatographic fractions of the reaction tars could be detected by the occurrence in their spectra of the sulfur-oxygen asymmetric stretching band at 7.4 μ characteristic of aromatic sulfonamides. In the spectra of the phenothiazinyl sulfones this band appears at the normal position for aromatic sulfones (7.6 μ). In addition, the band at 3.0 μ (N—H) present in the spectra of phenothiazine and its sulfone derivatives is absent from those of the 10-sulfonyl derivatives.

Spectral data for 3,7-diphenylsulfonylphenothiazine, obtained from reaction no. 18 (Table I), was consistent with the data presented above. The shift in absorption of 12 mμ (from 268 to 280 mμ) resulting from the addition of a second benzenesulfonyl group to the 7-position of 3-phenylsulfonylphenothiazine compares closely with the shift of 14 mμ (from 254 to 268 mμ) resulting from the addition of a single benzenesulfonyl group to the 3-position of phenothiazine. In addition, the 11.1-μ band in the spectrum of 3,7-diphenylsulfonylphenothiazine was stronger than that in the spectra of any of the 3-phenothiazinyl sulfones, as expected, because of the presence of two isolated aromatic C—H bonds at the 4- and 6-positions of this disulfone.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES[

4-(5-Nitro-2-furyl)thiazoles[1a]

WILLIAM R. SHERMAN AND DONALD E. DICKSON

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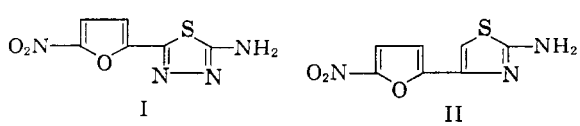
A number of 4-(5-nitro-2-furyl)thiazoles have been prepared. The antibacterial activity of these compounds is briefly discussed.

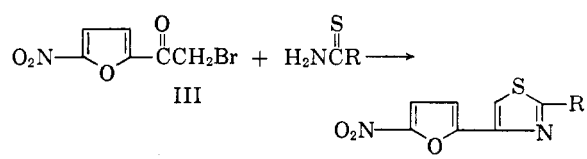
In a recent publication from this laboratory,[1b] it was shown that the antibacterial properties of 5-nitrofurans are not dependent on a linear —C=N—N—C= system in the 2- position. Thus, incorporation of this atomic arrangement into a heterocycle does not diminish in any way the antibacterial activity of the resulting nitrofuran. It was also shown that the azine portion of the heterocycle associated with the nitrofuran could be completely discarded, and still retain full antibacterial activity. It is this latter type of nitrofuryl heterocycle which is the subject of this paper.

While considering a group of heterocyclic types which did not contain an azine system, we were attracted by the similarity between the antibacterial 2 - amino - 5 - (5 - nitro - 2 - furyl) - 1,3,4-thiadiazole[1b,2] (I) and 2-amino-4-(5-nitro-2-furyl)-thiazole (II). This and other thiazoles may be easily obtained by the general procedure first described by Hantzsch[3]—the reaction of an α-halo ketone with thioamide-type compounds. Thus the action of thioamides, thioureas, dithiocarbamates, and acetone thiosemicarbazone on 2-bromoacetyl-5-nitrofuran[4] (III) gives rise to 4-(5-nitro-2-furyl)-thiazoles with various groups in the 2-position (IV). Reactions of this type are well described in the literature,[5] and for the most part proceeded smoothly in this series. 2-Methyl-4-(5-nitro-2-furyl)-



I

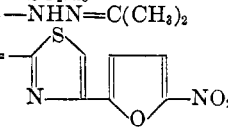
II



III

IV

IVa. R = —H
b. R = —CH_3
c. R = —NH_2
d. R = —$NHCH_3 \cdot HBr$
e. R = —NHC_2H_5
f. R = —NHC_6H_5
g. R = —SCH_3
h. R = —SC_2H_5
i. R = —$NHN{=}C(CH_3)_2$
j. R =



(1)(a) Presented at the 139th Meeting of the American Chemical Society, Medicinal Section, St. Louis, Mo., March 27–30, 1961. (b) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(2) K. Skagius, K. Rubinstein, and E. Ifversen, *Acta Chem. Scand.* **14**, 1054 (1960).

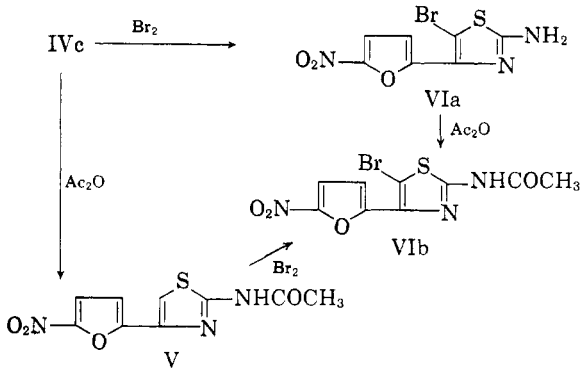
(3) A. Hantzsch *et. al.*, *Ann.*, **249**, 1 (1888).

(4) O. Dann, H. Ulrich, and E. F. Moller, *Z. Naturforsch.*, **7b**, 344 (1952).

(5) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., Wiley, New York, 1957.

thiazole (IVb) was also prepared by nitration of 2-methyl-4-(2-furyl)thiazole[6] with nitric acid in acetic anhydride.

Bromination of the 2-aminonitrofurylthiazole IVc and its acetyl derivative V gave monobromo compounds. These are considered to be the 5-bromothiazoles because of the inactivity of the nitrofuran ring toward bromination and the ease with which aminothiazoles with an unoccupied 5-position undergo halogenation.[5] Acetylation of 2-amino-5-bromo-4-(5-nitro-2-furyl)thiazole (VIa) provided an alternate route to the acetyl bromo compound VIb and related the two structures.



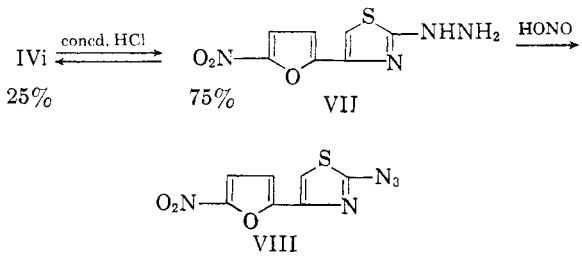
When 2-(2-isopropylidinehydrazino)-4-(5-nitro-2-furyl)thiazole (IVi) was dissolved in concentrated hydrochloric acid at room temperature, an equilibrium mixture resulted which contained about 75% of 2-hydrazino-4-(5-nitro-2-furyl)thiazole (VII) and 25% of the isopropylidine hydrazine IVi. To establish that this was an equilibrium process, equimolar amounts of VII and acetone were treated in concentrated hydrochloric acid to give the same mixture.

2-Hydrazino-4-(5-nitro-2-furyl)thiazole (VII) is a bright red compound of such low basicity that its hydrochloride salt decomposes to the free base in water. Treatment of VII with nitrous acid gives rise to 2-azido-4-(5-nitro-2-furyl)thiazole (VIII). This compound shows the expected[7] 4.67 μ absorption in the infrared, in chloroform solution.[8] The formation of the azide and not the isomeric thiazolotetrazole supports the proposition that electron-withdrawing groups stabilize azides while destabilizing the tetrazole isomer.[9] The azide VIII is quite unstable in the light, darkening rapidly on exposure.

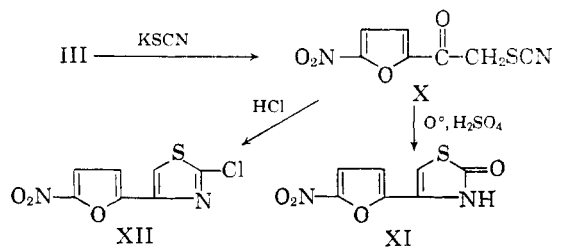
Treatment of the hydrazinothiazole VII with boiling formic acid gave only 2-(2-formylhydrazino)-4-(5-nitro-2-furyl)thiazole (IX), with no indication of any thiazolotriazole.

Both the azide VIII and the formhydrazide IX could also be prepared from the isopropylidinehydrazine IVi under suitable conditions.

The hydrazinothiazole VII also underwent the expected reaction with phenylisothiocyanate to give the phenyl thiosemicarbazide. Either one or two acetyl groups could be introduced into VII by appropriate temperature control.



One of the general methods for preparing 2-hydroxythiazoles is the cyclization of an α-thiocyano ketone.[5] Treatment of 2-bromoacetyl-5-nitrofuran (III) with potassium thiocyanate gave thiocyanomethyl 5-nitro-2-furyl ketone (X). When X was treated with concentrated sulfuric acid at 0°, a high yield of 4-(5-nitro-2-furyl)thiazol-2-one (XI) was obtained. The assignment of the thiazolone structure, at least in the solid state, is based on the strong absorption at 6.06 μ (Nujol) in the infrared. The action of hydrogen chloride in ether on the thiocyano ketone X produced 2-chloro-4-(5-nitro-2-furyl)thiazole (XII).



Nearly all of the compounds which have been described in this paper have demonstrated antibacterial activity *in vitro* and many are also effective in the control of experimental infections in mice. In general, the greatest activity is shown against *Staphylococcus aureus, Salmonella typhimurium,* and *Escherichia coli.* Complete growth inhibition *in vitro* was usually obtained by agar dilutions of 1 part in 160,000 or greater.[10]

The greatest interest in this series has centered about the 2-aminothiazole IVc and its acetyl derivative V. These compounds are effective in the control of experimental mouse infections, when

(6) E. B. Knott, *J. Chem. Soc.*, 1656 (1947).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd. ed., Methuen and Co. Ltd., London, 1958, p. 273.

(8) Infrared spectra were determined by W. Washburn and staff of Abbott Laboratories, whose aid in the interpretation of this data is acknowledged. Spectra were measured on a Perkin-Elmer Model 21 spectrophotometer.

(9) J. H. Boyer and E. J. Miller, *J. Am. Chem. Soc.*, 81, 4671 (1959).

(10) Detailed information regarding the *in vitro* and *in vivo* antibacterial activity of these compounds will be published elsewhere. This work has been carried out by J. C. Holper and R. H. Otto and their staffs at Abbott Laboratories.

administered by either the oral or intramuscular route. Of particular interest is V, which displays a favorable therapeutic index in the control of experimental infections in mice of the organisms described above. This compound displays the unusual property of dependence on crystal form for activity in animals. It is possible to form several polymorphs of Va, each of which is distinctly different in x-ray diffraction pattern and in infrared spectrum in Nujol mull. When examined in dimethylformamide solution in the 10–15-μ region, the forms are all identical. The dependence on proper crystal form for activity appears to be related to the different solubilities of each of the modifications.

EXPERIMENTAL[11]

Typical procedure for preparing 2-substituted 4-(5-nitro-2-furyl)thiazoles (IV). *4-(5-Nitro-2-furyl)thiazole* (IVa). A solution of 1.8 g. (0.030 mole) of thioformamide in 25 ml. of ethanol was heated to 40° and 7.0 (0.03 mole) of 2-bromoacetyl-5-nitrofuran[4] (III) was added portionwise. When the exothermic reaction had subsided, the mixture was heated under reflux for 15 min. and then cooled. The product which separated was crystallized from ethanol to provide 3.6 g. (61%) of product melting from 152–154°.

Anal. Calcd. for $C_7H_4N_2O_3S$: C, 42.87; H, 2.06; N, 14.29. Found: C, 43.15; H, 2.11; N, 14.15.

2-Methyl-4-(5-nitro-2-furyl)thiazole (IVb). *Method A.* Following the Typical Procedure used in the preparation of IVa, above, 9.6 g. (0.120 mole) of thioacetamide in 120 ml. of ethanol was heated to 60° and 30 g. (0.128 mole) of bromo ketone III added. After crystallization the product weighed 13.5 g. (50%) and melted at 141–142°.

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.72; H, 2.88; N, 13.33. Found: C, 45.63; H, 2.94; N, 13.11.

Method B. To a stirred solution containing 2.4 ml. of concentrated nitric acid and 25 ml. of acetic anhydride maintained at 40°, was added 5.3 g. (0.032 mole) of 2-methyl-4-(2-furyl)thiazole.[6] After 30 min. the solution was cooled and 40 ml. of water containing 3.6 g. of sodium hydroxide added. After stirring for 30 min. at 60° followed by 1 hr. at 0°, the product separated partly as an oil, partly as a solid. The solid was collected and recrystallized from ethanol. The oil was extracted with ethanol, which on dilution with water provided additional product. The combined crops melted at 140–142° and weighed 0.41 g. (61%). Recrystallization from ethanol gave yellow needles, m.p. 142–143°, identical in all ways with material obtained by *Method A*.

2-Amino-4-(5-nitro-2-furyl)thiazole (IVc). Following the Typical Procedure used in the preparation of IVa 3.54 g. (0.0466 mole) of thiourea in 60 ml. of ethanol was heated to 60° and 10.9 g. (0.0466 mole) of bromo ketone III added. Cooling and scratching provided 11.4 g. (84%) of the hydrobromide salt of IVc, m.p. 226–227° (dec., block). Crystallization from ethanol raised the m.p. to 235° (dec., block).

Anal. Calcd. for $C_7H_5N_3O_3S \cdot HBr$: C, 28.78; H, 2.07; N, 14.38. Found: C, 28.87; H, 2.04; N, 14.19.

The hydrobromide salt obtained above could be converted to the free base by simply slurrying in water. Thus 4 g. of crude hydrobromide gave 2.1 g. of free base, m.p. 233–235° (dec., block) after 1.5 hr. in water. Crystallization from ethanol gave product m.p. 235–237° (dec., block).

Anal. Calcd. for $C_7H_5N_3O_3S$: C, 39.81; H, 2.39; N, 19.90. Found: C, 39.82; H, 2.53; N, 19.77.

(11) All melting points are uncorrected and were determined in capillary tubes, unless otherwise noted. Analyses were carried out by E. F. Shelberg and staff of Abbott Laboratories.

2-Methylamino-4-(5-nitro-2-furyl)thiazole; hydrobromide (IVd). In the same way as in the Typical Procedure for the preparation of IVa, 3.85 g. (0.0427 mole) of methylthiourea reacted with 10 g. (0.0421 mole) of bromoketone III in 32 ml. of ethanol at 60°. The product was obtained as the hydrobromide salt by precipitation from the reaction mixture with ether. After crystallization from ethanol, it melted at 191–193° (dec.), and weighed 7.3 g. (54%).

Anal. Calcd. for $C_8H_7N_3O_3S \cdot HBr$: C, 31.38; H, 2.63; N, 13.73. Found: C, 31.14; H, 2.90; N, 13.70.

2-Ethylamino-4-(5-nitro-2-furyl)thiazole (IVe). Following the typical procedure used in preparing IVa, 4.44 g. (0.0426 mole) of ethylthiourea was treated with 10 g. (0.0426 mole) of bromo ketone III in 70 ml. of ethanol at 70°. The free base was obtained by solution in pyridine and precipitation with water. After crystallization from ethanol, the product weighed 4.6 g. (45%) and melted at 158–159°.

Anal. Calcd. for $C_9H_9N_3O_3S$: C, 45.19; H, 3.79; N, 17.57. Found: C, 44.97; H, 3.73; N, 17.65.

2-Anilino-4-(5-nitro-2-furyl)thiazole (IVf). Following the typical procedure used in preparing IVa, 19.5 g. (0.128 mole) of phenylthiourea was treated with 30 g. (0.128 mole) of bromo ketone III in 150 ml. of ethanol at 65°. Addition of ether to the reaction mixture precipitated the product as its hydrobromide salt. Solution in pyridine followed by precipitation with water gave the free base, which, after crystallization from ethanol, melted at 141–143° and weighed 15.5 g. (42%).

Anal. Calcd. for $C_{13}H_9N_3O_3S$: C, 54.35; H, 3.16; N, 14.63. Found: C, 54.45; H, 3.34; N, 14.51.

2-Methylthio-4-(5-nitro-2-furyl)thiazole (IVg). A solution of 24 g. (0.103 mole) of 2-bromoacetyl-5-nitrofuran in 60 ml. of ethanol was maintained at 60° while 11 g. (0.103 mole) of methyl dithiocarbamate dissolved in 60 ml. of ethanol was added. Following the addition the temperature was held at 60° for 10 min., and the mixture cooled. The product was collected and crystallized from ethyl acetate to provide 11 g. (45%), m.p. 140–142°.

Anal. Calcd. for $C_8H_6N_2O_3S_2$: C, 39.68; H, 2.50; N, 11.57. Found: C, 39.81; H, 2.67; N, 11.82.

2-Ethylthio-4-(5-nitro-2-furyl)thiazole (IVh). This was prepared in the same way as the methylthio compound, above. Using 3.8 g. (0.0162 mole) of bromo ketone III, and 1.92 g. (0.0162 mole) of ethyl dithiocarbamate, 2.0 g. (48%) of pure IVh, m.p. 120–121°, was obtained.

Anal. Calcd. for $C_9H_8N_2O_3S_2$: C, 42.19; H, 3.15; N, 10.94. Found: C, 42.07; H, 3.31; N, 10.77.

2-(2-Isopropylidinehydrazino)-4-(5-nitro-2-furyl)thiazole (IVi). Following the typical procedure used in preparing IVa, 7.8 g. (0.060 mole) of acetone thiosemicarbazone was treated with 14.0 g. (0.060 mole) of bromoketone III in 120 ml. of ethanol, at 70°. The product which separated from the reaction mixture appeared to be the hydrobromide salt. This was crystallized from pyridine water to give pure IVi, m.p. 216–217° (dec., block), weighing 10.0 g. (63%).

Anal. Calcd. for $C_{10}H_{10}N_4O_3S$: C, 45.11; H, 3.79; N, 21.05. Found: C, 44.95; H, 4.07; N, 20.92.

2,2'-Bi[4-(5-nitro-2-furyl)thiazole] (IVj). Following the Typical Procedure used for the preparation of IVa, 2.4 g. (0.02 mole) of dithioöxamide[12] and 9.4 g. (0.04 mole) of bromo ketone III were treated in 360 ml. of ethanol at 60°. The resulting precipitate was crystallized from dimethylformamide to give 2.0 g. (26%) of product, m.p. 340–343° (dec., preheated bath).

Anal. Calcd. for $C_{14}H_6N_4O_6S_2$: C, 43.07; H, 1.55; N, 14.36. Found: C, 43.29; H, 1.86; N, 14.37.

2-Acetamido-4-(5-nitro-2-furyl)thiazole (V). 2-Amino-4-(5-nitro-2-furyl)thiazole (IVc) hydrobromide (101 g., 0.344 mole) was dissolved in pyridine (1400 ml.), heated to 60°, and acetic anhydride (105 ml.) added. The solution was heated at 70° for 2 hr. with continual stirring. The resulting suspension was cooled to 0° and the product collected by filtration. In this way was obtained 78 g. (89%) of product melting at 290–294° (dec.). Crystallization from dimethyl-

formamide-water gave analytically pure product, m.p. 296° (dec.).

Anal. Calcd. for $C_9H_7N_3O_4S$: C, 42.69; H, 2.79; N, 16.60. Found: C, 42.98; H, 2.69; N, 16.54.

2-Amino-5-bromo-4-(5-nitro-2-furyl)thiazole (VIa). A solution of 9.9 g. (0.0467 mole) of 2-amino-4-(5-nitro-2-furyl)thiazole (IVc) in 360 ml. of glacial acetic acid was stirred at 40° while 7.5 g. (0.0467 mole) of bromine in a few milliliters of acetic acid was added. Following the addition, the mixture was warmed to 65° for a few minutes and cooled. The solid which separated was crystallized from acetic acid to provide 15 g. (86%) of product, m.p. 184–186°. This appeared to be the hydrobromide salt, and was converted to the free base by crystallization from ethanol, or treatment. with pyridine. The pure free base melted at 232–233° (dec.).

Anal. Calcd. for $C_7H_4N_3O_3Br$: C, 28.98; H, 1.34; N, 14.48. Found: C, 29.14; H, 1.53; N, 14.60.

2-Acetamido-5-bromo-4-(5-nitro-2-furyl)thiazole (VIb). A solution of 12.7 g. (0.05 mole) of 2-acetamido-4-(5-nitro-2-furyl)thiazole (V) in 200 ml. of glacial acetic acid was heated to 55° and stirred while 8.8 g. (0.055 mole) of bromine in a small amount of glacial acetic acid was added. After completing the addition, the mixture was stirred for 10 minutes at 65° and cooled. The solid product was collected and recrystallized from acetic acid to give 7.5 g. (45%) of product, m.p. 266–268° with decomposition.

Anal. Calcd. for $C_9H_6BrN_3O_4S$: C, 35.54; H, 1.82; N, 12.68. Found: C, 32.68; H, 1.91; N, 12.85.

The above compound was also obtained by acetylation of 2-amino-5-bromo-4-(5-nitro-2-furyl)thiazole with acetic anhydride. The product was identical by melting point and mixture melting point with the product obtained by the method above.

2-Hydrazino-4-(5-nitro-2-furyl)thiazole (VII). Ten grams (0.0376 mole) of 2-(2-isopropylidinehydrazino)-4-(5-nitro-2-furyl)thiazole (IVi) was added with stirring to 150 ml. of concentrated hydrochloric acid. The resulting solution was stirred overnight at room temperature. During this time, the hydrazine VII precipitated as its hydrochloride salt. The equilibrium mixture contained the isopropylidene compound IVi in solution and the hydrazine salt as the precipitate. The suspension was filtered and the filtrate neutralized with ammonium hydroxide to return 2.47 g. (24.7%) of starting material IVi. The solid hydrazine hydrochloride was slurried on the filter with dilute ammonium hydroxide, the pH being kept at about 5. In this way the bright red hydrazine was obtained as the free base in a yield of 6.28 g. (74%) melting at 209° (dec., block). One crystallization from dimethylformamide-water gave 5.42 g. of fine red needles, m.p. 219° (dec., block).

The decomposition point of this product depends on the rate of heating. After three crystallizations from dimethylformamide-water pure material was obtained which melted at 223.5° (dec., block) when heated from room temperature, or 228.5° (dec., block) when heated on a block preheated to 220°.

Anal. Calcd. for $C_7H_6N_4O_3S$: C, 37.17; H, 2.67; O, 21.21; N, 24.78. Found: C, 37.27; H, 2.76; O, 21.10; N, 24.67.

Equilibrium between IVi *and* VII *in acid solution.* In order to show that the partial conversion of isopropylidine compound IVi to the hydrazine VII was due to an equilibrium having been established, the following reaction was carried out. A mixture of 1.00 g. (0.00442 mole) of pure 2-hydrazino-4-(5-nitro-2-furyl)thiazole (VII) and 0.256 g. (0.00442 mole) of acetone in 15 ml. of concentrated hydrochloric acid was stirred at room temperature for 3 hr. The suspension was then worked up as in the preparation of VII above. In this way was obtained 0.28 g. (23.7%) of isopropylidine compound IVi (identical in melting point and infrared spectrum with authentic IVi) and 0.72 g. (72%) of starting hydrazine VII.

2-Azido-4-(5-nitro-2-furyl)thiazole (VIII). *Method A.* A suspension of 1.00 g. (0.00376 mole) of 2-(2-isopropylidinehydrazino)-4-(5-nitro-2-furyl)thiazole (IVi) in 15 ml. of concentrated hydrochloric acid was cooled to 10°. To this was added dropwise, with stirring, 0.260 g. (0.00377 mole) of sodium nitrite dissolved in a few ml. of water. The resulting suspension was stirred at 10° for 1 hr., and the yellow product collected on a filter. After drying this weighed 0.86 g. (96%) and melted at 130° (dec., block). Crystallization from ethanol with charcoal treatment gave bright yellow needles, wt. 0.53 g. (60%), m.p. 132° (dec., block) which darken in the light.

Method B. The same procedure as above was followed using 1.00 g. (0.00442 mole) of 2-hydrazino-4-(5-nitro-2-furyl)-thiazole (VII) and 0.305 g. (0.00442 mole) of sodium nitrite. After crystallization from ethanol, the product weighed 0.62 g. (59.3%), m.p. 131° (dec., block), and was in all ways identical with material from *Method A.*

Anal. Calcd. for $C_7H_3N_5O_3S$: C, 35.45; H, 1.28; N, 29.54. Found: C, 35.69; H, 1.39; N, 29.40.

2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole (IX). *Method A.* A solution of 2.00 g. (0.00752 mole) of 2-(2-isopropylidinehydrazino)-4-(5-nitro-2-furyl)thiazole (IVi) in 20 ml. of 90% formic acid and 10 ml. of water was heated under reflux for 2 hr. and then diluted with water. The resulting precipitate was collected and crystallized from *n*-butyl alcohol. In this way was obtained 0.95 g. (50%) of bright yellow product, m.p. 215.5° (dec., block).

Method B. A solution of 1.00 g. (0.00442 mole) of 2-hydrazino-4-(5-nitro-2-furylthiazole (VII) in 10 ml. of 90% formic acid was heated on a steam bath for 1 hour. The solution was then cooled and the product precipitated by addition of water. After crystallization from *n*-butyl alcohol the product, which was identical in all ways with that obtained by Method A above, weighed 0.74 g. (66%).

Anal. Calcd. for $C_8H_6N_4O_4S$: C, 37.80; H, 2.38; N, 22.05. Found: C, 37.92; H, 2.43; N, 21.81.

2-(2-Acetylhydrazino)-4-(5-nitro-2-furyl)thiazole. A suspension of 1.00 g. (0.00442 mole) of 2-hydrazino-4-(5-nitro-2-furyl)thiazole (VII) in 20 ml. of acetic anhydride was heated to 50° with stirring. After all the red color of the hydrazine had been discharged, the mixture was cooled, filtered, and the precipitate washed with acetic acid-water. In this way was obtained 0.97 g. (82%) of product melting at 235° (dec., block). Crystallization from dimethylformamide-water raised the m.p. to 236° (dec.).

Anal. Calcd. for $C_9H_8N_4O_4S$: C, 40.30; H, 3.01; N, 20.89. Found: C, 40.35; H, 3.17; N, 20.71.

2-(1,2-Diacetylhydrazino)-4-(5-nitro-2-furyl)thiazole. A mixture of 1.00 g. (0.00442 mole) of 2-hydrazino-4-(5-nitro-2-furyl)thiazole (VII) and 20 ml. of acetic anhydride was heated at 110° for 5 min. The solution was then filtered and poured into ice and concentrated hydrochloric acid. This was stirred until all the anhydride had reacted and the solid yellow product collected. This weighed 1.17 g. (85%) and melted with decomposition at 223.5° (block). Crystallization from dimethylformamide-water raised the m.p. to 225° (dec.)

Anal. Calcd. for $C_{11}H_{10}N_4O_5S$: C, 42.59; H, 3.25; N, 18.06. Found: C, 42.84; H, 3.46; N, 18.07.

2-(4-Phenyl-1-thiosemicarbazido)-4-(5-nitro-2-furyl)thiazole. A solution containing 1.00 g. (0.00442 mole) of 2-hydrazino-4-(5-nitro-2-furyl)thiazole (VII) and 0.90 g. (0.00666 mole) of phenyl isothiocyanate in 20 ml. of dimethylformamide was heated on a steam bath for 15 min. The solution was then brought to a boil and 25 ml. of water added. After cooling, the product which precipitated was collected on a filter and washed with methanol. The brownish-yellow product weighed 1.21 g. (76%) and melted at 181° (dec., block). After crystallization from dimethylformamide-water with charcoal treatment, 1.00 g. was recovered with unchanged melting point.

Anal. Calcd. for $C_{14}H_{11}N_5O_3S_2$: C, 46.54; H, 3.07; N, 19.39. Found: C, 46.92; H, 3.11; N, 19.38.

Thiocyanomethyl 5-nitro-2-furyl ketone (X). A solution of 2.57 g. (0.011 mole) of bromo ketone III in 140 ml. of ethanol was heated to 65° and added to a solution of 9.8 g.

(0.10 mole) of potassium thiocyanate in 260 ml. of ethanol maintained at 65°. The mixture was heated to a boil for a brief time, and then cooled to 50°, filtered, and the filtrate concentrated to 100 ml. After charcoal treatment and cooling, the product along with some potassium bromide separated. The solid was collected by filtration and washed with water. The residual material was then recrystallized from ethanol to give 1.1 g. (47%) of product melting at 81–83°.

Anal. Calcd. for $C_7H_4N_2O_4S$: C, 39.63; H, 1.90; N, 13.21. Found: C, 39.75; H, 2.14; N, 13.44.

4-(5-Nitro-2-furyl)thiazol-2-one (XI). A solution of 11 g. (0.052 mole) of thiocyanomethyl 5-nitro-2-furyl ketone and 50 ml. of concentrated sulfuric acid was prepared at −10° and allowed to stand at 0° for 2 days. At the end of this time the solution was poured into ice water and the precipitated product collected by filtration. When dry, this material melted with decomposition at 223–226° and weighed 10.5 g. (95%). Crystallization from ethanol gave bright yellow-orange crystals, m.p. 225–227° with decomposition, with a 40% recovery.

Anal. Calcd. for $C_7H_4N_2O_4S$: C, 39.63; H, 1.90; N, 13.21. Found: C, 39.71; H, 2.02; N, 13.05.

2-Chloro-4-(5-nitro-2-furyl)thiazole (XII). A solution of 0.25 g. (0.0012 mole) of thiocyanomethyl 5-nitro-2-furyl ketone in 70 ml. of diethyl ether was cooled to 5° and hydrogen chloride bubbled through in a slow stream. After 30 min. the solution was concentrated to 15 ml. and cooled. The product which separated was collected by filtration. Recrystallization from ether gave 0.10 g. (36%) of yellow powder, m.p. 164–166°. Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_7H_3ClN_2O_3S$: C, 36.45; H, 1.31; Cl, 15.38; N, 12.15. Found: C, 36.46; H, 1.56; Cl, 15.24; N, 12.07.

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Chemistry of Pyrazine and Its Derivatives. V. Acylation and Alkylation of 2,6-Dimethylpyrazine and Certain Other Pyrazine Derivatives[1]

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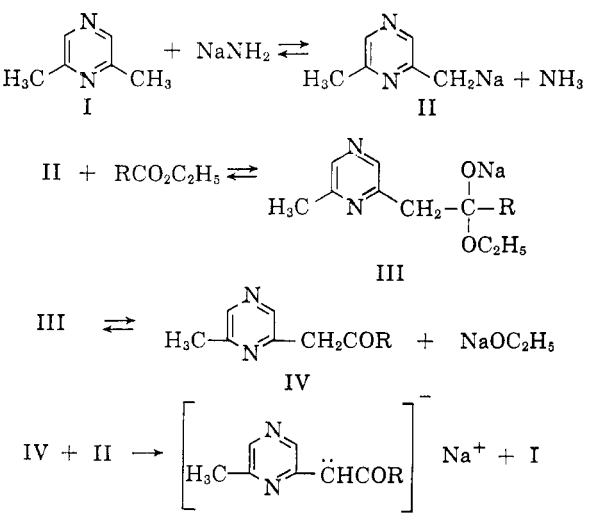
Sodium amide in liquid ammonia was used to effect the metalation of the side chains of 2,6-dimethylpyrazine and 1-pyrazyl-3-dimethylaminopropane. The metallated intermediates were condensed with aliphatic, aromatic, and heterocyclic esters to yield the corresponding ketones. In addition, several alkyl halides and benzyl chloride were condensed with 2-methyl-6-pyrazylmethylsodium leading to the corresponding 2-methyl-6-alkylpyrazines and 2-methyl-6-phenylethylpyrazine, respectively, in good yields. Phenacylpyrazine was also alkylated with β-dimethylaminoethyl chloride to give only the *O*-alkylated product, the enol ether [(1-phenyl-2-pyrazyl)-1-ethenyl]2-dimethylaminoethyl ether.

It has been previously established in these and other laboratories, that the side chains of methylpyrazine and 2,5-dimethylpyrazine are active centers in acid and base effected reactions. Thus Franke[3] has shown that the methyl groups of 2,5-dimethylpyrazine react with aromatic aldehydes using zinc chloride as a catalyst. In the previous papers of this series it was reported that methylpyrazine can be acylated by the reaction[4] of its sodio derivative with esters to give the corresponding pyrazylmethyl ketones, $PzCH_2COR$. Sodium amide in liquid ammonia was shown to be an effective condensing agent for such acylations while phenyllithium did not lead to any appreciable metalation of the side chain, in spite of its usefulness in the metalation of the side chain of 2-picoline.[5,6]

In the present study we have found that the side chain of 2,6-dimethylpyrazine can be effectively metalated by using the sodium amide–liquid ammonia method to yield 2-methyl-6-pyrazyl methyl ketones. The molar ratio of the reactants used was 2:2:1, *i.e.*, two equivalents of 2,6-dimethylpyrazine: two equivalents of sodium amide: one equivalent of ester. This condensation can be pictured by the following sequence of reactions.



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(2) This paper is based on part of a thesis presented by M. R. Kamal to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

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