[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

# Antitubercular Substances. IV. Thioamides

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It had been found in these laboratories that thioisonicotinamide had significant antitubercular activity and in an effort to find substances of still greater activity a group of seventeen amides and thioamides or derivatives was prepared. It is shown that methylation of both N,N-dimethyl-2-thiofuramide and methyl N-methyl-2-thiofurimidate gives the same methyl N-methyl-2-thiofurimidate methiodide and the structure of this latter substance is discussed. Thioisonicotinamide and 2-thiofuramide were oxidized with iodine to products considered to be 3,5-diheteryl-1,2,4-thiadiazoles.

In our recent synthetic program directed toward the preparation of potential antitubercular substances[1-3] we had occasion to prepare thioisonicotinamide as an intermediate. When this compound was subjected to microbiological screening it was found to have significant tuberculostatic activity by the drug–diet technique in mice infected with the virulent bovine $D_4M_3$ strain of *Mycobacterium tuberculosis*, although it was without activity *in vitro* against the virulent human strain $H_{37}Rv$ or the $D_4M_3$ strain in Dubos medium. The present paper describes the synthesis of the substances used in continuing this study.

Although the chemical and microbiological literature is replete with reports on the synthesis and evaluation of oxygenated nitrogenous derivatives of carboxylic acids, comparatively little attention has been paid to the corresponding sulfurated compounds. Kushner and co-workers[4] have reported the inactivity, by the drug–diet technique, of pyrazinethioamide, and at the same time our work was being done there appeared the report by Bavin, Drain, Seiler and Seymour[5] describing the *in vitro* activity against the $H_{37}Rv$ strain of 4-aminothiobenzamide, thionicotinamide and several thiohydrophthalazine derivatives; none of these had sufficient activity for the authors to determine even the toxicity or *in vivo* activity of the compounds. Rogers and co-workers[6] at about the same time also reported thionicotinamide to lack any demonstrable effect on tuberculosis in a standardized mouse assay. Subsequently Gardner, Wenis and Lee[7] have reported the same observation we made, namely, the relatively high activity of thioisonicotinamide in tuberculosis in mice, and have described another thirteen thioamides all of which were inactive. Jensen and Miquel[8] prepared thiobenzhydrazide, and Jensen and Jensen[9] have reported that it and eleven other thiohydrazides were antibacterial, without further defining the test conditions. Very recently König, Siefken and Offe[10] have described thioisonicotinic hydrazide and some derivatives thereof and said that Domagk has found them to have moderate to good activity.

In following the activity lead we uncovered in thioisonicotinamide, we prepared thionicotinamide,[11] thiobenzamide,[12] 2-thiofuramide[13] and 2-thiothenamide, all by the addition of hydrogen sulfide to the corresponding nitrile in the presence of ammonia.

Because thioisonicotinamide exhibited antitubercular activity *in vivo* but failed to do so *in vitro*, we entertained the possibility that the compound might be undergoing some metabolic conversion from an initially innocuous substance to an active bacteriostatic material in the living organism. Two of the more prominent pathways by which drugs are altered after administration are by methylation and by oxidation, so it seemed desirable to synthesize a small group of methylated derivatives of thioisonicotinamide as well as one of its oxidation products, in order to test this hypothesis.

Reaction of isonicotinyl chloride with methyl-, dimethyl- and isopropylamine furnished the respective N-substituted isonicotinamides and treatment of these with phosphorus pentasulfide yielded the corresponding N-substituted thioisonicotinamides. Attempted preparation of S-methyl thioisonicotinimidate by the addition of methyl mercaptan to isonicotinonitrile failed; in ammoniacal solution no reaction occurred and in acid solution the cyanopyridine salt was precipitated. The oxidation of thioisonicotinamide is discussed in a later paragraph.

We then turned to the furan series for the preparation of a more complete series of thioamide methylation products, this ring system being chosen because in our own laboratories as well as in others 2-furoic hydrazide had been found earlier to have antitubercular activity resembling that of isonicotinic hydrazide and we as yet had no microbiological data to indicate any divergence from this similarity in the thioamide class of compounds.

Reaction of 2-furoyl chloride with methyl- and dimethylamine gave the respective N-substituted-2-furamides and these were transformed to the corresponding thioamides by treatment with phosphorus pentasulfide. In the conversion of N-

(1) J. Shavel, Jr., F. Leonard, F. H. McMillan and J. A. King, *J. Am. Pharm. Assoc., Sci. Edn.*, **42**, 402 (1953).

(2) F. H. McMillan, F. Leonard, R. I. Meltzer and J. A. King, *ibid.*, **42**, 457 (1953).

(3) R. I. Meltzer, A. D. Lewis, F. H. McMillan, J. D. Genzer, F. Leonard and J. A. King, *ibid.*, **42**, 594 (1953).

(4) S. Kushner, H. Dalalian, J. L. Sanjurjo, F. L. Bach, Jr., S. R. Safir, V. K. Smith, Jr., and J. H. Williams, THIS JOURNAL, **74**, 3617 (1952).

(5) E. M. Bavin, D. J. Drain, M. Seiler and D. E. Seymour, *J. Pharm. Pharmacol.*, **4**, 844 (1952).

(6) E. F. Rogers, W. J. Leanza, H. J. Becker, A. R. Matzuk, R. C. O'Neill, A. J. Basso, G. A. Stein, M. Solotorovsky, F. J. Gregory and K. Pfister, 3rd, *Science*, **116**, 253 (1952).

(7) T. S. Gardner, E. Wenis and J. Lee, *J. Org. Chem.*, **19**, 753 (1954).

(8) K. A. Jensen and J. F. Miquel, *Acta Chim. Scand.*, **6**, 189 (1952).

(9) K. A. Jensen and C. L. Jensen, *ibid.*, **6**, 957 (1952).

(10) H. B. König, W. Siefken and H. A. Offe, *Chem. Ber.*, **87**, 825 (1954).

(11) P. Karrer and J. Schukri, *Helv. Chim. Acta*, **28**, 820 (1945).

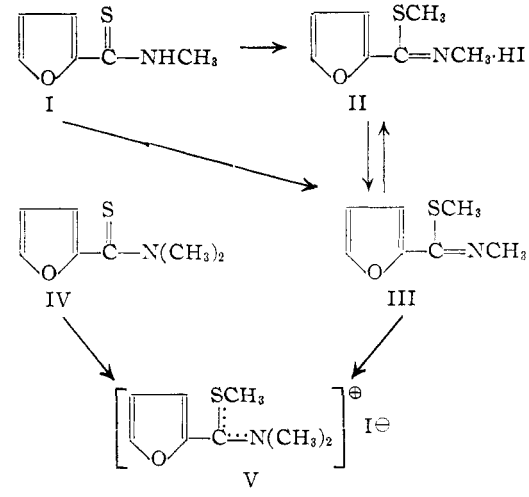
(12) A. Bernthsen, *Ber.*, **10**, 1241 (1877).

(13) P. Douglas, *ibid.*, **25**, 1311 (1892).

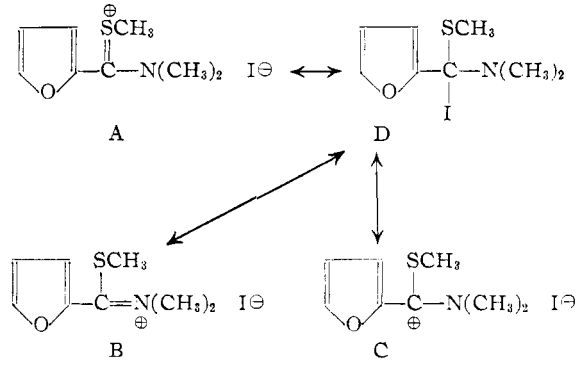
methyl-2-furamide to N-methyl-2-thiofuramide the yield was only 14% when the amide was fused with phosphorus pentasulfide at 140–150°, but was increased to 25% when refluxing xylene was used as a diluent and increased still further to 60% when an even lower temperature was maintained by using toluene as a diluent. In the sulfuration of N,N-dimethyl-2-furamide, however, the yield of 22% in refluxing xylene fell to 13% in refluxing toluene. Because of the low yield attendant to this conversion, recourse was had to a modified Willgerodt–Kindler reaction. At a temperature of 125° furfuraldehyde and dimethylamine polymerized exothermically whether sulfur was present or not. However, Hardman[14] had found that passing hydrogen sulfide into a mixture of furfural, sulfur and secondary amine at 45–50° would give good yields of substituted ammonium dithiofuroates and we modified this, somewhat similarly to the method of Chabrier and Renard,[15] to induce thermal elimination of hydrogen sulfide from the dithiofuroate and obtain the thioamide directly; dimethylamine was passed into a refluxing pyridine suspension of sulfur and furfuraldehyde and a 31% yield of the dimethylthiofuramide was obtained in one step.

The addition of methyl mercaptan to 2-furonitrile in the presence of hydrogen chloride, by the method of Condo and co-workers,[16] furnished S-methyl 2-thiofurimidate hydrochloride. This compound could be recrystallized from isopropyl alcohol if one worked rapidly, but prolonged heating with alcohols caused extensive decomposition with formation of ammonium chloride; acetonitrile proved to be a much better recrystallization solvent. Attempts to liberate the base from its hydrochloride and then alkylate it with methyl iodide, according to the procedure of Knunyants and Razvadovskaya,[17] gave a product that analyzed for a furonitrile polymer. This is analogous to the finding of Bernthsen[18] that S-ethyl thiobenzimidate, on standing, eliminated ethyl mercaptan and was converted to a trimer of benzonitrile.

N-Methyl-2-thiofuramide (I) was methylated easily to give a hydriodide II, from which the stable non-crystalline base III could be liberated and reconverted to II with hydriodic acid. III also could be formed directly, without isolation of II, by alkylation of I with methyl iodide in the presence of sodium ethoxide. N,N-Dimethyl-2-thiofuramide (IV) did not give II on similar treatment with hydriodic acid and the ultraviolet absorption spectra of N,N-dimethyl-2-thiofuramide (IV) and methyl N-methyl-2-thiofurimidate (III) clearly demonstrated the non-identity of the two compounds. However, when either III or IV was methylated further with methyl iodide, the reaction product in each case was methyl N-methyl-2-thiofurimidate methiodide (V), a relatively unstable compound that decomposed on standing and whose identity from both routes was established by decomposition temperature and ultraviolet absorption spectrum.



The reaction product of IV with methyl iodide might normally be formulated as A, and similarly the reaction product of III with methyl iodide might normally be formulated as B. However, both reaction products are experimentally the same and Goulden[19] has concluded from a study of the infrared spectra of some other N,N-disubstituted thioamide methiodides that the sulfonium form A definitely contributes to the predominating ammonium form B in such compounds. It is also possible to consider these substances as analogous to Hantzsch's pseudo salts,[20] and it may be helpful at times to picture them as form D, in which



the covalent carbon–iodine bond so closely approaches an ionic bond as to cause the compounds to react as if they were form C. All of these forms are probably contributory to the true structure, the actual predominance of one form over another being dependent upon the individual compound, the solvent and the other reactants. To encompass this conception, and without further proof of structure, we have selected structure V to indicate the extant equilibria.

Because Shpanir and Chertkova[21] said N-benzyl-2-furamide had some antitubercular activity it

(14) A. F. Hardman, U. S. Patent 2,386,111 (to Wingfoot Corporation, Jan. 5, 1944).

(15) P. Chabrier and S. H. Renard, *Compt. rend.*, **228**, 850 (1949).

(16) F. E. Condo, E. T. Hinkel, A. Fassero and R. L. Shriner, THIS JOURNAL, **59**, 230 (1937).

(17) I. Knunyants and L. Razvadovskaya, *J. Gen. Chem. (U.S.S.R.)*, **9**, 557 (1939); *C.A.*, **34**, 391 (1940).

(18) A. Bernthsen, *Ann.*, **197**, 341 (1897).

(19) J. D. S. Goulden, *J. Chem. Soc.*, 997 (1953).

(20) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 575 *et seq.*

(21) F. L. Shpanir and E. I. Chertkova, *Problems of Tuberculosis*, **4**, 9 (1944); *C.A.*, **44**, 747 (1950).

TABLE I

AMIDES, THIOAMIDES AND DERIVATIVES

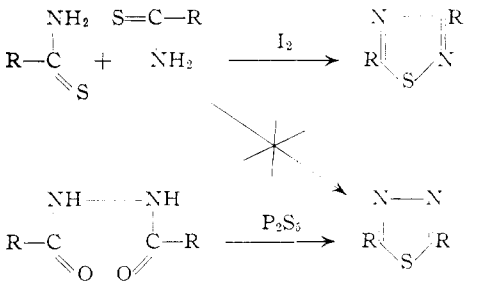
| Compound | M.p., °C. | Formula | Yield, % | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| Thioisonicotinamide[a] | 210–210.5 | $C_6H_6N_2S$ | 81[e] | S, 23.20 | S, 23.00 | | | 20.27 | 20.35 |
| Thionicotinamide[b] | 191.5–192.5 | $C_6H_6N_2S$ | 92[e] | 52.15 | 52.01 | 4.38 | 4.30 | S, 23.20 | S, 23.00 |
| Thiobenzamide[c] | 119.5–120 | $C_7H_7NS$ | 78[e] | 61.28 | 61.12 | 5.15 | 5.08 | | |
| 2-Thiofuramide[d] | 131.5–132.5 | $C_5H_5NOS$ | 75[e] | Not analyzed | | | | | |
| 2-Thiothenamide | 110–111 | $C_5H_5NS_2$ | 98[e] | 41.93 | 41.69 | 3.53 | 3.56 | 9.78 | 9.71 |
| N-Methylisonicotinamide | 116.5–117 | $C_7H_8N_2O$ | 25[f] | 61.75 | 61.64 | 5.92 | 5.65 | 20.57 | 20.52 |
| N,N-Dimethylisonicotinamide | 58.5–59.5 | $C_8H_{10}N_2O$ | 32[g] | 63.98 | 64.29 | 6.71 | 6.49 | | |
| N-Isopropylisonicotinamide | 108.5–110.5 | $C_9H_{12}N_2O$ | 55[h] | 65.82 | 65.71 | 7.37 | 7.27 | 17.06 | 16.72 |
| N-Methylthioisonicotinamide | 105–105.5 | $C_7H_8N_2S$ | 24[h] | 55.24 | 55.41 | 5.30 | 5.34 | S, 21.06 | S, 21.26 |
| N,N-Dimethylthioisonicotinamide | 67.5–68 | $C_8H_{10}N_2S$ | 63[g] | 57.80 | 57.77 | 6.06 | 5.91 | 16.86 | 16.92 |
| N-Isopropylthioisonicotinamide | 145.5–146.5 | $C_9H_{12}N_2S$ | 44[i] | 59.96 | 60.00 | 6.71 | 6.67 | 15.54 | 15.50 |
| N,N-Dimethyl-2-furamide | 45–46 | $C_7H_9NO_2$ | 68[g] | 60.42 | 60.23 | 6.52 | 6.42 | | |
| N-Methyl-2-thiofuramide | 71–71.5 | $C_6H_7NOS$ | 60[g] | 51.04 | 51.01 | 5.00 | 5.27 | 9.92 | 10.05 |
| N,N-Dimethyl-2-thiofuramide | 34.5–35 | $C_7H_9NOS$ | 31[g] | 54.17 | 54.27 | 5.84 | 5.74 | S, 20.66 | S, 20.33 |
| N-Benzyl-2-thiofuramide | 48.5–50 | $C_{12}H_{11}NOS$ | 36[g] | 66.33 | 66.11 | 5.10 | 5.21 | S, 14.75 | S, 14.73 |
| S-Methyl 2-thiofurimidate hydrochloride | 178–180 d. | $C_6H_7NOS \cdot HCl$ | 87[j] | 40.56 | 40.64 | 4.54 | 4.76 | Cl, 19.97 | Cl, 19.96 |
| Methyl N-methyl-2-thiofurimidate hydriodide | 110–112 | $C_7H_9NOS \cdot HI$ | 97[k] | 29.69 | 29.61 | 3.56 | 3.82 | I, 44.83 | I, 44.58 |
| Methyl N-methyl-2-thiofurimidate methiodide | 128–128.5 | $C_8H_{12}INOS$ | 46[l] | 32.33 | 32.40 | 4.07 | 4.02 | | |
| 3,5-Di-(4-pyridyl)-1,2,4-thiadiazole | 196.5–197 | $C_{12}H_8N_4S$ | 72[i] | 59.98 | 60.19 | 3.35 | 3.36 | 23.32 | 23.13 |
| 3,5-Di-(2-furyl)-1,2,4-thiadiazole | 105.5–107 | $C_{10}H_6N_2O_2S$ | 65[g] | 55.03 | 55.04 | 2.27 | 2.88 | 12.84 | 12.85 |

[a] Gardner, Wenis and Lee[7] reported this compound. [b] Karrer and Schukri[11] reported m.p. 180–181°. [c] Bernthsen[12] reported m.p. 115–116°. [d] Douglas[13] reported m.p. 127°. [e] Recrystallized from water. [f] Recrystallized from ethyl acetate. [g] Recrystallized from petroleum ether (b.p. 60–68°). [h] Recrystallized from carbon tetrachloride. [i] Recrystallized from benzene. [j] Recrystallized from acetonitrile. [k] Recrystallized from isopropyl alcohol. [l] Recrystallized from acetone–ether.

seemed worthwhile to prepare the corresponding thioamide. This was accomplished by reaction of benzylamine with 2-thiofuramide, by a procedure patterned after the method of Schlatter.[22]

In order to obtain some thioamide oxidation products, both 2-thiofuramide and thioisonicotinamide were treated with iodine, by the method of Hofmann.[23] Oxidation of the thiofuramide proceeded normally and required less than one molar equivalent of iodine, but the pyridylthioamide consumed about twice as much iodine and gave a dark purple crystalline iodine-containing product which was assumed without experimental data to be a molecular compound analogous to the now-common pyridine perbromide. Treatment of this product with either sodium hydroxide or sodium thiosulfate resulted in a white product that analyzed correctly for the expected thiadiazole.

Chabrier, Renard and Smarzewska[24] indicated that the product obtained on iodine oxidation of thiobenzamide was a 1,3,4-thiadiazole, m.p. 94°; however, Hofmann's degradative work on a diphenylthiadiazole, m.p. 90°, similarly prepared showed it to be a 1,2,4-thiadiazole. Stollé[25] prepared a diphenylthiadiazole, m.p. 141–142°, by phosphorus pentasulfide treatment of dibenzoylhydrazine and, barring a rearrangement, this must be the 1,3,4-thiadiazole because of its method of synthesis. Accordingly, the thiadiazoles prepared by iodine oxidation of thioamides must be the 1,2,4-thiadiazoles. This assignment of structure also is confirmed by earlier work of this group. It was reported[2] that treatment of thioisonicotinamide with hydrazine produced a dipyridylthiadiazole of m.p. 240.5–241.5°. This compound was considered to be 2,5-di-(4-pyridyl)-1,3,4-thiadiazole, formed by elimination of hydrogen sulfide from 1,2-dithioisonicotinylhydrazine produced by further reaction of thioisonicotinamide with the expected thioisonicotinyl hydrazide. Because that product (m.p. 240.5–241.5°) was considerably higher melting than and different from the dipyridylthiadiazole (m.p. 196.5–197°) produced by iodine oxidation of thioisonicotinamide, further support is lent to the latter substance's being 3,5-di-(4-pyridyl)-1,2,4-thiadiazole, in agreement with the above reasoning.




The results of the microbiological *in vitro* and *in vivo* evaluation of the substances herein described will be reported elsewhere by the responsible investigators. It can be said now, as Gardner, Wenis and Lee[7] also found with their thioamides, that none of the additional compounds we prepared surpassed thioisonicotinamide in antitubercular activity.

## Experimental[26]

**Isonicotinonitrile** and **nicotinonitrile** were prepared by phosphorus pentoxide dehydration of the corresponding amides and 2-furonitrile was prepared by acetic anhydride dehydration of furfuraldehyde oxime.[27]

(22) M. J. Schlatter, THIS JOURNAL, **64**, 2722 (1942).

(23) A. W. Hofmann, *Ber.*, **2**, 645 (1869).

(24) P. Chabrier, S. H. Renard and K. Smarzewska, *Bull. soc. chim. France*, 237 (1949).

(25) R. Stollé, *Ber.*, **32**, 797 (1899).

(26) Microanalyses were carried out by Miss Linda Einstein. Melting points and boiling points are uncorrected; melting points were taken on a Fisher–Johns melting point block.

(27) H. Goldschmidt and E. Zanoli, *Ber.*, **25**, 2573 (1892).

**2-Thenonitrile.**—This preparation was patterned after the outlined procedure of Putokhin and Egorova.[28] 2-Thenaldehyde oxime was placed in a round-bottomed flask and treated with acetic anhydride (122 g., 1.2 moles). The reaction mixture became hot, the oxime dissolved, and the solution was then heated on the steam-bath for one hour. The mixture was then cooled, diluted with an equal volume of water, and made basic with 50% sodium hydroxide solution. The alkaline mixture was extracted three times with ether, the combined ethereal extracts were dried over magnesium sulfate and then distilled to give 55.4 g. (39.4% yield) of 2-thenonitrile, b.p. 74° (10 mm.), $n^{25}D$ 1.5620; reported[28] b.p. 77.5–78° (11–12 mm.), $n^{15}D$ 1.5641.

**Unsubstituted Thioamides.**—All of the unsubstituted thioamides were prepared by the method of Bernthsen.[12] The general procedure was to dissolve the corresponding nitrile in sufficient absolute alcohol to make a 10% solution, then to saturate the cooled solution first with ammonia and then with hydrogen sulfide. The product usually crystallized rapidly.

**N-Methylisonicotinamide and N,N-dimethylisonicotinamide** were prepared from isonicotinyl chloride hydrochloride and the appropriate amine in pyridine. The mixture was heated on the steam-bath for three hours and then concentrated to dryness under vacuum. The residue was made strongly alkaline with 50% sodium hydroxide, then weakly acidic with acetic acid and evaporated to dryness to remove the pyridine. This residue was leached with hot ethyl acetate, from which on cooling and concentration there was obtained the product.

**N-Isopropylisonicotinamide.**—A mixture of ethyl isonicotinate (15.1 g., 0.10 mole) and isopropylamine (17.7 g., 0.30 mole) was heated at 120° for two hours in a glass-lined high-pressure rocking autoclave, and then cooled. After removal from the autoclave, the mixture was evaporated to dryness and the residue was recrystallized three times.

**N-Methyl-2-furamide.**—This compound has been prepared[29] by treatment of O-methyl 2-furimidate with methyl iodide; we found it expedient to use the following procedure. Addition of 2-furoyl chloride (75 g., 0.575 mole) to a solution of methylamine (40 g., 1.29 moles) in 400 cc. of anhydrous ether at −30° gave a precipitate of methylamine hydrochloride. The mixture was allowed to warm to room temperature overnight and then filtered. Evaporation of the filtrate furnished the product which, after recrystallization from U.S.P. ether, weighed 36 g. (50% yield) and melted at 62–64.5°; reported[29] m.p., 64°. **N,N-Dimethyl-2-furamide** was made analogously.

**N-Isopropylthioisonicotinamide.**—Equal weights (4.0 g.) of N-isopropylisonicotinamide (0.024 mole) and phosphorus pentasulfide (0.018 mole) were finely ground together in a mortar and then placed in a heating bath at 120°. The temperature of the mixture was raised to 140–150° and held there for 1.5 hours, with occasional stirring of the melt. The cooled melt was ground with 40 g. of sodium carbonate and 25 cc. of water, this mixture was transferred to an extraction thimble, and then extracted with ether in a Soxhlet extractor. The ethereal extract was dried over magnesium sulfate and evaporated to leave 4.4 g. of residue. **N-Methylthioisonicotinamide** was prepared analogously, as also were **N,N-dimethylthioisonicotinamide** (except that refluxing xylene, 150 cc. for 10 g. of amide, was used as the reaction diluent) and **N-methyl-2-thiofuramide** (except that the sodium carbonate was omitted).

**N,N-Dimethyl-2-thiofuramide. Method A.**—The yields obtained by variation of the diluent in the same procedure as was used for the monomethylthioamide already have been mentioned.

**Method B.**—A solution of furfuraldehyde (14.4 g., 0.15 mole) in 58 cc. of dry pyridine was heated to reflux with stirring and sulfur (7.2 g., 0.225 mole) was then added. Dimethylamine was passed into the mixture at a rate sufficient to keep the mixture at reflux temperature without the application of external heat. After 30 minutes no more dimethylamine was being absorbed so the addition was stopped and the mixture was externally heated to reflux for 1.5 hours. The pyridine was removed under vacuum and the residue was extracted with petroleum ether (b.p. 60–68°) from which the pure product was obtained by fractional crystallization. When a mixture of furfuraldehyde, dimethylamine and sulfur was heated at 100° and then extracted with petroleum ether (b.p. 88–110°) only a 4% yield of product was obtained; when the reaction temperature was 150° the result was an intractable resin.

When a solution of 0.17 g. of pure N,N-dimethyl-2-thiofuramide in 1.0 cc. of absolute ethanol was treated with 0.3 cc. of 57% hydriodic acid there was no precipitate formed, either immediately or after the addition of 20 cc. of anhydrous ether, or 16 hours later. Because methyl N-methyl-2-thiofurimidate treated similarly (*vide infra*) easily forms the insoluble hydriodide this is additional reason for concluding the non-identity of the two compounds.

**N-Benzyl-2-thiofuramide.**—Because Bernthsen[30] had shown that in the presence of air this type of reaction could produce an amidine, the reaction was carried out in a nitrogen atmosphere. A mixture of equal weights of 2-thiofuramide and benzylamine was allowed to stand three weeks at room temperature and then excess benzylamine was removed under vacuum. The residual oil was leached with hot petroleum ether (b.p. 60–68°) which on chilling deposited a gummy solid.

**S-Methyl 2-Thiofurimidate Hydrochloride.**—Thirty-five grams of methyl mercaptan was added to a cooled (5–10°) solution of 2-furonitrile (40.0 g., 0.43 mole) in 200 cc. of absolute ether and the mixture then was saturated with anhydrous hydrogen chloride at 5–10° and allowed to stand several hours at that temperature until no further precipitation occurred. The product was almost analytically pure.

**Methyl N-Methyl-2-thiofurimidate Hydriodide. Method A.**—To a solution of sodium (0.55 g., 24 mmoles) in 10 cc. of absolute ethanol there was added a solution of N-methyl-2-thiofuramide (3.13 g., 22 mmoles) in 10 cc. of absolute ethanol. After the addition of a solution of methyl iodide (4.0 g., 28 mmoles) in 10 cc. of absolute ethanol the mixture was refluxed for ten minutes and then allowed to stand at room temperature for two hours. The solvent was removed under vacuum, the residue was slurried with 150 cc. of absolute ether, the insoluble sodium iodide was removed by filtration, and the ethereal filtrate was evaporated to dryness. The ethereal residue was taken up in a little alcohol, 67% hydriodic acid was added until the solution was acid to congo red paper, and ether was added to cloudiness. Chilling of the mixture caused precipitation of 1.8 g. of product, m.p. 107–109.5°.

**Method B.**—Methyl iodide (32 g., 0.225 mole) was added to N-methyl-2-thiofuramide (6.8 g., 0.048 mole) and the mixture was refluxed on the steam-bath. After five minutes, an oil began to separate and after 15 minutes the oil started to solidify. Refluxing was continued another 15 minutes, then the mixture was chilled and solid was filtered and washed with methyl iodide. There was obtained 13.2 g. of product, m.p. 105–107°.

To a solution of the hydriodide (0.49 g.) in the minimal quantity of water there was added 0.20 g. of sodium carbonate. The aqueous solution was extracted four times with 10-cc. portions of ether, the combined ethereal extract was dried over magnesium sulfate and then evaporated to dryness. **The methyl N-methyl-2-thiofurimidate** was allowed to stand in a stoppered flask at room temperature for 41 days but showed no signs of crystallizing. It was then dissolved in 1.5 cc. of absolute ethanol and 0.40 cc. of 57% hydriodic acid was added, the solution then being strongly acid to congo red paper. Ether was added to cloudiness, the solution was cooled for several hours and then filtered. The precipitate of methyl N-methyl-2-thiofurimidate hydriodide was washed with anhydrous ether containing a little ethanol and then dried. It weighed 0.17 g. (35% recovery) and melted identically with the pure starting material.

This material was not obtained on attempted methylation of S-methyl 2-thiofurimidate. To a solution of S-methyl 2-thiofurimidate hydrochloride in a minimal quantity of water there was added a solution of a 10% equivalent excess of sodium carbonate in a minimal quantity of water, while the temperature of the solutions was maintained below 5°. The aqueous solution was extracted four times

(28) N. I. Putokhin and V. S. Egorova, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **18**, 1866 (1948); *C.A.*, **43**, 3816 (1949).

(29) H. L. Wheeler and M. D. Atwater, *Am. Chem. J.*, **23**, 145 (1900).

(30) A. Bernthsen, *Ann.*, **184**, 321 (1877).

with ether, the combined ethereal extract was dried over magnesium sulfate, and then treated with a seven-fold molar excess of methyl iodide. After the mixture had stood at room temperature for several hours it was filtered and the filtrate was evaporated to dryness to leave an oil that was crystallized from methanol and recrystallized from benzene. The material melted at 244.5–245°, analyzed for furonitrile, and probably was **furonitrile trimer**.

*Anal.* Calcd. for $C_5H_3NO$: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.30; H, 3.36; N, 15.27.

**Methyl N-Methyl-2-thiofurimidate Methiodide. Method A.**—To a solution of methyl N-methyl-2-thiofurimidate hydriodide (2.0 g., 7 mmoles) in a minimal quantity of water there was added a solution of sodium carbonate (0.83 g., 8 mmoles) also in a minimal quantity of water. The resultant alkaline solution was extracted four times with ether, the combined ethereal extract was dried over magnesium sulfate, and then evaporated to dryness. The residual **methyl N-methyl-2-thiofurimidate** was dissolved in 10 cc. of acetone, there was then added to this solution 2.5 cc. (48 mmoles) of methyl iodide, and the mixture was allowed to stand five days at room temperature. The crystalline product removed by filtration weighed 1.3 g. and an additional 0.1 g. was obtained by the addition of ether to the filtrate. The two crops were combined and recrystallized from acetone to obtain the pure product. On standing for two weeks the melting point of the material dropped and its melting range broadened.

**Method B.**—To a solution of N,N-dimethyl-2-thiofuramide (4.2 g., 0.027 mole) in 25 cc. of acetone was added methyl iodide (15.4 g., 0.108 mole). An exothermic quaternization occurred and after five minutes the reaction mixture was nearly solid. It was then refluxed 15 minutes on a steam-bath, chilled and filtered. The crude product, which weighed 7.6 g. and melted at 117–120°, was recrystallized to give 3.7 g. of pure product.

**3,5-Di-(2-furyl)-1,2,4-thiadiazole.**—To a solution of 2-thiofuramide (2.0 g., 0.0157 mole) in 20 cc. of absolute ethanol there was added a solution of iodine (8.2 g., 0.0324 mole) in 80 cc. of absolute ethanol. After three hours at room temperature some sulfur had precipitated and after three days at room temperature the sulfur was removed by filtration. The filtrate required 415 cc. of 0.1 *N* sodium thiosulfate to effect decolorization (0.69 molar equivalent of iodine consumed per mole of thioamide), during which the product was precipitated. The crude product weighed 1.3 g., melted at 104–105.5°, and after recrystallization weighed 1.1 g.

**3,5-Di-(4-pyridyl)-1,2,4-thiadiazole.**—To a solution of thioisonicotinamide (2.0 g., 0.0145 mole) in 50 cc. of warm absolute ethanol there was added a solution of iodine (11.0 g., 0.0435 mole) in 110 cc. of absolute ethanol. The reaction was slightly exothermic and maintained itself just under reflux temperature for about an hour. The mixture then was allowed to stand at room temperature overnight, during which time a large mass of dark needles had deposited. The mixture was refluxed 45 minutes, during which the needles dissolved, and the remaining insoluble sulfur was (difficultly) removed by filtration. The filtrate was chilled in an ice-bath and the precipitated dark needles (4.7 g.) were removed by filtration and washed with cold ethanol. The filtrate from which the dark needles had been removed also, coincidentally, required 415 cc. of 0.1 *N* sodium thiosulfate for decolorization (1.52 molar equivalents of iodine consumed per mole of thioamide). The dark crystals were suspended in 30 cc. of water, the mixture was made alkaline with 2 cc. of 4 *N* sodium hydroxide, and then treated with an excess of solid sodium thiosulfate to effect decolorization. The mixture was warmed gently to hasten the reduction of the iodine and then chilled to precipitate 1.5 g. of product. Recrystallization of the product from methanol or benzene did not raise its melting point.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CONNECTICUT]

# Friedel–Crafts Isopropylation of Methyl 2-Thienyl Ketone[1a]

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The Friedel–Crafts monoisopropylation of methyl 2-thienyl ketone has been studied to determine the product compositions. Regardless of catalyst or reaction conditions, the major product of this reaction is 4-isopropyl-2-thienyl methyl ketone. Small amounts of 5-isopropyl-2-thienyl methyl ketone also are formed. The 3-isopropyl isomer was not detected in any reaction product.

Few reports have appeared on the alkylation of a thiophene compound containing an electron-withdrawing substituent in an $\alpha$-position. The directive effect of such a substituent on an incoming alkyl group would be of interest.[2,3] The only study of isomer composition in such alkylations is on the alkylation of ethyl 2-thiophenecarboxylate with *t*-butyl chloride and aluminum chloride.[4] A mixture of isomeric esters was produced which, when saponified, gave a mixture of *t*-butyl-2-thiophenecarboxylic acids containing approximately 60% of the 5-*t*-butyl isomer.

(1) (a) Abstracted in part from the 1953 Ph.D. thesis of Christine B. Germain. Presented in part before the Organic Division, American Chemical Society, Chicago, Ill., Sept., 1953. (b) Research Corporation Fellow, 1952–1953.

(2) W. G. Appleby, A. F. Sartor, S. H. Lee, Jr., and S. W. Kapranos, THIS JOURNAL, **70**, 1552 (1948); W. M. Kutz and B. B. Corson, *ibid.*, **68**, 1477 (1946); **71**, 1503 (1949); H. Pines, B. Kvetinskas and J. A. Vesely, *ibid.*, **72**, 1568 (1950).

(3) W. Steinkopf and T. Höpner, *Ann.*, **501**, 184 (1933).

(4) N. Messina and E. V. Brown, Abstracts of Papers, XII International Congress of Pure and Applied Chemistry, Organic Chemistry Division, Sept., 1951, p. 425; N. Messina, Ph.D. Dissertation, Fordham University, 1951, p. 50.

The monoisopropylation of methyl 2-thienyl ketone was chosen for study. The product of this reaction should contain only 5-isopropyl-2-thienyl methyl ketone (I), 4-isopropyl-2-thienyl methyl ketone (II) and 3-isopropyl-2-thienyl methyl ketone (III). In order to detect and estimate the amount of each of these in an alkylation reaction mixture, authentic samples were necessary.

**5-Isopropyl-2-thienyl Methyl Ketone (I).**—This substance was prepared by acetylation of 2-isopropylthiophene with acetyl chloride and aluminum chloride.[5] It is likely that this reaction produces only I. Hartough[6] has reported that an analogous compound, 2-methylthiophene, undergoes less than 1%, if any, of $\beta$-substitution during a similar acetylation reaction. 2-Isopropylthiophene was prepared from methyl 2-thienyl ketone by reaction with methylmagnesium iodide, dehydration of the resulting tertiary alcohol, and catalytic hydrogenation of the isopropenyl group. Inasmuch as

(5) H. Scheibler and M. Schmidt, *Ber.*, **54**, 147 (1921).

(6) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 145.