when admixed with authentic specimens of diarylthioureas, and their infrared spectra were identical. Thus the following 1,3-diarylthioureas were obtained (aryl and yields are given): phenyl- (39%), *m*-tolyl- (28%), *p*-tolyl- (56%) and *p*-chlorophenyl- (67%).

1-(o-Tolyl)-3-carboxyethylthiourea from 3-aminopropionic acid. The same procedure as described above for the formation of 1,3-diarylthioureas was applied. The acid, obtained in 46% yield, was recrystallized from ethanol, m.p. 144°. Mixed m.p. with the compound 10 was undepressed and their infrared spectra were identical.

2-Phenylimino-3,4,5,6-tetrahydro-1,3-thiazin-6-one (IV. R = C_6H_5). If 1-phenyl-3-carboxyethylthiourea was cyclized with acetic anhydride and heated on a water bath at 90° the solution turned yellow and after 1 hr. the mixture was cooled and poured slowly in water. On standing crystals separated (yield, 32%) and upon recrystallization from ethanol the yellow crystals melted at 142°.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.13; H, 4.98; N, 13.69.

In ethanol λ_{max} 2460 Å, ϵ 12,160 and 2950 Å, ϵ 10,250.

The same compound was obtained with heating the corresponding 1,3-diazine derivative (III. R = C_6H_5) (0.1 g.) with acetic anhydride (5 ml.) and concd. sulfuric acid (2 drops) on a water bath at about 70° for 2 hr; yield, 8% m.p. and mixed m.p. with the above prepared sample was undepressed.

2-(o-Tolylimino)-3,4,5,6-tetrahydro-1,3-thiazin-6-one (IV. R = *o*-CH_3—C_6H_4) was similarly prepared according the above procedure from the acid in 27% yield. Yellow crystals (from ethanol), m.p. 127°.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.70; H, 5.69; N, 12.81.

Reactions of 3-phenyl-2-thio-4-oxo-hexahydro-1,3-diazine. A. *With 5% hydrochloric acid.* The compound was heated on a water bath with the acid for 20 min. and on cooling colorless crystals separated which were identified as 1-phenyl-3-carboxyethylthiourea (compound 9), m.p. 110°.

B. *With 5% sodium hydroxide.* The same reaction conditions as above were used. On cooling and acidification the solution was left overnight. The separated crystals were collected and identified as the acid (compound 9), m.p. 110°.

C. *With monochloroacetic acid.* Equivalent amounts of the compound and monochloroacetic acid as 20% aqueous solution were heated under reflux for 30 min. and left overnight. The separated *S*-carboxymethyl compound V upon recrystallization from aqueous acetic acid melted at 126°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54,54; H, 4,58; N, 10.60. Found: C, 54,31; H, 4,69; N, 10.68.

Acknowledgment. The authors are much indebted to Dr. S. Detoni for recording and interpreting the infrared spectra.

LJUBLJANA, YUGOSLAVIA

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF SMITH KLINE AND FRENCH LABORATORIES AND THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

The Synthesis of Phenothiazines. VII.[1] Methyl- and Arylsulfonylation of Phenothiazine and Its 10-Substituted Derivatives

JOHN J. LAFFERTY, ELEANOR GARVEY, EDWARD A. NODIFF,[2] WALTER E. THOMPSON, AND CHARLES L. ZIRKLE

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3-Methyl-, 3-phenyl-, and 3-*p*-tolylsulfonylphenothiazine were obtained from the reactions of phenothiazine or its 10-sulfonyl derivatives with the corresponding sulfonyl chlorides in the presence of aluminum chloride. The same products also were obtained from the rearrangement of the corresponding 10-sulfonyl derivatives in the presence of aluminum chloride. 3-Methylsulfonylphenothiazine also was prepared by a Smiles rearrangement of 2'-formamido-2-nitro-4-methylsulfonyldiphenyl sulfide.

To provide sulfonylphenothiazines as intermediates for analogs of the tranquilizing agent, chlorpromazine, we studied the Friedel-Crafts reaction of phenothiazine and some of its 10-substituted derivatives with sulfonyl chlorides. No example of the sulfonylation of this ring system has been reported previously, although the corresponding acylation reactions have been studied by various investigators.[3-8]

In acylation reactions of 10-alkylphenothiazines, the entering acyl group orients *para* (3- position) to the phenothiazine nitrogen atom.[5] On the other hand, acylation of 10-acylphenothiazines occurs in the 2-position, *para* to the sulfur atom, to yield 2,10-diacyl derivatives.[4,6-8] In the case of phenothiazine itself, the position of acylation apparently has never been established conclusively.[3,4,7] The reaction, in this case, is complicated by the fact that 10-acylation may occur to a great extent prior to C-acylation.[4] Thus, according to the literature cited, the reactions of phenothiazine with sulfonyl chlorides might be expected to lead to 3-sulfonyl and/or 2,10-disulfonyl derivatives,

(1) Paper VI of this series: P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. J. Saggiomo, and C. L. Zirkle, *J. Org. Chem.*, **26**, 1138 (1961).

(2) Research Institute of Temple University.

(3) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).

(4) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(5) G. Cauquil and A. Casadevall, *Bull. soc. chim. France*, 1061 (1955).

(6) G. Cauquil and A. Casadevall, *Compt. rend.*, **240**, 538 (1955).

(7) S. P. Massie, I. Cooke, and W. A. Hills, *J. Org. Chem.*, **21**, 1006 (1956).

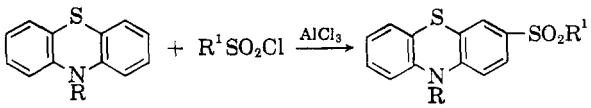
(8) J. Schmitt, J. Boitard, P. Comoy, A. Hallot, and M. Suquet, *Bull. soc. chim. France*, 938 (1957).

whereas 10-acyl- or 10-sulfonylphenothiazines might yield predominantly the corresponding 2-sulfonyl derivatives.

The results of our investigation of the sulfonylation reactions are summarized in Table I. All reactions were carried out in ethylene dichloride at room temperature, and, with one exception noted in the table, the reaction period for all experiments was seventy-two hours. Although ethylene dichloride is not as satisfactory a solvent as carbon disulfide for the acylation of 10-acylphenothiazine,[9] it was chosen for this work after we found, in preliminary experiments, that sulfonylation of 10-acetylphenothiazine in carbon disulfide or nitrobenzene led to complex reaction mixtures consisting chiefly of tars, from which no product could be isolated. Moreover, as Truce and Vriesen[10] have pointed out, the complex of aluminum chloride with methanesulfonyl chloride is not soluble in carbon disulfide. That ethylene dichloride does not react to a great extent with phenothiazine under the conditions employed in the sulfonylation reactions was shown by the fact that the latter was recovered in 85% yield from a mixture of the two components and aluminum chloride that had been stirred at room temperature for seventy-two hours.

TABLE I

REACTIONS OF PHENOTHIAZINE AND ITS 10-SUBSTITUTED DERIVATIVES WITH SULFONYL CHLORIDES IN THE PRESENCE OF ALUMINUM CHLORIDE[a]



Reaction No.	R	R¹	Mole Ratio $AlCl_3/Pz^b$	3-Sulfone Yield, %
1	H	CH_3	1	2.5
2	H	CH_3	2	Trace[c]
3	H	CH_3	2.4	2.0
4	H	C_6H_5	1	19
5	H	C_6H_5	2	45
6	H	C_6H_5	3	37
7	H	C_6H_5	4	30
8	H	$4\text{-}CH_3C_6H_4$	3	27[d]
9	H	$4\text{-}CH_3C_6H_4$	3	40
10	CH_3CO	CH_3	2	13
11	CH_3CO	CH_3	3	9.0[e]
12	CH_3SO_2	CH_3	1	1.6
13	CH_3SO_2	CH_3	2	25
14	$C_6H_5SO_2$	CH_3	2.4	20
15	$C_6H_5SO_2$	C_6H_5	1	27
16	$C_6H_5SO_2$	C_6H_5	2	36
17	$C_6H_5SO_2$	C_6H_5	3	57
18	$C_6H_5SO_2$	C_6H_5	4	60[e]
19	$4\text{-}CH_3C_6H_4SO_2$	$4\text{-}CH_3C_6H_4$	2	62

[a] Reactions carried out in ethylene dichloride at room temperature employing equimolar quantities of phenothiazine derivative and sulfonyl chloride; except when noted otherwise, the reaction period was 72 hours. [b] Pz equals phenothiazine derivative. [c] 10-Methylsulfonylphenothiazine (5–10%) was also isolated. [d] Twenty-four-hour reaction time. [e] A small amount of 3,7-diphenylsulfonylphenothiazine was also isolated.

As shown by the data in Table I (reactions no. 1–9), the only sulfone products isolated from the reaction of phenothiazine with methane-, benzene-, or *p*-toluenesulfonyl chloride in the presence of aluminum chloride were the 3-phenothiazinyl sulfones. The yields were generally poor, particularly those from the reaction of methanesulfonyl chloride. In all cases the crude reaction mixtures contained large amounts of tarry materials which made isolation of products difficult. The methyl sulfone obtained from the Friedel-Crafts reaction was different from 2-methylsulfonylphenothiazine,[11] and was found to be identical with 3-methylsulfonylphenothiazine prepared by a different route (see below). Structures of the 3-arylsulfonylphenothiazines were assigned on the basis of spectral data (see Experimental).

In attempts to direct sulfonylation to the 2-position of phenothiazine, a series of reactions was carried out employing 10-acetyl-, 10-methylsulfonyl-, 10-phenylsulfonyl-, and 10-*p*-tolylsulfonylphenothiazine. The results of these experiments are also presented in Table I (reactions no. 10–19). Again, the only sulfone products isolated were 3-phenothiazinyl sulfones. As in the corresponding reaction of phenothiazine, the reaction of 10-acetyl phenothiazine with methanesulfonyl chloride led to a large amount of tar formation, although the yield of 3-sulfone isolated from the latter reaction was somewhat higher. However, in the case of the sulfonylations of the 10-sulfonyl derivatives, the yields of 3-sulfones, when two to three moles of aluminum chloride were used, were considerably higher than those obtained in the corresponding reactions of phenothiazine.

From reactions no. 10–19, not only were none of the 10-substituted-2-sulfonylphenothiazines isolated, but no evidence was found for the presence of the 10-substituted derivatives of the 3-sulfones. These observations suggested that cleavage of the 10-acetyl and 10-sulfonyl groups occurred prior to sulfonylation. In contrast to these results, 10-acylphenothiazines in carbon disulfide are readily acylated in the 2- position without loss of the 10-acyl group.[4,6–8] In the systems studied in this work, apparently either the cleavage of the 10-substituent is a much more rapid reaction than it is in the acylation reactions or the sulfonylating agents are so much less reactive than the acylating agents that the deactivating influence on the phenothiazine nucleus of the 10-substituent must be removed before sulfonylation can occur.

(9) Unpublished results from these laboratories.

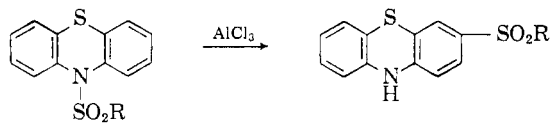
(10) W. E. Truce and C. W. Vriesen, *J. Am. Chem. Soc.*, 75, 5032 (1953).

(11) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.*, 25, 60 (1960).

The cleavage and rearrangement of arylsulfonamides of arylamines to form sulfones has been known for many years.[12-14] Thus, the 3-phenothiazinyl sulfones obtained from the reactions of the 10-sulfonyl derivatives could possibly be formed, at least in part, by rearrangement of the sulfonamides. To determine the extent to which the cleaved 10-sulfonyl group may participate in the sulfonylation of phenothiazine, the 10-sulfonyl derivatives were treated with aluminum chloride under the conditions described above for the reactions with sulfonyl chlorides. As indicated by the results summarized in Table II, all three

TABLE II

REARRANGEMENT OF 10-SULFONYLPHENOTHIAZINES TO 3-SULFONES IN THE PRESENCE OF ALUMINUM CHLORIDE[a]



Reaction No.	R	Mole Ratio $AlCl_3/Pz$[b]	3-Sulfone Yield, %
20	CH_3	1	14
21	CH_3	2	12
22	C_6H_5	1	21
23	C_6H_5	2	43
24	C_6H_5	3	60
25	C_6H_5	4	29
26	$4\text{-}CH_3C_6H_4$	1	24
27	$4\text{-}CH_3C_6H_4$	2	64
28	$4\text{-}CH_3C_6H_4$	3	68
29	$4\text{-}CH_3C_6H_4$	3	45[c]

[a] Reactions carried out in ethylene dichloride at room temperature for 72 hr., except when noted otherwise. [b] Pz = phenothiazine derivative. [c] 24-hr. reaction time.

sulfonamides under these conditions underwent rearrangement to the 3-sulfones. In fact, with the exception of reaction no. 25, the yields of 3-sulfones from the rearrangement of the 10-phenyl- and 10-*p*-tolylsulfonyl derivatives were quite comparable with those from the corresponding reactions in which sulfonyl chlorides were added (Table I). Thus, in the latter reactions, the presence of excess sulfonylating agent does not result in an increased yield of 3-sulfone. However, these results cannot be interpreted to mean that the added sulfonyl chloride does not participate in the sulfonylation process.

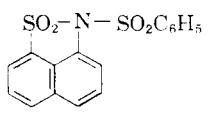
In an attempt to gain information on the extent to which the added sulfonylating agent may participate in sulfone formation, we carried out two experiments in which (1) 10-phenylsulfonylphenothiazine was treated with *p*-toluenesulfonyl chloride and (2) 10-*p*-tolylsulfonylphenothiazine was treated with benzenesulfonyl chloride under the conditions employed in reaction no. 17. The only products isolated were the 3-phenylsulfonyl derivative (47% yield) from reaction 1 and the 3-*p*-tolylsulfonyl derivative (62% yield) from reaction 2. None of the 3-sulfones corresponding to the sulfonyl halides could be isolated from the reaction mixtures, which, as in the other cases discussed earlier, contained considerable amounts of tars. Although we could not demonstrate participation of the sulfonyl halides, because of the difficulty in isolating pure products from the complex reaction mixtures we cannot rule out the possibility that some of the sulfones derived from the sulfonyl halides were formed. In this regard, it is noteworthy that Mustafa and Ali[13] have reported that when *N*-phenylsulfonyl-1,8-naphthosultam[14] was treated with *p*-tolylsulfonyl chloride in the presence of aluminum chloride, the *N*-phenylsulfonyl group was eliminated and the only product obtained was the 4-*p*-tolylsulfonyl-1,8-naphthosultam—a result just the opposite of those observed in the present work.

For all of the reactions listed in Tables I and II, with the exceptions of the methanesulfonylations and the rearrangement of 10-methylsulfonylphenothiazine, the optimal amount of aluminum chloride appears to be between two to three mole equivalents. The generally poor yields of 3-methylsulfonylphenothiazine, even when two or more mole equivalents of aluminum chloride are used, and the beneficial effect of excess sulfonylating agent upon the yield of 3-sulfone from 10-methylsulfonylphenothiazine are probably explained by the fact that the methanesulfonyl ion is unstable in the presence of excess aluminum chloride.[10] In the rearrangement of 10-phenylsulfonylphenothiazine, increasing the amount of aluminum chloride from three to four mole equivalents resulted in extensive decomposition of starting material or product and decreased the yield of 3-sulfone from 60 to 29%. In the corresponding experiment in which a mole equivalent of benzenesulfonyl chloride was added, the yield of sulfone was not decreased when four mole equivalents of aluminum chloride was used.

(12) (a) S. Searles and S. Nukina, *Chem. Revs.*, **59**, 1077 (1959); (b) J. Halberkann, *Ber.*, **55**, 3074 (1922).

(13) A. Mustafa and M. I. Ali, *J. Am. Chem. Soc.*, **77**, 4593 (1955).

(14) For example, treatment of the *p*-toluenesulfonamide of diphenylamine with concentrated sulfuric acid at room temperature for four days gave in 52% yield, the isomeric 2-phenylaminodiphenyl sulfone (ref. 12b). More recently, Mustafa and Ali (ref. 13) have reported that compound i, when heated with aluminum chloride in nitrobenzene, underwent rearrangement to form a phenylsulfonyl-1,8-naphthosultam to which they assigned structure ii by analogy to Friedel-Crafts products obtained from 1-naphthol derivatives. These authors also found that *N,N*-di(*p*-tolylsulfonyl)aniline, when heated with aluminum chloride, was converted to *p*-aminophenyl *p*-tolyl sulfone.



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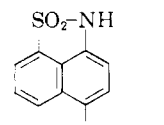
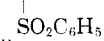




ii

TABLE III

SPECTRAL DATA FOR SULFONYLPHENOTHIAZINES

Sulfonylphenothiazine		Ultraviolet Spectra				Infrared Spectra					
		Phenothiazine ring absorption		Aromatic sulfone absorption				Aromatic C—H out-of-plane bending			
Position of RSO_2	R	λ_{max} mμ	log ε	λ_{max}, mμ	log ε	SO_2 asymmetric stretching, μ	SO_2 symmetric stretching, μ	Isolated H, μ	2H in row, μ	2,4 or 5H in row, μ	5H in row μ
2	CH_3[a]	268	4.64	238	4.12	7.6(s), 7.8(s)[b]	8.8(s)		12.6(w)	13.0(m), 13.2(s), 13.8(m)	
3	CH_3	268	4.59	235	4.06	7.6(s)	8.7(s)	11.2(w)	12.2(m)	12.9(m), 13.2(s), 13.6(m)	
3	C_6H_5	268	4.58	235	4.35	7.6(s)	8.7(s)	11.3(w)	12.1(w)	13.0(m), 13.2(s), 13.3(s), 13.8(s), 13.9(m)	14.5(m)
3	p-$CH_3C_6H_4$	268	4.58	236	4.39	7.6(s)	8.7(s)	11.2(w)	12.2(m) 12.3(w)	13.2(m), 13.4(s), 14.0(w), 14.2(w)	
3,7	di-C_6H_5	280	4.79	226	4.60	7.5(s), 7.7(s)	8.7(s)	11.1(m) 11.3(m)	12.3(m)	13.0(s), 13.9(s), 14.1(m)	
10	CH_3	256	3.88	227	4.40	7.4(s)	8.7(s)			13.1(s), 13.6(m), 14.5(w)	
10	C_6H_5	273	3.83	236	4.28	7.4(s)	8.6(s)			13.1(s), 13.2(m), 13.3(s), 13.7(m), 13.8(s), 13.9(m)	14.6(m)
10	p-$CH_3C_6H_4$	—	—	—	—	7.4(s)	8.6(s)		12.3(m), 12.5(m)	13.1(s), 13.8(s)	

[a] Ref. 11. [b] s = strong, m = medium, w = weak.

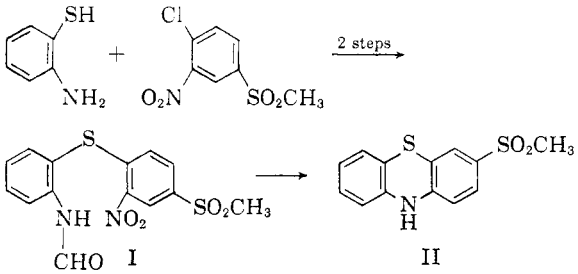
Perhaps, in this reaction, the sulfonyl halide, in complexing with the catalyst, exerted a protective action by decreasing the effective concentration of aluminum chloride to approximately three mole equivalents.

Sulfone formation in the reactions of the 10-sulfonyl derivatives is undoubtedly determined to a large extent by the ease of cleavage of the sulfonyl groups, which will probably increase in the order of increasing stability of the sulfonyl ions formed in the process. As Truce and Vriesen[10] have pointed out, the methanesulfonyl ion is less stable than the benzenesulfonyl ion, which is stabilized by resonance. *p*-Toluenesulfonyl ion, by virtue of the inductive effect of the *p*-methyl group, should be more stable than the benzenesulfonyl ion. Thus the ease of cleavage of the 10-sulfonyl groups might be expected to follow the order: $CH_3SO_2 < C_6H_5SO_2 < p$-$CH_3C_6H_4SO_2$. As the data in Tables I and II indicate, the yields of sulfones from the 10-sulfonyl phenothiazine derivatives increase according to this order.

One might expect that about the same yields of 3-sulfones would be obtained from both phenothiazine and its 10-sulfonyl derivatives. However, in all cases, the yields of sulfone from the latter were higher than those from phenothiazine. A possible explanation of these results is that phenothiazine reacts rapidly with aluminum chloride to form an aluminum complex of type R_2NAlCl_2 which precipitates from solution and is not readily available for the subsequent sulfonylation reaction. We found that when clear solutions of phenothiazine and of aluminum chloride in ethylene dichloride were mixed, the resulting solution rapidly darkened and became cloudy, and eventually the metal complex of phenothiazine precipitated as an oily solid. The phase of the reaction mixture containing the complex may also contain a considerable amount of aluminum chloride which may catalyze the decomposition of the phenothiazine-aluminum complex to tars and other by-products. On the other hand, the cleavage of the 10-sulfonyl derivatives may occur at such a slow rate that the aluminum complex is generated in low concentration and is sulfonylated before it precipitates from the reaction mixture.

To provide an authentic sample of 3-methylsulfonylphenothiazine (II) for comparison with the methyl sulfone obtained from the Friedel-Crafts

reaction and for use as a reference in the spectral analyses of the aryl sulfones, II was prepared by the following route involving a Smiles rearrangement of 2'-formamido-2-nitro-4-methylsulfonyl-diphenyl sulfide (I).



As the methylsulfonylphenothiazine obtained by this method was different from authentic 2-methylsulfonylphenothiazine,[11] which would be formed if ring closure of I occurred without rearrangement, the former compound must be the 3-sulfone II.

EXPERIMENTAL[15]

10-Methylsulfonylphenothiazine. A mixture of 200 g. of phenothiazine, 172 g. of methanesulfonyl chloride, and 500 ml. of pyridine was stirred at 27° for 24 hr. The reaction mixture was poured onto ice, the resulting mixture was adjusted to *p*H 2–3 by addition of hydrochloric acid, and the product was collected on a filter. After recrystallization of the solid from ethanol, 50 g. (18%) of sulfonamide, m.p. 231–233°, was obtained.

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 56.29; H, 4.00. Found: C, 56.32; H, 4.25.

10-Phenyl- and 10-p-tolylsulfonylphenothiazine were prepared as described in the literature.[16,17]

General procedure for the Friedel-Crafts and rearrangement reactions (Tables I and II). To a mechanically stirred solution of 0.05 mole of phenothiazine or its 10-sulfonyl derivative and 0.05 mole of sulfonyl chloride (omitted in the experiments listed in Table II) in 500 ml. of ethylene dichloride was added the appropriate quantity of aluminum chloride at such a rate that the temperature did not rise above 27°. Through out the reaction period of 72 hr. the mixture was stirred while a gentle stream of nitrogen was passed over the contents of the flask which was vented through a calcium chloride tube.

At the end of the reaction period, the mixture was poured onto an ice water mixture. At this point a portion of the phenyl or *p*-tolyl sulfone separated at the solvent-water interface. The solid was collected on a filter and purified by recrystallization. Upon fractional crystallization of the solid from reaction no. 18 (Table I), 3,7-diphenylsulfonylphenothiazine was obtained in 2.3% yield. After removal of the solid material from the mixture, the ethylene dichloride layer was separated and washed in turn with water, 20% sodium hydroxide solution, and water again. Upon evaporation of the ethylene dichloride solution *in vacuo* a black, tarry residue was obtained. The mixture, dissolved in a minimum volume of chloroform, was placed on an alumina column and eluted with benzene-chloroform solutions of varying composition. Crystalline fractions which, according to spectral data, appeared to have similar compositions were combined and purified by recrystallization from acetone or acetone-benzene mixtures.

The following compounds were isolated:

3-Methylsulfonylphenothiazine, m.p. 220–221.5°, identical in all respects with a sample prepared by the route described below.

3-Phenylsulfonylphenothiazine, m.p. 196.5–198°.

Anal. Calcd. for $C_{18}H_{13}NO_2S_2$: C, 63.69; H, 3.86. Found: C, 63.75; H, 4.15.

3,7-Diphenylsulfonylphenothiazine, m.p. 242–243°.

Anal. Calcd. for $C_{24}H_{17}NO_4S_3$: C, 60.10; H, 3.57; S, 20.06. Found: C, 60.41; H, 3.89; S, 20.14.

3-p-Tolylsulfonylphenothiazine, m.p. 249–250°.

Anal. Calcd. for $C_{19}H_{15}NO_2S_2$: C, 64.56; H, 4.28; N, 3.99. Found: C, 64.51; H, 4.51; N, 3.93.

2'-Amino-2-nitro-4-methylsulfonyldiphenyl sulfide. To a solution of 8.0 g. (0.2 mole) of sodium hydroxide, 25 g. (0.2 mole) of *o*-aminobenzenethiol, and 60 ml. of water in 600 ml. of ethanol was added 47.7 g. (0.2 mole) of 4-chloro-3-nitrophenyl methyl sulfone[18] suspended in 600 ml. of ethanol. The resulting mixture was heated at reflux for 2.5 hr. and then allowed to stand overnight at room temperature. The mixture was heated to boiling, filtered, and the solid collected on the filter was washed with 25 ml. of ethanol. From the combined filtrates, after cooling, 52.5 g. (81%) of orange needles, m.p. 149.5–150.5°, was obtained.

Anal. Calcd. for $C_{13}H_{12}N_2O_4S_2$: C, 48.15; H, 3.73. Found: C, 47.90; H, 3.77.

2'-Formamido-2-nitro-4-methylsulfonyldiphenyl sulfide (I). —A mixture of 4.0 g. (0.012 mole) of aminodiphenyl sulfide and 40 g. of 90% formic acid was heated at reflux overnight. The brown solution was poured onto 100 ml. of crushed ice and the solid which precipitated was collected on a filter. The product, after recrystallization from dioxane–carbon tetrachloride, was obtained as dull yellow crystals, m.p. 189.5–190°.

Anal. Calcd. for $C_{14}H_{12}N_2O_5S_2$: C, 47.71; H, 3.43. Found: C, 47.36; H, 3.69.

3-Methylsulfonylphenothiazine (II). A mixture of 5.28 g. of I and 15 ml. of 1N ethanolic sodium hydroxide in 100 ml. of acetone was heated at reflux for 4 hr. The hot reaction mixture was filtered to remove 0.76 g. of pale brown solid and the filtrate was concentrated *in vacuo*. The residual mixture of brown solid and black oil was collected on a filter and washed with petroleum ether (b.p. 30–60°) to give 3.0 g. of brown crystalline material. After two recrystallizations of the crude product from ethanol, II was obtained as glistening yellow plates, m.p. 220–221.5°.

Anal. Calcd. for $C_{13}H_{11}NO_2S_2$: C, 56.29; H, 4.00; N, 5.05. Found: C, 56.53; H, 4.17; N, 5.26.

Spectral data for the sulfonylphenothiazine derivatives (Table III). The ultraviolet spectra were obtained with the Cary Model 14 spectrophotometer using ethanol solutions in 1-cm. silica cells. Infrared spectra were obtained with the Perkin-Elmer Model 21 spectrophotometer employing both mineral oil mulls and potassium bromide discs. Spectra of samples in the two media showed no significant differences.

The molecular extinction coefficient for the phenothiazine 268-mμ band is remarkably constant for all of the 3-sulfonylphenothiazines (log ϵ 4.58–4.59). The 2-methylsulfonylphenothiazine absorption is stronger (log ϵ 4.64). The absorption of the 3-sulfones in the 11.2–11.3 μ region, attributed to the isolated C—H bond in position 4 of the phenothiazine nucleus, is absent from the spectrum of the 2-methylsulfonyl derivative, although there is an isolated C—H bond in the 1-position of this phenothiazine derivative. The 3-phenothia-

(15) We wish to thank Mrs. Doris Rolston and co-workers, Analytical and Physical Chemistry Section, Smith Kline & French Laboratories, for the microanalyses, and Mr. Richard J. Warren and Miss Barbara Petruzzo of the same section for the spectral data.

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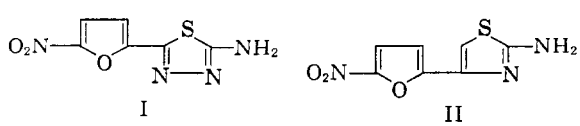
A number of 4-(5-nitro-2-furyl)thiazoles have been prepared. The antibacterial activity of these compounds is briefly discussed.

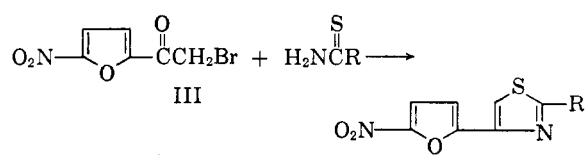
In a recent publication from this laboratory,[1b] it was shown that the antibacterial properties of 5-nitrofurans are not dependent on a linear —C=N—N—C= system in the 2- position. Thus, incorporation of this atomic arrangement into a heterocycle does not diminish in any way the antibacterial activity 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

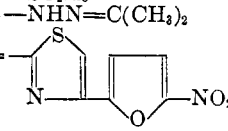
II



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 =



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