7.95, and 9.0 μ. The n.m.r. spectrum (CH_2Cl_2) showed triplets at 3.00 and 3.27 and a quartet at 3.67 (morpholino groups), singlets at 4.02 (olefinic proton) and 4.29 (CH_2), and a multiplet at 7.48 p.p.m. (aromatic protons).

Anal. Calcd. for $C_{17}H_{24}N_2O_4S$: C, 57.9; H, 6.9; N, 8.0; S, 9.1. Found: C, 57.9; H, 6.8; N, 7.6; S, 9.1.

4,4'-(1-Methylethylsulfonyl)vinylidenedimorpholine (X) and 4,4'-(2-Chloro-1-methylethylsulfonyl)vinylidenedimorpholine (XI).—Under the general procedure with THF as solvent, 2-propanesulfonyl chloride and 4,4'-vinylidenedimorpholine gave a 21% yield of a mixture of X and XI, m.p. 136–143°. The n.m.r. spectrum ($CHCl_3$) of the mixture indicated that it was a 40:60 mixture of X and XI. This ratio was determined by comparison of the area under the peaks for the *gem*-dimethyl protons in the spectrum of XI with the area under the peaks for the methyl protons of the isopropyl group in the spectrum of X. Infrared absorptions of the mixture (KBr) were at 6.5, 7.85, and 9.0 μ. The n.m.r. spectra ($CHCl_3$) showed for X, a doublet at 1.33 (methyl protons of isopropyl group), triplets at 3.22 and 3.43, and a multiplet at 3.69 (methylidyne proton of the isopropyl group and protons of morpholino groups), and a singlet at 4.15 p.p.m. (olefinic proton); for XI, a singlet at 1.89 (*gem*-dimethyl group), triplets at 3.22 and 3.43, a multiplet at 3.69 (protons of morpholino groups), and a singlet at 4.15 p.p.m. (olefinic proton).

Anal. Calcd. for 40% X and 60% XI: Cl, 6.3. Found: Cl, 6.3.

Repeated recrystallizations from benzene gave pure XI, m.p. 151–152°. Infrared absorptions (KBr) were at 6.55, 7.8, and 9.0 μ.

Anal. Calcd. for $C_{13}H_{23}ClN_2O_4S$: C, 46.1; H, 6.8; Cl, 10.5; N, 8.3; S, 9.5. Found: C, 46.5; H, 7.0; Cl, 10.3; N, 7.9; S, 9.8.

4,4'-(Phenylsulfonyl)vinylidenedimorpholine (XIII).—Under the general procedure with THF as solvent, benzenesulfonyl chloride and 4,4'-vinylidenedimorpholine gave a 37% yield of XIII, m.p. 162–163°. Infrared absorptions (KBr) were at 6.5, 7.9, and 9.0 μ. The n.m.r. spectrum ($C_2H_2Cl_4$) showed broad unresolved peaks at 3.20 and 3.62 (morpholino groups), a singlet at 4.41 (olefinic proton), and a multiplet at 7.60 p.p.m. (aromatic protons).

Anal. Calcd. for $C_{16}H_{22}N_2O_4S$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.8; H, 6.4; N, 8.2.

3-(N-Methylanilino)thiete 1,1-Dioxide (XIV).—A mixture of 1.89 g. (0.01 mole) of II and 1.44 g. (0.01 mole) of N-methylaniline hydrochloride in 20 ml. of benzene was refluxed for 1.5 hr. The hot benzene layer was decanted from the solid present. Evaporation of the benzene gave 2.0 g. of solid residue, m.p. 65–70°. One recrystallization from ethyl alcohol gave 1.15 g. (55%) of XIV, m.p. 99–102°. A sample recrystallized again from ethyl alcohol melted at 101.5–103°. Infrared absorptions (KBr) were at 6.25, 6.3, 7.9, 8.25, and 9.1 μ. The n.m.r. spectrum (CH_2Cl_2) showed singlets at 3.24 (methyl group), 4.29 (CH_2), and 5.37 (olefinic proton), and a multiplet at 7.23 p.p.m. (aromatic protons).

Anal. Calcd. for $C_{10}H_{11}NO_2S$: C, 57.4; H, 5.3; N, 6.7; S, 15.3. Found: C, 56.9; H, 5.1; N, 6.3; S, 15.3.

2,2-Dimethyl-3-thietanone 1,1-Dioxide (XVa).—A mixture of 8 g. (0.046 mole) of Ib and 44 g. of the acid form of Amberlite IR-120 ion-exchange resin and 50 ml. of water was stirred for 3 hr. at 25°. After removal of the resin and evaporation of the water *in vacuo*, there was obtained 6.5 g. (95%) of XVa, m.p. 108–110°. A sample after recrystallization from benzene and sublimation at 75° (0.07 mm.) melted at 108.5–110.5°. Infrared absorptions (KBr) were at 3.35 (w), 3.45 (w), 5.6, 5.7, 7.6, 8.4, 8.95, and 9.4 μ. The n.m.r. spectrum ($CHCl_3$) showed singlets at 1.67 (*gem*-dimethyl groups) and 4.91 p.p.m. (CH_2).

Anal. Calcd. for $C_5H_8O_3S$: C, 40.5; H, 5.4; S, 21.6; neut. equiv., 148.2. Found: C, 40.7; H, 5.5; S, 21.3; neut. equiv., 147.2; pK_a (H_2O) = 4.41.

3-Thietanone 1,1-Dioxide (XVb).—A mixture of 168 g. (0.89 mole) of crude II (m.p. 118–128°, contaminated with III), 900 g. of the acid form of Amberlite IR-120 ion-exchange resin and 1.3 l. of water was stirred at room temperature for 3 hr. After removal of the resin and evaporation of the water *in vacuo* at room temperature, there was left a residue of 75.5 g. of crude XVb. Washing with 125 ml. of THF gave 54 g. (51%) of XVb, m.p. 205–211°. A sample after recrystallization from tetrachloroethane and sublimation at 95° (0.05 mm.) melted at 218–223° dec. Infrared absorptions (KBr) were at 3.4 (doublet), 5.5 (w), 5.65, 7.45, 7.6, 8.35, and 8.85 μ. The n.m.r. spectrum ($C_2H_2Cl_4$) showed a single peak at 4.98 p.p.m. (CH_2).

Anal. Calcd. for $C_3H_4O_3S$: C, 30.0; H, 3.4; S, 26.7; neut. equiv., 120.1. Found: C, 29.8; H, 3.8; S, 26.3; neut. equiv., 120.7; pK_a (H_2O) = 4.14.

Sulfonyl Fluorides as Intermediates in Organic Synthesis. II. Synthesis and Alkaline Hydrolysis of 2-(Acylacetyl)aminothiazoles Containing Fluorosulfonyl Substituents

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Received April 17, 1964

The synthesis of 2-aminothiazole derivatives, containing 5-fluorosulfonyl or 4-fluorosulfonylphenyl substituents, is described. These compounds can be condensed with β-ketonic esters. The resulting fluorosulfonyl-substituted 2-(acylacetyl)aminothiazoles are converted by alkaline hydrolysis to the corresponding alkali sulfonates. These reactions constitute further examples of the usefulness of fluorosulfonyl-substituted intermediates in the synthesis of sulfonic acid derivatives, which are unaccessible by conventional sulfonation techniques.

The condensation of β-ketonic esters with aminobenzenesulfonyl fluorides and the subsequent alkaline hydrolysis of the resulting N-(acylacetyl)aminobenzenesulfonyl fluorides have been described in a previous paper.[1] This method, which is illustrated by the following reaction, proved to be a generally useful synthetic way to N-(acylacetyl)aminoarylsulfonates (X = aryl). It has now been extended to include fluorosulfonyl derivatives of the 2-aminothiazole series (X = a group containing the thiazole nucleus).

$$RCOCH_2COOC_2H_5 + H_2NXSO_2F \longrightarrow RCOCH_2CONHXSO_2F \xrightarrow{NaOH} RCOCH_2CONHXSO_2ONa$$

2-Aminothiazoles with a nuclear fluorosulfonyl substituent could be synthesized according to the reaction sequence shown in Scheme I.

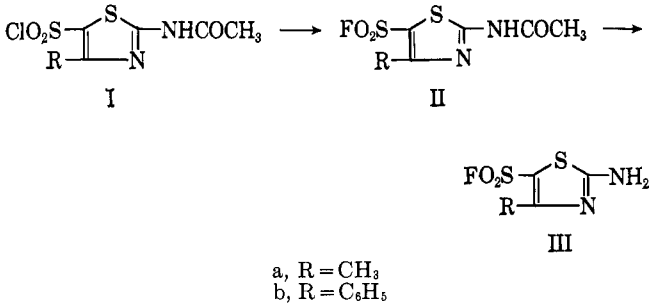
2-Acetylamino-4-methyl-5-chlorosulfonylthiazole (Ia)[2] and the corresponding 4-phenyl derivative (Ib)[3] were converted to the corresponding 5-fluorosulfonyl derivatives IIa and IIb, and subsequently hydro-

(1) A. De Cat and R. Van Poucke, *J. Org. Chem.*, **28**, 3426 (1963).

(2) H. Backer and J. de Jonge, *Rec. trav. chim.*, **62**, 164 (1943).

(3) B. Das and M. Rout, *J. Indian Chem. Soc.*, **32**, 665 (1955).

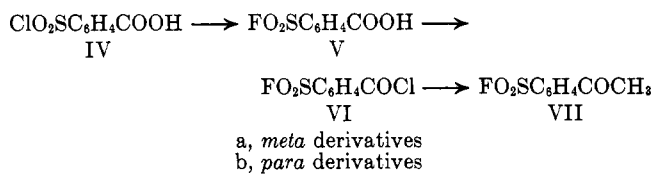
SCHEME I



a, R = CH_3
b, R = C_6H_5

lyzed to the corresponding 2-amino-4-methyl- (or phenyl-) 5-fluorosulfonylthiazoles (IIIa and b).

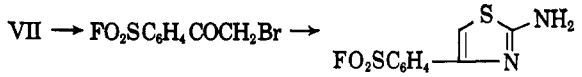
Considering the excellent yields of 2-aminothiazoles which are usually obtained by condensation of thiourea with phenacyl halides,[4] we expected the fluorosulfonylphenacyl bromides (VIIIa and b) to be promising precursors for the synthesis of 4-fluorosulfonylphenyl-substituted 2-aminothiazoles. Consequently we had to work out a practical synthesis for fluorosulfonylacetophenones (VIIa and b). These could be prepared according to the following reaction sequence.



a, *meta* derivatives
b, *para* derivatives

The fluorosulfonylbenzoic acids Va and b had already been obtained by Steinkopf[5] by the action of fluorosulfonic acid on *m*-chlorosulfonylbenzoic acid (yield 58%) and by chromium trioxide oxidation of *p*-toluenesulfonyl fluoride (yield 32%). A more convenient synthesis, however, proved to be the reaction of the readily available *m*- and *p*-chlorosulfonylbenzoic acids (IVa and b) with potassium fluoride in aqueous dioxane medium. Condensation of the corresponding acid chlorides VIa and b with diethyl ethoxymagnesiummalonate produced the corresponding fluorosulfonylbenzoyl diethylmalonates, which upon acid-catalyzed hydrolysis and simultaneous decarboxylation gave the fluorosulfonylacetophenones (VIIa and b). The method used was derived from a similar conversion of *p*-nitrobenzoyl chloride to *p*-nitroacetophenone.[6]

The fluorosulfonylbenzoylacetophenones (VIIa and b) were brominated in dioxane solution and the resulting fluorosulfonylphenacyl bromides (VIIIa and b) were condensed in the usual way[4] with thiourea to give the aminothiazoles IXa and b.



a, *meta* derivative
b, *para* derivative

The aminothiazoles IIIa, IIIb, IXa, and IXb were condensed with β-ketonic esters, by heating equimolecular quantities of the reactants in refluxing xylene, while distilling the alcohol resulting from the condensation. The resulting fluorosulfonyl-substituted 2-(acylacetyl)aminothiazoles (Xa–j), together with their physical data, yields, and analyses, are listed in Table I.

When the nitrobenzoyl derivatives Xa–c of Table I were hydrogenated over Raney nickel W-2[7] at 80° in dioxane solution, 3 moles of hydrogen was consumed at a fairly constant rate between 1.25–2 × 10^{-3} moles/min./ml. of catalyst. Since the hydrogen uptake stopped completely after consumption of 3 moles of hydrogen, the aminobenzoyl derivatives XIa–c, which were obtained in very high yields, could be expected to be free from any appreciable amount of side products resulting from β-carbonyl hydrogenation.[8] This was confirmed by analysis (see note *e* of Table I).

The 2-(aminobenzoyl)acetylaminothiazole derivatives XI were treated with palmitoyl chloride in dioxane solution in the presence of pyridine as a hydrogen chloride acceptor to give the palmitoylamido derivatives XIIa–c (Table I).

The 2-(acylacetyl)fluorosulfonyl-substituted aminothiazoles of Table I were suspended in boiling acetone and treated with 3 equiv. of aqueous sodium or potassium hydroxide to produce the corresponding sodium or potassium sulfonates.

These compounds which constitute yellow image color couplers for color photography[9] were obtained in yields up to 94%.

These reactions present further evidence of the usefulness of fluorosulfonyl intermediates to prepare sulfonated derivatives with well-defined positions of the sulfonic group and which cannot be obtained by conventional sulfonation techniques.

Experimental

Melting points were determined on a Kofler hot bench melting point apparatus and are corrected.

Sulfonyl Chlorides.—The necessary sulfonyl chlorides were prepared according to described procedures: *m*-chlorosulfonylbenzoic acid,[10] *p*-chlorosulfonylbenzoic acid,[11] and 2-acetylamino-4-methyl-5-chlorosulfonylthiazole.[2]

2-Acetylamino-4-phenyl-5-chlorosulfonylthiazole (Ib).—Initial attempts made to obtain this previously prepared but inadequately described[3] compound were completely unsatisfactory. Low yields of the sulfonyl chloride could be obtained according to the following modified procedure.

To 66 ml. (1 mole) of chlorosulfonic acid, cooled to about 10–15°, were added gradually with stirring 21.8 g. (0.1 mole) of 2-acetylamino-4-phenylthiazole,[3] while maintaining the temperature at about 20°. After that, the reaction temperature was raised and kept at 60° during 1 hr. and at 80° during 3 hr.

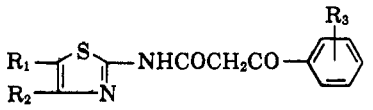
(4) R. Wiley, D. England, and L. Behr, *Org. Reactions*, **6**, 373 (1951).
(5) W. Steinkopf, *J. prakt. Chem.*, [2] **117**, 1 (1927).
(6) L. Long and H. Troutman, *J. Am. Chem. Soc.*, **71**, 2473 (1949).
(7) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.
(8) Previous experience with structurally related nitrobenzoylacetyl compounds, derived from simple aromatic amines, indicated that during the hydrogenation of such compounds over Raney nickel the two following consecutive reactions may take place.

$$O_2NC_6H_4COCH_2CONH\text{-aryl} \xrightarrow{3H_2} H_2NC_6H_4COCH_2CONH\text{-aryl} \xrightarrow{H_2} H_2NC_6H_4CHOHCH_2CONH\text{-aryl}$$

The insufficient difference between the rates of hydrogenation of the β-carbonyl group and the nitro group does not permit the hydrogenation of nitrobenzoylacetarylides in a highly selective way. When the hydrogenations are stopped after consumption of 3 moles of hydrogen, repeated recrystallizations are generally necessary to isolate pure aminobenzoylacetarylides from the complex reaction mixture in low and unreproducible yields.
(9) J. Jaeken (Gevaert Photo-Producten N.V.), German Patent 1,038,916 (1957); *Chem. Abstr.*, **55**, 8136 (1961).
(10) S. Smiles and J. Stewart, *J. Chem. Soc.*, 1795 (1921).
(11) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

TABLE I

2-(ACYLACETYL)AMINOTHIAZOLES X, XI, AND XII



Compd.	R_1	R_2	R_3	Yield,[a] %	M.p., °C.	Recrystn. solvent[b]	% N Calcd.	% N Found	% S Calcd.	% S Found	% F Calcd.	% F Found
Xa	FSO_2	CH_3	m-NO_2	74	204	A	10.85	11.09	16.53	16.92	4.89	4.87
Xb	H	m-$FSO_2C_6H_4$	p-NO_2	(93)[c]	247–248	B	9.35	9.29	14.25	14.16	4.23	4.04
Xc	H	m-$FSO_2C_6H_4$	m-NO_2	(88)[c]	200–202	B	9.35	9.43	14.25	14.35	4.23	3.96
Xd	FSO_2	C_6H_5	p-$C_{16}H_{33}O$	66	145	C	4.35	4.31	9.97	9.81	...	...
Xe	H	m-$FSO_2C_6H_4$	p-CH_3O	46	222	D	...	...	14.74	14.68	...	...
Xf	H	m-$FSO_2C_6H_4$	p-$C_{16}H_{33}O$	80	144	B	4.35	4.50	9.97	10.04	2.94	2.63
Xg	H	p-$FSO_2C_6H_4$	p-$C_{16}H_{33}O$	68	146	C	4.35	4.26	9.97	9.84	...	...
Xh	FSO_2	CH_3	o-$C_{16}H_{33}S$	70	101	E	...	...	16.05	15.95	...	...
Xj	H	m-$FSO_2C_6H_4$	o-$C_{16}H_{33}S$	78	119	F	...	...	14.54	14.58	...	...
XIa	FSO_2	CH_3	m-H_2N[d]	84	196–197	G	11.76	11.80	17.92	18.00	5.32	5.36
XIb	H	m-$FSO_2C_6H_4$	p-H_2N[d]	(90)	210	H	10.03	9.95	15.26	15.00	...	...[e]
XIc	H	m-$FSO_2C_6H_4$	m-H_2N[d]	(93)	201–202	I	10.03	9.89	15.26	15.17	...	...[e]
XIIa	FSO_2	CH_3	m-$C_{15}H_{31}CONH$[f]	80	130	J	7.06	6.95	10.75	10.50	...	...[e]
XIIb	H	m-$FSO_2C_6H_4$	p-$C_{15}H_{31}CONH$[f]	90	186	B	6.39	6.41	9.74	9.72	...	...[e]
XIIc	H	m-$FSO_2C_6H_4$	m-$C_{15}H_{31}CONH$[f]	85	182	B	6.39	6.45	9.74	9.84	...	...[e]

[a] Figures in parentheses refer to yields of products, isolated directly from the reaction mixture as indicated in the Experimental part, and which were sufficiently pure for subsequent transformations without further recrystallization. Their melting points were within 1° or a maximum of 2° from that of the analytical sample, obtained by recrystallization from the indicated solvents. [b] Solvents: A, chlorobenzene–dioxane (1:2); B, Methyl Cellosolve; C, benzene; D, acetic acid; E, ethanol, F, methanol–Methyl Cellosolve; G, dichloroethane; H, dioxane–dichloroethane; I, acetonitrile; J, ethanol–water (9:1). [c] Crude product was only washed with acetone or ether. [d] Samples (0.1 mole) of the corresponding nitro derivatives Xa–c were hydrogenated in 65 ml. of pure dioxane over 2 ml. of Raney nickel at 80° and 1500 p.s.i. After removal of the catalyst, the product was isolated by adding about 30 ml. of water to the boiling solution and cooling to room temperature. [e] Purity of these compounds was also confirmed by titration with $KOCH_3$ in n-butylamine with azoviolet as indicator. During the titration 2 equiv. of $KOCH_3$ were consumed by the N-n-butylsulfonamido group and by hydrogen fluoride, which resulted from the reaction between n-butylamine and the fluorosulfonyl group. The consumption of a third equivalent of titrant is proof for the presence of the acidic methylene group. Acidic properties would have been lost by partial hydrogenation of the adjacent ketonic carbonyl group. [f] Samples (0.1 mole) of the amino derivatives XIa–c were treated with 0.1 mole of palmitoyl chloride in 200 ml. of benzene in the presence of 0.11 mole of pyridine. The reaction mixture was stirred at 45° for 1 hr. and at 65° for 2 hr. The product which crystallized out upon cooling to room temperature was washed with diluted acetic acid then with water and recrystallized.

The sulfonyl chloride was precipitated on ice and extracted with chloroform. The chloroform solution was washed with water and dried over magnesium sulfate. After distilling the chloroform, the yield of crude sulfonyl chloride melting at about 210° was 11.2 g. Recrystallization from acetonitrile yielded 5.7 g. (18%) of a product (m.p. 214°) with still unsatisfactory analytical figures, but which was found sufficiently pure for the subsequent conversion to the corresponding sulfonyl fluoride IIb.

Anal. Calcd. for $C_{11}H_9ClN_2O_3S_2$: Cl, 11.21; N, 8.84; S, 20.22. Found: Cl, 13.67; N, 8.43; S, 18.49.

Conversion of Sulfonyl Chlorides to Sulfonyl Fluorides. A. 2-Acetylamino-4-methyl-5-fluorosulfonylthiazole (IIa).—To a stirred suspension of 127.3 g. (0.5 mole) of 2-acetylamino-4-methyl-5-chlorosulfonylthiazole (Ia)[2] in 300 ml. of dioxane was added a solution of 49.5 g. (0.75 mole) of potassium fluoride in 45 ml. of water. The reaction mixture was heated at 45° for 3 hr. and poured out into 3 l. of ice–water. The white to tan precipitate was isolated by suction filtration, washed with water, and dried. Recrystallization from acetic acid–water (1:10) gave 95 g. (80%) of white crystals with m.p. 190–191°.

Anal. Calcd. for $C_6H_7FN_2O_3S_2$: F, 7.98; N, 11.76; S, 26.89. Found: F, 8.15; N, 11.50; S, 26.69.

B. 2-Acetylamino-4-phenyl-5-fluorosulfonylthiazole (IIb) was prepared by the same procedure used in A. The product obtained from 15.8 g. (0.05 mole) of the corresponding sulfonyl chloride Ib was recrystallized from acetonitrile to give 11.5 g. (76.5%) of white crystals with m.p. 260°.

Anal. Calcd. for $C_{11}H_9FN_2O_3S_2$: F, 6.33; N, 9.33; S, 21.33. Found: F, 6.00; N, 9.24; S, 20.93.

C. m-Fluorosulfonylbenzoic Acid (Va).—The product with m.p. 155°, which was isolated from the reaction mixture, proved to be pure, without further recrystallization; yield 80%.

Anal. Calcd. for $C_7H_5FO_4S$: C, 41.20; H, 2.45; F, 9.32; S, 15.68. Found: C, 41.16; H, 2.37; F, 9.72; S, 15.50.

D. p-Fluorosulfonylbenzoic Acid (Vb).—The crude product as isolated from the reaction mixture was pure without further recrystallization: yield 92%, m.p. 266°.

Anal. Calcd. for $C_7H_5FO_4S$: F, 9.31; S, 15.68. Found: F, 9.66; S, 15.50.

m-Fluorosulfonylbenzoyl Chloride (VIa).—Reaction of 204 g. (1 mole) of m-fluorosulfonylbenzoic acid (Va) with excess (4.5 moles) thionyl chloride gave 213 g. (96%) of m-fluorosulfonylbenzoyl chloride, b.p. 116–117° (2 mm.).

Anal. Calcd. for $C_7H_4ClFO_3S$: Cl, 15.94. Found: Cl, 15.79 (by alkaline hydrolysis followed by argentometric titration).

p-Fluorosulfonylbenzoyl Chloride (VIb).—The yield of acid chloride, obtained from 102 g. (0.5 mole) of p-fluorosulfonylbenzoic acid (Vb) was 105.5 g. (95%). After distillation (b.p. 96–97° at 0.7 mm.), the product solidified slowly to a crystalline mass with m.p. 46–47°.

Anal. Calcd. for $C_7H_4ClFO_3S$: C, 37.74; H, 1.80; Cl, 15.94. Found: C, 37.94; H, 1.84; Cl, 15.97.

m-Fluorosulfonylacetophenone (VIIa).—m-Fluorosulfonylbenzoyl chloride (VIa) was converted to the corresponding acetophenone, essentially according to the procedure developed by Long and Troutman[6] for the synthesis of p-nitroacetophenone. The crude product, which was obtained after hydrolysis of diethyl m-fluorosulfonylbenzoylmalonate, was washed with a saturated sodium bicarbonate solution to remove about 5% of m-fluorosulfonylbenzoic acid formed during hydrolysis. From 523.5 g. (2.38 moles) of m-fluorosulfonylbenzoyl chloride was obtained after recrystallization from about 350 ml. of methanol 367.5 g. (76%) of a white crystalline product with m.p. 92.°

Anal. Calcd. for $C_8H_7FO_3S$: C, 47.52; H, 3.47; S, 15.84. Found: C, 47.60; H, 3.47; S, 15.80.

p-Fluorosulfonylacetophenone (VIIb).—From 667.5 g. (3 moles) of p-fluorosulfonylbenzoyl chloride (VIb) was obtained 431 g. (71%) of p-fluorosulfonylacetophenone, m.p. 75°. The recrystallization solvent was methanol–water (2:1) or isopropyl ether.

Anal. Calcd. for $C_8H_7FO_3S$: C, 47.52; H, 3.46; F, 9.40; S, 15.84. Found: C, 48.08; H, 3.46; F, 9.17; S, 15.94.

m-Fluorosulfonylphenacyl Bromide (VIIIa).—A solution of 363.6 g. (1.8 moles) of m-fluorosulfonylacetophenone (VIIa) in

450 ml. of dioxane was brominated at 40–50° with 288 g. (1.8 moles) of bromine. The oily bromo ketone which separated upon diluting the reaction mixture with water was collected and the aqueous phase was extracted with methylene chloride. The oil and the methylene chloride solution were combined, washed with aqueous sodium bicarbonate solution, and dried over magnesium sulfate. After removal of the solvent, the bromo ketone distilled at 170° (2 mm.). The oily product slowly solidified to a crystalline mass with m.p. 48–50°. The yield was 397 g. (78.5%).

Anal. Calcd. for $C_8H_6BrFO_3S$: C, 34.17; H, 2.13; Br, 28.46; S, 11.38. Found: C, 33.57; H 2.22; Br, 28.50; S, 11.30.

p-**Fluorosulfonylphenacyl Bromide (VIIIb).**—This compound was prepared following the procedure used for the *meta* isomer, except that more dioxane was used to dissolve the ketone (250 ml. for 101 g. = 0.5 mole of the ketone). The crude phenacyl bromide was precipitated with water, collected, washed with water, and dried *in vacuo* over $CaCl_2$. Recrystallization from carbon tetrachloride gave 112 g. (80%) of VIIIb with m.p. 120°.

Anal. Calcd. for $C_8H_6BrFO_3S$: C, 34.17; H, 2.13; Br, 28.46; F, 6.76; S, 11.38. Found: C, 34.37; H, 2.25; Br, 29.09; F, 6.47; S, 11.37.

Preparation of 2-Aminothiazoles. A. 2-Amino-4-methyl-5-fluorosulfonylthiazole (IIIa).—A mixture of 238 g. (1 mole) of 2-acetylamino-4-methyl-5-fluorosulfonylthiazole (IIa), 600 ml. of ethanol, and 300 ml. of 10 *N* hydrochloric acid (3 moles) was refluxed during 3 hr. The cooled reaction mixture was diluted with water and neutralized with about 340 g. of solid sodium bicarbonate. The aminothiazole derivative was collected by suction filtration, washed with water, and dried. The yield of the crude material, m.p. 153–154°, was 167 g. (85%). Recrystallization from 1600 ml. of 25% alcohol gave 157 g. (80%) of tan crystals with m.p. 154°.

Anal. Calcd. for $C_4H_5FN_2O_2S_2$: C, 24.49; H, 2.55; F, 9.69; N, 14.28; S, 32.65. Found: C, 24.40; H, 2.47; F, 10.10; N, 14.42; S, 32.30.

B. 2-Amino-4-phenyl-5-fluorosulfonylthiazole (IIIb).—Applying the same experimental procedure as for the preceding methyl derivative we obtained upon recrystallization from acetonitrile 5.2 g. (67%) of white leaflets with m.p. 248°.

Anal. Calcd. for $C_9H_7FN_2O_2S_2$: F, 7.36; N, 10.85; S, 24.80. Found: F, 7.16; N, 10.83; S, 24.57.

C. 4-*m*-Fluorosulfonylphenyl-2-aminothiazole (IXa).—To a suspension of 137 g. (1.8 moles) of thiourea in 400 ml. of boiling ethanol was added a solution of 506 g. (1.8 moles) of *m*-fluorosulfonylphenacyl bromide (VIIIa) in 450 ml. of dioxane at such a rate that the heat developed by the reaction was sufficient to keep the reaction mixture boiling (40–60 min.). The hydrobromide of IXa, obtained by cooling the reaction mixture to room temperature, was dissolved at 80–90° in about 1.2 l. of water (containing about 15% of Methyl Cellosolve) and neutralized with sodium bicarbonate. The white to yellow precipitate was collected, washed with water, and dried at 90° to give 280–300 g. (60–65%) of a product with m.p. 154–156°. According to potentiometric titration with perchloric acid in acetic acid, the product was shown to be about 98% pure. Evaporating the dioxane mother liquor gave a further amount of 50–70 g. (5–10%) of a slightly more colored product with m.p. 154° and with a purity of about 95–96%. The total yield was 70–75%. A sample recrystallized from methanol had m.p. 156°.

Anal. Calcd. for $C_9H_7FN_2O_2S_2$: C, 41.88; H, 2.71; N, 10.85; S, 24.80. Found: C, 41.65; H, 2.80; N, 10.40; S, 24.63.

D. 4-*p*-Fluorosulfonylphenyl-2-aminothiazole (IXb) was obtained similarly from *p*-fluorosulfonylphenacyl bromide (VIIIb). The crude aminothiazole derivative (yield 75%, m.p. 245°) was recrystallized consecutively from Methyl Cellosolve and from acetonitrile to give a 65% yield of a product with m.p. 250–252°.

Anal. Calcd. for $C_9H_7FN_2O_2S_2$: C, 41.88; H, 2.71; F, 7.35; N, 10.85; S, 24.80. Found: C, 41.98; H, 2.61; F, 7.50; N, 10.72; S, 25.00.

β-Ketonic Esters. A. Methyl *o*-Hexadecylthiobenzoylacetate.—A solution of 154 g. (1 mole) of thiosalicylic acid,[12] 80 g. (2 moles) of sodium hydroxide, and 306 g. (1 mole) of hexadecyl bromide in 1100 ml. of Methyl Cellosolve was refluxed during 1 hr. The solution was acidified with 350 ml. of acetic acid and poured out into ice–water. The precipitate was recrystallized from 2-propanol. The yield of white crystalline material with m.p. 98° was 341 g. (90%).

Anal. Calcd. for $C_{23}H_{38}O_2S$: COOH, 2.64 mequiv./g. Found (by titration with $KOCH_3$ in dimethylformamide): COOH, 2.66 mequiv./g.

One mole (378 g.) of the above prepared *o*-hexadecylthiobenzoic acid was treated with thionyl chloride. The resulting crude acid chloride, obtained after removing the excess thionyl chloride *in vacuo*, was dissolved in 150 ml. of anhydrous benzene. This solution was added in the course of 30 min. to a stirred suspension of 304 g. (2 moles) of ethyl sodium acetylacetate in 500 ml. of anhydrous benzene. The resulting red-brown solution was stirred during 5 hr.; acetic acid (350 ml.) was added, followed by 500 ml. of hot water. The benzene layer, which separated, was washed with water until acid free and dried over anhydrous magnesium sulfate. After evaporation of the benzene *in vacuo*, the residual oil was treated with a solution of sodium methylate, prepared from 40 g. of sodium and 700 ml. of anhydrous methanol.

The tan-white precipitate of the sodium derivative of methyl *o*-hexadecylthiobenzoylacetate (transesterification occurred under the influence of sodium methylate) which was formed in the course of 48 hr. was collected and dissolved in 300 ml. of acetic acid at 75°.

Methanol (1000 ml.) was added and after cooling to room temperature the resulting precipitate was filtered, washed with water, and recrystallized from methanol. The methyl *o*-hexadecylthiobenzoylacetate weighed 265 g. (61%) and melted at 45–46°.

Anal. Calcd. for $C_{26}H_{42}O_3S$: C, 71.89; H, 9.67; S, 7.37; acidic methylene group, 2.30 mequiv./g. Found: C, 71.57; H, 9.56; S, 7.44; acidic methylene group (by titration with $KOCH_3$ in dimethylformamide), 2.23 mequiv./g. (97% of the theoretical value).

B.—The other β-ketonic esters were prepared by published procedures: ethyl *m*-nitrobenzoylacetate,[13] ethyl *p*-nitrobenzoylacetate,[13] ethyl *p*-methoxybenzoylacetate,[14] and methyl *p*-hexadecyloxybenzoylacetate.[15]

2-(Acylacetyl)aminothiazoles (Table I).—The condensation of 2-aminothiazoles with β-ketonic esters was carried out according to the general procedure, previously used for aminobenzenesulfonyl fluorides.[1]

The nitrobenzoylacetamido derivatives Xa–c which were only very slightly soluble in hot xylene started to crystallize out during the reaction and could be isolated by suction filtration after cooling the reaction mixture to room temperature.

In the other cases the reaction solvent was removed for the greater part *in vacuo*, and the residue was recrystallized from the appropriate solvent. The data on yields, recrystallizing solvents, physical properties, and analyses are listed in Table I.

Experimental details on the catalytic hydrogenation of the nitro compounds Xa–c and the subsequent condensation of the resulting amino derivatives XIa–c with palmitoyl chloride are given as footnotes to Table I.

Alkaline Hydrolysis of Fluorosulfonyl-Substituted 2-(Acylacetyl)aminothiazoles.—The following description of the hydrolysis of XIIc will serve to illustrate the general hydrolysis procedure.

To a stirred suspension of 65.7 g. (0.1 mole) of N-2-[α-(*m*-palmitoylaminobenzoyl)acetyl]amino-4-(*m*-fluorosulfonylphenyl)thiazole in 400 ml. of boiling acetone were added 60 ml. of 5 *N* aqueous sodium hydroxide solution (0.3 mole) over a period of 20 min.

After further refluxing for about 0.5 hr., 12.5 ml. of acetic acid was added cautiously, which caused the sodium sulfonate corresponding to XIIc to precipitate. The reaction mixture was then refluxed for 5 min. with vigorous stirring. After cooling to room temperature, the white precipitate was collected by suction filtration. The precipitate was stirred with 400 ml. of water at 20° (to remove sodium acetate and fluoride which coprecipitated with the sulfonate) and filtered again. This operation was repeated twice and the precipitate was then dried at 80° during 5 hr. The yield of white product was 64 g. (94%).

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(13) C. Bülow and E. Hailer, *Chem. Ber.*, **35**, 931 (1902).

(14) V. Wallingfordt, A. Homeyer, and D. Jones, *J. Am. Chem. Soc.*, **63**, 2253 (1941).

(15) A. De Cat and R. Van Poucke (Gevaert Photo-Producten N.V.), British Patent 808,276 (1955); *Chem. Abstr.*, **53**, 21308 (1959).

The product can be recrystallized from 2-propanol–water (2:1) with very little loss, but is already very pure as shown by the following analysis.

Anal. Calcd. for $C_{34}H_{44}N_3NaS_2$: acidic methylene group, 1.48 mequiv./g. Found (by titration with $KOCH_3$ in dimethylformamide): acidic methylene group, 1.48 mequiv./g.

This procedure was used for the compounds containing a long aliphatic chain. Recrystallization from a suitable solvent (acetic acid or Methyl Cellosolve) produced the sulfonates with a purity of 98.5–100% in yields between 85 and 93%. The lower molecular weight sulfonates are highly soluble in water. Therefore, after acidifying the reaction mixture with acetic acid, they had to be salted out by the addition of sodium acetate or chloride.

Acknowledgment.—We wish to thank Professor Dr. A. Van Dormael, Director of the Chemical Research Department, for his kind interest in this work. We are indebted to Dr. Moelants, Head of the Analytical Department, for the analyses.

Reactions of Thiols with Sulfoxides. III. Catalysis by Acids and Bases

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Received September 8, 1964

The oxidation of 1-dodecanethiol by tetramethylene sulfoxide was studied in the presence of four amines at 100 ± 0.1°. The disappearance of thiol adhered to good pseudo-first-order kinetics in the presence of excess sulfoxide and a catalytic amount of the amine. In the presence of N,N-dimethylaniline and 2,6-lutidine (thiol–amine = 10) the rate of oxidation of 1-dodecanethiol was increased by a factor of only 2 to 3. In the presence of 1-dodecylamine and tri(*n*-butyl)amine a rate increase of 84 to 269 was observed. The catalytic nature of the amine was also established. A plot of the log of the observed rate constant for oxidation *vs.* the concentration of amine at various thiol–amine ratios resulted in a linear relationship. It is proposed that the amine, thiol, and sulfoxide form a more favorable transition state for the production of an unstable thiol–sulfoxide adduct during the rate-determining step in these reactions. The effect of pyrrole, phosphoric acid, and acetic acid on these reactions was also determined. A mild catalysis, rather than inhibition, was observed in the presence of these acids. This is apparently due to a more favorable transition state for protonation of the sulfoxide. The general acid–base catalysis of these reactions was confirmed by kinetic studies in the presence of 2-hydroxypyridine. The implications of these results with respect to the mechanism of thiol–sulfoxide reactions are discussed.

Previous publications from these laboratories[1-3] have described in detail the oxidation of thiols to disulfides by tetramethylene sulfoxide (TMSO) and dimethyl sulfoxide (DMSO). Variation of the reaction temperature indicated that the order of thiol reactivity was aryl > aralkyl ≫ alkyl. Subsequent kinetic studies[3] established that the rate of thiol–sulfoxide reactions was markedly dependent on the acidity of the thiol. For example, benzenethiol was oxidized about 10^5 times faster than 1-dodecanethiol in the presence of TMSO at 100°. Further, the reactions were first order in thiol and sulfoxide indicating that the reactions were over-all second order in nature. Thus, it was concluded that the rate-determining step in these reactions was initial reaction of the thiol with a sulfoxide molecule to form an unstable thiol–sulfoxide adduct that is rapidly destroyed by reaction with another molecule of thiol.

$$RSH + R_2SO \xrightarrow{\text{slow}} [R_2\ddot{S}(OH)SR] \quad (1)$$

$$[R_2\ddot{S}(OH)SR] + RSH \xrightarrow{\text{fast}} RSSR + R_2S + H_2O \quad (2)$$

The present paper is an extension of our previous studies in this area. Kinetic studies in the presence of acidic and basic catalysts have been carried out in an effort to uncover suitable methods of accelerating aliphatic thiol–sulfoxide reactions and to gain more definitive knowledge on the nature of the transition state in these reactions. Specifically, the effect of acidic and basic nitrogen compounds on the oxidation of 1-dodecanethiol by TMSO, the effect of acetic acid on the oxidation of α-toluenethiol by TMSO, and the effect of phosphoric acid on the oxidation of 1-dodecanethiol by TMSO have been determined. An attempt to establish that these reactions are subject to general acid and base catalysis has also been made.

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Results

Kinetic studies on the oxidation of 1-dodecanethiol by TMSO have been carried out in the presence of four basic amines and the acidic amine, pyrrole. All reactions were conducted under nitrogen in sealed vials. Rate measurements were obtained by sampling the reaction mixture with a syringe and subsequently analyzing the aliquot by gas chromatography according to the procedure outlined in the Experimental section. Quantitative data were obtained by measuring the area of the thiol peak using an internal hydrocarbon standard as a reference. Initially, the oxidation of 1-dodecanethiol by TMSO at 100 ± 0.1° was investigated in the presence of N,N-dimethylaniline, 2,6-lutidine, 1-dodecylamine, and tri(*n*-butyl)amine. A 4 *M* excess of sulfoxide to thiol was employed and the molar ratio of thiol to amine catalyst was 10. In all cases, good pseudo-first-order kinetics for thiol disappearance was observed. This point is demonstrated in Figure 1 which contains two first-order rate plots for the disappearance of 1-dodecanethiol at two different molar ratios of the thiol to 1-dodecylamine. The observed first-order rate constants in the presence of each amine are summarized in Table I. Each rate constant has been calculated relative to the rate observed for the uncatalyzed reaction of 1-dodecanethiol with TMSO. As indicated, N,N-dimethylaniline and 2,6-lutidine increased the rate by a factor of only 2 to 3. The two