

blades were obtained from 50% ethanol, m.p. 118.5–119.5°.

Anal. Calcd. for $C_{19}H_{24}N_2OS$: C, 69.47; H, 7.36. Found: C, 69.69; H, 7.22.

3-Chloro-10-(3-diethylaminopropyl)-phenothiazine (XIII).—A deep red solution of 3.28 g. (0.01 mole) of 10-(3-diethylaminopropyl)-phenothiazine-5-oxide in 75 ml. of concentrated hydrochloric acid was refluxed for 3 hours, diluted with 50 ml. of water and made basic with 20% potassium hydroxide to destroy the red color of the small amount of unreacted phenazothionium salt leaving a pale green oil. The mixture was extracted with ether and worked up to give a pale yellow oil which was converted to the oxalate in ether solution. The minute granules (from acetone) weighed 3.8 g. (87%), m.p. 163–164°. The oxalate loses carbon dioxide in a vacuum and cannot be dried above 30°.

Anal. Calcd. for $C_{19}H_{23}ClN_2S \cdot C_2H_2O_4$: C, 57.72; H, 5.77. Found: C, 57.30; H, 6.18.

10-(3-Diethylaminopropyl)-phenothiazine-N,5-dioxide (XIV).—A pale yellow solution of 9.36 g. (0.03 mole) of freshly distilled 10-(3-diethylaminopropyl)-phenothiazine, 75 ml. of ethanol and 6.9 g. (0.06 mole) of 30% hydrogen peroxide was refluxed for 17 hours and the solvent removed at the aspirator. The residual pale yellow oil solidified to a colorless mass on cooling. Recrystallization from ace-

tone gave 8.85 g. (80%) of fine colorless granules of the sesquihydrate, m.p. 141–141.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S \cdot 1\frac{1}{2}H_2O$: C, 61.45; H, 7.33; N, 7.54. Found: C, 61.75; H, 7.26; N, 7.30.

The picrate crystallized from ethanol as fine yellow needles, m.p. 182–183°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S \cdot C_6H_3N_3O_7$: C, 52.35; H, 4.75. Found: C, 52.35; H, 4.92.

The pink, granular hydrochloride, m.p. 174–176°, crystallized from absolute ethanol.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S \cdot HCl$: C, 59.90; H, 6.62. Found: C, 59.48; H, 6.59.

Reductive Chlorination of 10-(3-Diethylaminopropyl)-phenothiazine-N-5-dioxide.—A mixture of 1.64 g. (4.42 millimoles) of the N,5-dioxide and 50 ml. of concentrated hydrochloric acid was refluxed for 47 hours and cooled. The precipitated green solid was extracted with 150 ml. of ethanol, the extract concentrated to 75 ml. and diluted with water. The product was recrystallized from 50% ethanol (Norit) to give 0.55 g. (46%) of light green flakes, m.p. 200–202°.

Anal. Calcd. for $C_{12}H_7Cl_2NS$: C, 53.74; H, 2.63. Found: C, 53.95; H, 2.85.

CHARLOTTESVILLE, VIRGINIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

p-Nitrophenyl *p*-Acylphenyl Sulfides and Related Compounds

BY H. HARRY SZMANT AND GEORGE LEVITT¹

RECEIVED APRIL 16, 1954

The preparation of *p*-(4-nitrophenylmercapto)-benzoic acid and the utilization of this compound in the synthesis of a number of unsymmetrically substituted phenyl sulfides and sulfones is described.

The main purpose of the work described in this paper was the development of a synthetic procedure for the preparation of disubstituted phenyl sulfides containing the nitro and acyl groups in the respective *para* positions. The convenient preparation of such compounds from a simple monosubstituted phenyl sulfide seems unlikely for the following reasons.

The acylation of *p*-nitrophenyl phenyl sulfide fails under ordinary Friedel-Crafts conditions which are successful with phenyl sulfide.² This may be so because of the ability of the sulfur atom to transmit the electron-withdrawing effect of the nitro substituent into the other phenyl group—a phenomenon for which there already exists spectroscopic evidence³—and thus the unsubstituted phenyl group becomes resistant to electrophilic substitution reactions. Experimental conditions designed to force the Friedel-Crafts reaction of *p*-nitrophenyl phenyl sulfide are being currently investigated.

The nitration of a mono-*p*-acylated phenyl sulfide also fails to give the desired *p'*-nitration product since the nitration reaction is accompanied by the oxidation of the sulfide function⁴ as well as by the oxidative degradation of the acyl group. Thus, for example, from the nitration reaction of *p*-phenylmercaptostearophenone⁵ there was isolated phenyl sulfoxide 4-carboxylic acid.

(1) From the M. S. Thesis of G. L., Duquesne University, June, 1952.

(2) H. H. Szmant and F. P. Palopoli, *THIS JOURNAL*, **72**, 1757 (1950).

(3) H. H. Szmant and J. J. McIntosh, *ibid.*, **73**, 4356 (1951).

(4) B. Ciocca and L. Canonica, *Gazz. chim. ital.*, **76**, 113 (1946).

(5) H. H. Szmant and Mien Chao, unpublished work.

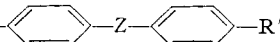
In view of the above-mentioned difficulties in the synthesis of *p*-(4-nitrophenylmercapto)-phenyl alkyl ketones from a monosubstituted phenyl sulfide, it was decided to prepare the desired compounds *via* *p*-(4-nitrophenylmercapto)-benzoic acid (I), and two reactions were considered for the preparation of this intermediate.

The first consisted of the reaction of *p*-mercapto-benzoic acid with *p*-chloronitrobenzene under alkaline conditions. While such a reaction was found⁶ to take place when a reactive halide such as benzyl chloride is employed, it was possible in our case to isolate only unreacted *p*-chloronitrobenzene and phenyl disulfide *p,p'*-dicarboxylic acid. Apparently the nucleophilic displacement reaction on *p*-chloronitrobenzene is overshadowed by the extremely easy atmospheric oxidation of the *p*-mercaptobenzoate ion. It is noteworthy in this connection that Mann and Turnbull⁷ prepared several sulfides by a synthesis similar to the one proposed here except that they first converted the mercaptobenzoic acids to the corresponding esters. The success in the reaction of *p*-chloronitrobenzene with the mercaptobenzoate ester may be explained on the ground that the more electronegative carbomethoxy group would tend to decrease the undesired oxidation as compared to that in the doubly negative charged mercaptobenzoate ion.

These considerations led to the investigation of the alternative synthetic process in which *p*-nitro-

(6) W. S. Emerson and R. A. Heimsch, *THIS JOURNAL*, **73**, 1297 (1951).

(7) F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 747 (1951).

TABLE I
 SUBSTITUTED PHENYL SULFIDES AND SULFONES R——R'

R	R'	S	M.p., °C. ^a	Formula	Analyses, %		Hydrogen ^b	
					Carbon ^b Calcd.	Found	Calcd.	Found
NO ₂	CO ₂ H	S	236–238 ^c	C ₁₃ H ₉ O ₄ NS	56.79	56.67	3.30	3.31
NO ₂	CO·Cl	S	126–128 ⁱ	C ₁₃ H ₈ O ₃ NSCl	53.27	53.50	2.75	2.85
NO ₂	CO·OCH ₃	S	94–95 ^k	C ₁₄ H ₁₁ O ₄ NS	58.11	57.83	3.83	4.02
NO ₂	CO·NH ₂	S	186 ^j	C ₁₃ H ₁₀ O ₃ N ₂ S	56.90	56.51	3.67	3.71
NO ₂	CO·NHNH ₂	S	136	C ₁₃ H ₁₁ O ₃ N ₃ S	14.52 ^d	14.77 ^d
NO ₂	CO·CH ₃	S	118–119	C ₁₄ H ₁₁ O ₃ NS	61.52	61.61	3.70	3.76
NO ₂	C(CH ₃)NOH	S	162 ^k	C ₁₄ H ₁₂ O ₃ N ₂ S	58.31	58.23	4.20	4.33
NO ₂	COCH ₃ ·DNPH ^e	S	216 ^l	C ₂₀ H ₁₅ O ₆ N ₃ S	53.02	53.18	3.33	3.22
NO ₂	CO·C ₁₂ H ₂₅	S	wax	C ₂₅ H ₃₃ O ₃ NS	3.21 ^d	2.94 ^d
H ₂ N	CO·OCH ₃	S	129–130	C ₁₄ H ₁₃ O ₃ NS	64.84	65.11	5.05	5.07
H ₂ N	CO·NHNH ₂	S	159.5–160 ^k	C ₁₃ H ₁₃ ON ₂ S	60.21	60.04	5.05	5.38
NO ₂	CO·NH—C ₈ H ₁₇ ^f	S	114–115 ^h	C ₂₁ H ₂₅ O ₃ N ₂ S	65.25	65.20	6.78	6.64
NO ₂	CO ₂ H	SO ₂	300 ^g	C ₁₃ H ₇ O ₆ NS	50.81	50.41	2.95	2.75
NO ₂	CO·Cl	SO ₂	183 ⁱ	C ₁₃ H ₈ O ₃ NSCl	47.97	47.81	2.49	2.20
NO ₂	CO·NH·C ₈ H ₁₇ ^f	SO ₂	160–161 ^h	C ₂₁ H ₂₅ O ₃ N ₂ S	60.27	60.25	6.25	6.26
NO ₂	CO·CH ₃	SO ₂	180–181 ^k	C ₁₄ H ₁₁ O ₃ NS	55.08	54.88	3.62	3.63
H ₂ N	CO·NH·C ₈ H ₁₇ ^f	SO ₂	118–120 ^h	C ₂₁ H ₂₅ O ₃ N ₂ S	64.95	65.16	7.27	6.98
H ₂ N	CO·CH ₃	SO ₂	179–180	C ₁₄ H ₁₃ O ₃ NS	61.09	61.25	4.76	4.94

^a All melting points are uncorrected. ^b Analyses by Mr. George Stragand, University of Pittsburgh. ^c Neutralization equivalent: 269, 273; theory: 275.3. ^d Nitrogen analyses. ^e 2,4-Dinitrophenylhydrazine. ^f The C₈H₁₇ group has the 2,4,4-trimethyl-2-pentyl structure. ^g Neutralization equivalent: 303, 306; theory: 307.3. ^h Prepared by Mr. M. J. Segedi. ⁱ Crystallized from benzene. ^j Crystallized from isopropyl alcohol. ^k Crystallized from methanol. ^l Crystallized from glacial acetic acid.

thiophenolate ion was allowed to react with diazotized *p*-aminobenzoic acid. The conditions for this reaction were studied rather extensively because of the surprising insolubility of sodium *p*-nitrothiophenolate in water and in order to minimize the undesired oxidation of the thiophenolate by atmospheric oxygen or excessive nitrous acid.

The new acid I was converted to the corresponding acid chloride, its methyl ester, hydrazide, amide and *t*-octylamide, and the acid chloride was also subjected to the reaction with dialkyl cadmium reagents⁸ completing the synthesis of diaryl sulfides containing the nitro and acyl groups in the respective *p*,*p*'-positions. By reduction of the nitro group there were also prepared several analogous amino sulfides, and by oxidation of the sulfide function it was possible to synthesize a number of the related sulfones containing either the original nitro or the amino group. All of the compounds prepared in this study are listed in Table I.

In connection with the preparation of the *t*-octylbenzamides, there was made one noteworthy observation. While the *p*-(4-nitrophenylmercapto)- and the *p*-(4-nitrophenylsulfonyl)-benzamides showed no appreciable tendency to hydrolyze and thus could be handled without any special precautions, it was found that the *p*-(4-aminophenylsulfonyl)-benzamide was extremely sensitive to hydrolysis. It was possible to prepare the latter compound only by means of catalytic hydrogenation in an anhydrous medium and the product slowly hydrolyzed during crystallizations from wet solvents. This phenomenon is being further investigated in view of the theories concerning the variable electronic nature of the sulfone groups proposed in connection with other studies.⁹

(8) J. Cason, *Chem. Rev.*, **40**, 15 (1947).

(9) H. H. Szmant, *et al.*, *THIS JOURNAL*, **73**, 4175 (1951); **74**, 4395 (1952).

Chemotherapeutic tests of several of the compounds prepared in this study were carried out at the Sterling-Winthrop Research Institute and the results will be described elsewhere.

Experimental

Attempted Friedel-Crafts Reaction of *p*-Nitrophenyl Phenyl Sulfide. A.—Stearoyl chloride, 100 g., was dissolved in 50 cc. of nitrobenzene, and to this solution there was added 47 g. of aluminum chloride and 100 cc. of additional nitrobenzene. A solution of 41 g. of *p*-nitrophenyl phenyl sulfide¹⁰ in 50 cc. of nitrobenzene was then added and the reaction mixture was stirred at room temperature for nine hours, allowed to stand overnight, and heated to 70° for three additional hours. Upon hydrolysis the tarry mixture was steam distilled and attempts to obtain the desired product from the residue failed.

B.—Acetyl chloride, 16 g., was added to a mixture of 26 g. of aluminum chloride and 200 cc. of carbon disulfide. The mixture was stirred for one hour and then *p*-nitrophenyl phenyl sulfide, 46 g., dissolved in carbon disulfide was added. The reaction mixture was stirred for four days and refluxed for 30 hours. On working up the mixture there was isolated 30 g. of the original sulfide and there was no evidence of the presence of the acetylated product.¹¹

***p*-(4-Nitrophenylmercapto)-benzoic Acid.**—The preparation of this acid was studied rather extensively since it was needed in large quantities. In particular, the conditions were examined under which the relatively insoluble sodium salts of *p*-nitrothiophenol^{12,13} and of the desired acid would not necessitate very large volumes of solvents. The best results were obtained when the cold solution obtained by diazotization of 0.2 mole of *p*-aminobenzoic acid with an equimolar amount of sodium nitrite and 0.5 mole of hydrochloric acid was added to a mixture of 0.2 mole of *p*-nitrothiophenol, 1.1 moles of sodium hydroxide in 1 l. of water. The reaction mixture was stirred for several hours and then filtered. The precipitate obtained in this way was the impure sodium salt of the desired acid. In order to purify the acid, the precipitate from above was dissolved in hot water and filtered by gravity. The dissolved salt crystallized as orange leaflets which were removed by suction filtra-

(10) H. H. Hodgson and R. Smith, *J. Chem. Soc.*, 1634 (1937).

(11) Experiment by Mr. D. A. Irwin of this Laboratory.

(12) C. C. Price and G. W. Stacy, *THIS JOURNAL*, **68**, 498 (1946).

(13) F. E. Johnson and C. S. Hamilton, *ibid.*, **71**, 74 (1949).

tion. The product was then placed in a beaker and water was added to form a thin paste which was acidified using hydrochloric acid. The yellow sulfide acid was quite pure and was removed by filtration. The solid was washed on the funnel with cold dilute hydrochloric acid and then with cold water. The yield of the pure sulfide was 65–70%.

p-(4-Nitrophenylsulfonyl)-benzoic Acid.—*p*-(4-Nitrophenylmercapto)-benzoic acid, 5.5 g., was dissolved in 50 cc. of warm glacial acetic acid and an excess of 30% hydrogen peroxide was added to the cooled solution. After standing for 30 minutes the mixture was warmed to 70° and then allowed to stand overnight. The white solid was filtered, washed with water and crystallized from a mixture of acetic acid and water. The desired acid was obtained in a 98% yield (6 g.).

This acid was also obtained by the chromic acid oxidation of *p*-(4-nitrophenylsulfonyl)-toluene in acetic acid solvent. The oxidation of the tolyl compound to the acid has been previously reported¹⁴ using potassium permanganate. Chromic acid, 1 g., was added in small portions to a boiling glacial acetic acid solution of *p*-(4-nitrophenylsulfonyl)-toluene.¹⁵ The mixture was refluxed for one hour and then hydrolyzed by pouring into ice-water to dilute the acetic acid. The sulfone acid was purified as previously described and melted at 300°, in agreement with the report of Roblin.¹⁶

p-(4-Nitrophenylmercapto)-benzoic Acid Hydrazone.—The sulfide acid chloride was added to an excess of 85% hydrazine hydrate solution and the reaction mixture was filtered and washed with water. The desired hydrazone was purified by crystallization from a mixture of methanol and water. A much less soluble by-product, probably a secondary hydrazone, melting at 210° was also obtained.

Methyl *p*-(4-Aminophenylmercapto)-benzoate.—The corresponding nitro compound, 14.5 g., was heated in 400 cc. of 50% acetic acid with 15 g. of iron. After 3 hours the mixture was filtered and the filtrate was diluted. The resulting precipitate was recrystallized from aqueous methanol to give 9 g. of pure product.

N-*t*-Octyl *p*-(4-Nitrophenylmercapto)-benzamide.—The corresponding acid chloride, 18.5 g., was dissolved in 75 cc. of dry benzene and treated with 15.4 g. of 2,4,4-trimethylpentylamine.¹⁷ The reaction mixture was poured on ice containing dilute hydrochloric acid and the product was filtered and crystallized from alcohol to give 20.5 g. of pure material.

N-*t*-Octyl *p*-(4-Nitrophenylsulfonyl)-benzamide.—The corresponding sulfide was oxidized with hydrogen peroxide in glacial acetic acid and the product was crystallized from ethanol.

N-*t*-Octyl *p*-(4-Aminophenylsulfonyl)-benzamide.—The corresponding nitro compound on two attempted reductions with iron in acetic acid gave a mixture of products melting over a wide range (95–155°) and crystallizations did not yield the desired product. Catalytic hydrogenation in 95% ethanol using Raney nickel also gave a mixture of products the m.p. of which increased on successive crystallizations from ethanol. The product was finally obtained when 13.3 g. of the corresponding nitro compound in anhydrous dioxane was hydrogenated at 61 lb. in the presence of Raney nickel. Filtration of the catalyst from the warm hydrogenation mixture and cooling gave 11 g. of pure product. The filtration on standing gave additional precipitate which melted above 235° and was soluble in cold dilute alkali.

(14) R. O. Roblin, Jr., and J. W. Clapp, British Patent 568,157; C.A., **41**, 3817 (1947).

(15) H. Gilman and H. S. Broadbent, THIS JOURNAL, **69**, 2053 (1947).

(16) R. O. Roblin, Jr., private communication.

(17) "*t*-Octylamine" generously supplied by Rohm and Haas Co.

On acidifying the alkaline solution there was obtained *p*-(4-aminophenyl sulfonyl)-benzoic acid.¹⁶

p-(4-Nitrophenylmercapto)-acetophenone.—Methylcadmium was prepared by the addition of 45.5 g. of cadmium chloride to methyl iodide and 9.7 g. of magnesium shavings. The mixture was warmed and allowed to reflux until a negative Gilman test was obtained. Most of the ether was then removed by distillation, benzene was added and the mixture was distilled until the boiling point reached and remained at 78° for five to ten minutes. *p*-(4-Nitrophenylmercapto)-benzoyl chloride, 29.3 g., dissolved in benzene was added dropwise. On completion of the addition of the acid chloride, the mixture was warmed and allowed to reflux slowly for three hours. The reaction mixture was then hydrolyzed by pouring on a slurry of ice and 10% sulfuric acid, and after allowing the mixture to stand for several hours the benzene and water layers were separated. The benzene layer was washed with another 500-cc. portion of 10% sulfuric acid followed by several washings with water, and with two 850-cc. portions of 5% sodium hydroxide and two 1000-cc. portions of water. The benzene layer was concentrated and methanol was added to precipitate the desired but impure compound. The remaining red tarry mass was redissolved in a small portion of benzene and poured on a column of alumina. The column was eluted with isopropyl alcohol and on evaporation of the solvent more impure product was obtained. This, on repeated chromatographing, gave a pure product. The yield of the desired product was 35% based on acid chloride used.

p-(4-Nitrophenylmercapto)-phenyl dodecyl ketone was prepared using a procedure essentially identical to that used for the preparation of the acetophenone compound. In this case, however, lauryl bromide was used in place of methyl iodide. On hydrolysis of the reaction mixture a waxy substance was obtained by evaporation of the benzene layer. It was steam distilled to remove any hydrocarbon by-product and crystallization from either isopropyl alcohol or acetic acid yielded needle-like crystals which, however, on filtration proved to be waxy in nature. A sample was prepared for analysis by keeping the waxy solid at 100° in an Abderhalden pistol at 1 mm.

p-(4-Aminophenylsulfonyl)-acetophenone.—The corresponding nitro compound, 10.5 g., was heated with 10 g. of iron powder in 300 cc. of 50% acetic acid. After two hours the mixture was filtered and the filtrate was diluted with 800 cc. of water to give the crude product which was crystallized from methanol.

The Nitration of *p*-Phenylmercaptostearophenone.—The sulfide ketone,⁶ 11.5 g., was dissolved in 100 cc. of cold concd. sulfuric acid and the resulting solution was treated at 7–9° with 2.4 cc. of 90% nitric acid. The reaction mixture was poured on ice and 15 g. of the crude product was isolated by filtration. On crystallization of the product from benzene there was obtained a fraction, m.p. 201–202°, which proved to be *p*-phenylthionylbenzoic acid by analysis and by oxidation to the known *p*-phenylsulfonylbenzoic acid.

Anal. Calcd. for C₁₃H₁₀O₃S: C, 63.40; H, 4.10; neut. equiv., 246.2. Found: C, 63.61; H, 4.24; neut. equiv., 249, 250.

The crystallization of the crude nitration product from ethyl acetate did not result in a constant melting product which corresponded to the expected nitro sulfide or nitro sulfone.

Acknowledgment.—We acknowledge the financial aid of the Sterling-Winthrop Research Institute which made this work possible.

PITTSBURGH, PENNSYLVANIA