excess orthoformate was removed, by heating under reduced pressure, and the residue was washed with cold ethanol. A sample was recrystallized from ethanol and obtained as plates, m.p. 275°. The yield was 3.9 g. (90%).

Anal. Calcd. for $C_{10}H_6N_4O_2$: C, 56.07; H, 2.82; N, 26.16. Found: C, 56.23; H, 2.64; N, 25.86.

2-(2-Indolyl)-1,3,4-oxadiazole (VI).—A mixture of 3.5 g. (0.02 mole) of 2-indolecarboxylic acid hydrazide[9] and 100 ml. of triethyl orthoformate was heated under reflux overnight. The excess orthoformate was removed, by heating under reduced pressure, and a solid remained. After washing with ethanol the product (1.8 g., 50% yield) was collected on a filter and air-dried. It melted over the range 196–200°. An analytical sample was obtained by sublimation at 180° (0.1 mm.), m.p. 207–208°.

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 65.03; H, 3.84; N, 22.74.

A one-gram sample dissolved in a solution formed from 10 ml. of ethanol and 10 ml. of 3 *N* hydrochloric acid was evaporated on the steam-bath. The residue was dissolved in about 75 ml. of water and 1 *N* sodium hydroxide was added to *p*H 10. The mixture was extracted with ethyl acetate. After removal of the ethyl acetate, by evaporation, the residue was recrystallized from ethanol and obtained as plates, m.p. 250°. The melting point was unchanged when mixed with authentic 2-indolecarboxylic acid hydrazide. In addition, the hydrolysis product and 2-indolecarboxylic acid hydrazide showed identical absorption in the infrared.

1-Ethoxymethylene-2-picolinylhydrazine (IIa).—A mixture of 27.4 g. (0.2 mole) of picolinic acid hydrazide and 100 ml. of triethyl orthoformate was heated under reflux overnight. After removal of the excess orthoformate, the product was distilled under reduced pressure, b.p. 140° (0.1 mm.). The yield was 35 g. (90%). A sample was recrystallized from ethyl acetate and obtained as cubes, m.p. 87–88°.

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.83; H, 5.76; N, 22.04.

(9) A. Piccinini and L. Salmoni, *Gazz. chim. ital.*, **32**, [I], 252 (1902); [*Chem. Zentr.*, [1] **73**, 1229 (1902)].

2-(2-Pyridyl)-1,3,4-oxadiazole.—A two-gram sample of 1-ethoxymethylene-2-picolinylhydrazine was heated for three hours at 210°. The solid which formed on cooling was recrystallized from ethanol and obtained as needles, m.p. 115°.

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.22; H, 3.60; N, 28.31.

3-Pyrazolecarboxylic Acid Hydrazide and Ethyl Orthoformate.—A mixture of 6.3 g. (0.05 mole) of 3-pyrazolecarboxylic acid hydrazide[10] and 100 ml. of triethyl orthoformate was heated under reflux for three days. After removal of the solvent, by heating under reduced pressure, the residue was extracted with 50 ml. of cold ethanol. The insoluble material (2.5 g.) was essentially pure pyrazolo-[1,5-*d*]-*as*-triazin-4(5*H*)-one (V), m.p. 265°. It was soluble in 1 *N* sodium hydroxide and was reprecipitated by acid. A sample was recrystallized from water and obtained as needles, m.p. 265°.

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.49; H, 2.91; N, 40.96.

The ethanol extract was concentrated to dryness. Addition of ether caused 1 g. of 1-ethoxymethylene-2-(pyrazole-3-carbonyl)-hydrazine (IIb) to separate. It was collected and recrystallized from ethanol–ether and then from methanol, m.p. 177°.

Anal. Calcd. for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.52; N, 30.76. Found: C, 45.72; H, 5.33; N, 31.07.

2-Phenyl-1,3,4-thiadiazole.—A solution of 1.5 g. (0.01 mole) of thiobenzoic acid hydrazide[4] and 20 ml. of triethyl orthoformate was heated under reflux for two days. After removal of the solvent, by heating on the steam-bath under reduced pressure, the residue was extracted with ether. The ether was evaporated and 1 g. of oil remained. This was identified as 2-phenyl-1,3,4-thiadiazole by comparison of the infrared spectrum with that of an authentic sample.[5]

(10) L. Knorr, *Ber.*, **37**, 3520 (1904).

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

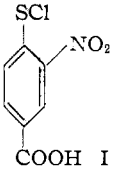
Derivatives of Sulfenic Acids. XIX. Synthesis and Characterization of 2-Nitro-4-carboxybenzenesulfenyl Chloride

BY ANTON J. HAVLIK[1] AND NORMAN KHARASCH

RECEIVED AUGUST 17, 1954

2-Nitro-4-carboxybenzenesulfenyl chloride, the first example of a compound of this type which contains both the carboxyl and sulfenyl chloride functions, has been synthesized and fully characterized. The possible utility of this compound for stereochemical studies is indicated and its stereospecific additions to the *cis*- and *trans*-2-butenes are reported.

The object of this work was to prepare and characterize 2-nitro-4-carboxybenzenesulfenyl chloride (I). In view of the known reactivities of aromatic



I

sulfenyl chlorides,[2] it was of interest to determine whether the carboxyl and sulfenyl chloride groups could coexist in a single molecule; but the main reason for seeking such a substance was in connection with eventual stereochemical studies, in which the carboxyl group could serve as a "handle" for resolution of racemic products formed *via* the sulfenyl chloride.[3]

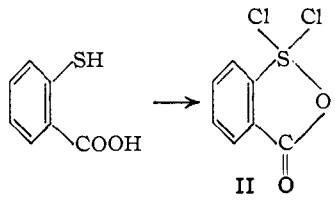
While the *in situ* synthesis of 2-carboxybenzenesulfenyl chloride, by chlorination of 2-mercaptobenzoic acid, had been claimed in the patent literature, Price and Smiles[4] were unable to substantiate this report, and succeeded only in the preparation (in solution) of a dichloro compound, which they designated as II. They also obtained the same product by treatment of bis-(2-carboxyphenyl) disulfide with chlorine. The dichloro compound was not iso-

(1) Atomic Energy Commission Predoctoral Fellow, University of Southern California, 1951–1953. This paper was abstracted from a portion of the doctoral dissertation of A.J.H., University of Southern California, June, 1954.

(2) N. Kharasch, S. J. Potempa and H. L. Wehrmeister, *Chem. Revs.*, **39**, 269 (1946).

(3) The synthesis of possible amino-substituted aromatic sulfenyl chlorides—in which the amino group could serve for purposes of resolving optical isomers—also was considered. We suspect, however, that sulfenyl chlorides containing amino groups in them would generally be too reactive to exist as such.

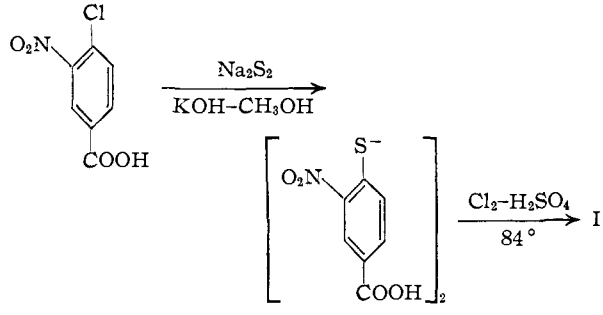
(4) W. B. Price and S. Smiles, *J. Chem. Soc.*, 2858 (1928); *cf.* also German Patent 35,230.



lated, and the evidence for its existence rested only on formation of certain solid derivatives, obtained by treating solutions of II with various reagents. Later, Hart and co-workers[5] reinvestigated these reactions and suggested a somewhat different mode of formation and structure for II; but these workers also could not isolate either 2-carboxybenzenesulfenyl chloride or II.

From the above considerations, it is evident that the synthesis of a molecule containing both the sulfenyl chloride and carboxyl functions can meet with difficulty if the interaction between these two reactive groups is not prevented. The synthesis of I was, however, considered feasible because: (a) the *para* arrangement of the –COOH and –SCl functions should prevent intramolecular interaction, (b) the presence of an *ortho* nitro group should favor a more stable product[6] and (c) the analogous 2,4-dinitrobenzenesulfenyl chloride is known, from other studies in this Laboratory, to remain unchanged on prolonged contact with dry acetic acid.

In the present study, the synthesis of I was achieved by chlorinolysis of bis-(2-nitro-4-carboxyphenyl) disulfide (III). Attempts to prepare III



by the method given in a patent[7] failed, and a more suitable procedure was developed. The use of sufficient potassium hydroxide to convert III to its dipotassium salt and of purified dioxane to extract III from the reaction mixture was found to be critical for the successful preparation. The 3-nitro-4-chlorobenzoic acid was obtained by the method of Tucker and co-workers.[8]

The chlorinolysis of III to I required the catalytic action of fuming sulfuric acid, in a manner similar to the use of this catalyst in the chlorinolysis of bis-(2,4-dinitrophenyl) disulfide.[9] The reaction was carried out in dry ethylene chloride, at 84°. The time at which the catalyst was added to the reaction mixture was found to be important for the facile cleavage of III. Under optimum conditions, the chlorinolysis was completed in a few minutes. The sulfenyl chloride was isolated readily and could be stored for extended periods. It was characterized by (1) elementary analysis, (2) formation and characterization of the 1:1 adduct with cyclohexene, (3) analysis for the sulfenyl chloride group, *via* the reaction $2ArSCl + 2I^- \rightarrow ArSSAr + I_2 + 2Cl^-$, and (4) the infrared spectrum. All of these were in accord with the structure assigned to I.

Like a number of other sulfenyl halides,[10] it was found that I adds stereospecifically to the *cis*- and *trans* 2-butenes. The β-chloro sulfides, which resulted in good yields, are undoubtedly the diastereomeric 1:1 adducts. These were shown to be different by their melting point behavior, their solubilities in methanol and their infrared spectra. In view of the well known high reactivities of the β-chlorine atoms in β-chloro sulfides, such as the mustard gases, it is of interest that the chlorine atoms in the present compounds did not interfere with the titrations with alkali.

Experimental[11,12]

Bis-(2-nitro-4-carboxyphenyl) Disulfide (III).—A mixture of sodium sulfide pentahydrate (16.8 g., 0.1 mole), sulfur (3.2 g., 0.1 mole) and 600 ml. of methanol was stirred at room temperature until solution resulted (*ca.* 1.5 hr.). Meanwhile, into a 5-liter flask, in the following order, were added: 40.2 g. (0.2 mole) of 3-nitro-4-chlorobenzoic acid[8] in 750 ml. of methanol, and 13.3 g. (0.24 mole) of potassium hydroxide completely dissolved in 250 ml. of methanol. The resulting solution was heated to reflux, and the methanol solution of sodium disulfide added during 20 min. through the top of the condenser. The jet black reaction mixture was refluxed about 6 hr., cooled to *ca.* 0°, diluted with 200 ml. of concd. hydrochloric acid and cooled again. The precipitated product was collected, dried (wt. 25 g.), extracted into 500 ml. of boiling, purified dioxane,[13] and the insoluble salts removed by filtration. The filtrate was cooled and the pale tan disulfide precipitated by adding 1500 ml. of Skellysolve F. The product, which melted at 298–300° dec. weighed 18.5 g. (47%). Recrystallization from dioxane–benzene raised the m.p. to 305–308° dec.

Anal. Calcd. for $C_{14}H_8N_2O_8S_2$: C, 42.42; H, 2.04. Found: C, 42.20; H, 1.79.

4-Carboxy-2-nitrobenzenesulfenyl Chloride.—In a 3-necked flask, fitted with a Vigreux column having an attached condenser, were placed 22.0 g. of III and 1400 ml. of dry ethylene chloride. To ensure fully anhydrous conditions, *ca.* 150 ml. of the solvent was distilled. The flask was then connected to a chlorine tank (through a sulfuric acid drying tower) and fitted with a mechanical stirrer and a reflux condenser protected with a calcium chloride drying tube. The reaction mixture was saturated with chlorine at room temperature, then heated. When the first drops of reflux appeared, *ca.* 1.5 ml. of Baker and Adamson 30% fuming sulfuric acid was added, the rate of stirring was increased, and the rate of chlorine introduction maintained quite vigorously (hood). Within 20 min., a clear solution resulted, and only a small amount of tar—from the charring

(5) L. E. Hart, E. W. McClelland and F. S. Fowkes, *J. Chem. Soc.*, 2114 (1938).

(6) On the basis of our own qualitative observations, as well as those in the literature (*cf.*, for example, *Chem. Revs.*, **39**, 269 (1946); and R. A. Turner and R. Connor, THIS JOURNAL, **69**, 1009 (1947)) the several *o*-nitro-substituted sulfenyl halides which are known are isolated more easily and are presumably less subject to thermal and hydrolytic decompositions than are those which do not have this substituent (or than the *para* nitro compounds, *e.g.*, *p*-nitrobenzenesulfenyl chloride).

(7) French Patent 765,840 (1933).

(8) H. G. Dunlop, T. F. Macrae and S. H. Tucker, *J. Chem. Soc.*, 1672 (1934).

(9) N. Kharasch, G. I. Gleason and C. M. Buess, THIS JOURNAL, **72**, 1796 (1950).

(10) N. Kharasch and A. J. Havlik, *ibid.*, **75**, 3734 (1953).

(11) We are indebted to W. J. Schenck of this Laboratory and M. Robinson of the Riker Laboratories, respectively, for assistance with the microanalyses and infrared spectra.

(12) Melting points were taken on a Fisher–Johns block.

(13) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 368–369.

action of the sulfuric acid—was evident. The boiling mixture was filtered immediately, and the filtrate cooled by aspirating the solvent with the water pump. The sulfenyl chloride I precipitated as a yellow, crystalline solid; wt. 17.0 g. (65%).

In other runs, in which the wt. of III was below 15 g., the chlorinolysis was complete in 4 to 6 min. The yields of I could be raised to *ca.* 75% by charging the reaction mixture with the mother liquor from a previous chlorinolysis in which the same weight of III was employed.

The analytical sample was prepared by two recrystallizations from ethylene chloride. It melted with decomposition (darkening at temperatures above 140°) at 183–185°.

Anal. Calcd. for $C_7H_4ClNO_4S$: C, 35.98; H, 1.73; Cl, 15.18; N, 5.97. Found: C, 36.02; H, 1.89; Cl, 15.37; N, 6.17.

The infrared spectrum revealed the presence of a carbonyl function by the characteristic absorption at 5.9 μ.[14]

Treatment of I (0.9527 g.) with potassium iodide liberated iodine, equivalent to 4.20 meq. of thiosulfate solution. This corresponds to an equivalent weight of 228.0 (theoretical, 233.5). The procedure used for the titration has been described previously.[15]

2-Chlorocyclohexyl 2'-Nitro-4'-carboxyphenyl Sulfide.—To 3.0 g. (0.013 mole) of I, dissolved in 100 ml. of dry ethylene chloride was added 10 ml. of redistilled cyclohexene ($n^{22}D$ 1.4445). The mixture was heated on the steam-bath for 10 min. and let stand. After 12 hr., the starch–iodide test was negative, and the yellow product was collected; wt., 4.0 g. (98%). The product melted at 205–212° dec. It was also noted that in the range of 145–155°, the crystals appeared to explode mildly, but no melt could be observed. Recrystallization from ethyl acetate gave a pale-yellow material which now melted at 217–219° dec.; and the same behavior again was noted at 145–155°.

Anal. Calcd. for $C_{13}H_{14}ClNO_4S$: C, 49.45; H, 4.47; Cl, 11.23. Found: C, 49.76; H, 4.66; Cl, 11.09.

Additions of I to *cis*- and *trans*-2-Butenes.—The diastereomeric racemates were obtained by the procedure previously described.[10] The addition to the *trans*-2-butene was carried out in 200 ml. of ethyl acetate, using 6.0 g. of I, and an initial butene pressure of 1.2 atm. The pressure was maintained at this level during the addition by manual adjustment of the mercury level. The reaction was complete (negative starch–iodide test) after 3 hr. The solvent was aspirated, while heating on the steam-bath, the residue taken up in chloroform, and product precipitated by adding Skellysolve F. The product weighed 5.6 g. (75%), m.p. 175–177°. Recrystallization from a mixture of benzene and chloroform gave a sample melting at 171–173°.

Anal. Calcd. for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.18; Cl, 12.24. Found: C, 45.61; H, 4.46; Cl, 12.33.

After keeping a few days, samples of the above materials increased in m.p. to 181–184°, but still gave a correct elemental analysis for the 1:1 adduct. Such a behavior has been noted previously in certain other sulfenyl halide-2-butene adducts.[10]

The addition of I to *cis*-2-butene was carried out in chloroform as solvent; 6.3 g. of I gave 6.5 g. (83%) of adduct; m.p. 166–168° after recrystallization from benzene.

Anal. Calcd. for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.18; Cl, 12.24. Found: C, 45.82; H, 4.03; Cl, 12.17.

The adducts to the *cis*- and *trans*-2-butenes differ not only in melting behavior, but also in the solubilities in methanol and infrared spectra (*cf.* footnote 14 and ref. 10).

Neutralization Equivalents of the Adducts of I to Alkenes.—The adducts were dissolved in acetone–water mixtures and titrated with standard sodium hydroxide, using 0.5% phenol red indicator. The end-point was taken as the first change of color from yellow to red which lasted 30 sec. or longer. The values were 286 and 292, respectively, for the adduct to the *cis*- and *trans*-2-butenes (calcd. 290); and 316 for the adduct to cyclohexene (calcd. 315). Under similar conditions, titration of the adduct[16] of 2,4-dinitrobenzenesulfenyl chloride to cyclohexene required only the same small amount of standard base as found for the blank in the case of the adduct of I to cyclohexene, showing that only the carboxyl group was involved in the titration of the latter.

(14) The full spectrum of this product and of the 2-butene adducts (see below) will be included in a later paper which will summarize the data on a considerable number of sulfenyl halides and related substances.

(15) N. Kharasch and M. M. Wald, *Anal. Chem.*, in press.

(16) N. Kharasch, H. L. Wehrmeister and H. Tigerman, THIS JOURNAL, **69**, 1612 (1947).

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Experimental Chemotherapy of Tuberculosis. III. Ethyl Mercaptan and Related Compounds in Tuberculosis

BY S. KUSHNER, H. DALALIAN, F. L. BACH, JR., D. CENTOLA,[1] J. L. SANJURJO AND J. H. WILLIAMS

RECEIVED SEPTEMBER 17, 1954

A series of mercaptans and esters have been compared for antituberculous activity. A study of the tuberculostatic action of these compounds, many of which are ethylthiol esters, indicates that activity resides in ethyl mercaptan itself. These active compounds are more effective than pyrazinamide in animal assays.

Utilizing the mouse test as an assay method for antituberculous agents, we showed in 1948,[2] the role of nicotinamide and its derivatives in the chemotherapy of tuberculosis. As a sequence to the study of pyridine derivatives, many pyrazine analogs were synthesized which led ultimately to the discovery of pyrazinamide[3a] (Aldinamide[3b]), an effective, clinical, chemotherapeutic agent. Pyrazinamide in combination with isoniazid now appears probably destined to be a protocol[4] of choice. While investigating various methods of preparing pyrazinaldehyde for the purpose of synthesizing a tibione-like analog, we prepared ethyl thiolpyrazinoate as an intermediate. Routine screening showed this compound[5] to be highly active both subcutaneously and orally in the mouse and guinea pig. This was a new and undeveloped lead in tuberculosis chemotherapy.

A series of thiolpyrazinoates was prepared, as indicated in Table I, for comparative studies. The

(1) At present in the Armed Forces.

(2) S. Kushner, H. Dalalian, R. T. Cassell, J. L. Sanjurjo, D. McKenzie and Y. SubbaRow, *J. Org. Chem.*, **13**, 834 (1948).

(3) (a) 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). (b) Trade mark American Cyanamid Co.

(4) W. S. Schwartz and R. E. Moyer, *Am. Rev. Tuberc.*, **70**, No. 3, 413 (1954).

(5) H. P. Dalalian and S. Kushner, U. S. Patent 2,646,431, July 21, 1953.