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

The Decomposition of Tetraphenylthiodiacetic Acid and Certain Related Compounds in Pyridine Solution at Room Temperature

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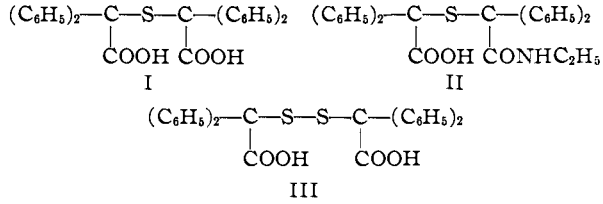
A novel decomposition of tetraphenylthiodiacetic acid to form diphenylacetic acid, thiobenzophenone and carbon dioxide is described. The reaction occurs in pyridine or quinoline solution at room temperature and in certain other solvents at higher temperatures. The limits of the reaction have been established and a mechanism is proposed. The following previously unreported sulfides were prepared: dimethyl tetraphenylthiodiacetate, butylmercaptodiphenylacetic acid, benzylmercaptodiphenylacetic acid and benzhydrylmercaptodiphenylacetic acid.

Discussion

Tetraphenylthiodiacetic acid (I) and N-ethyltetraphenylthiodiacetamic acid (II) have been reported as white solids which turn blue when heated.[2] Tetraphenyldithiodiacetic acid (III) is a

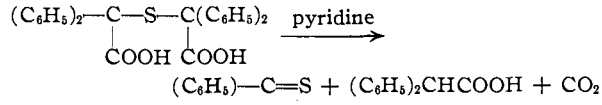


similar compound which decomposes at its melting point to give a blue liquid.[3] This acid has been observed to form a blue solution in pyridine but its dimethyl ester gave a colorless solution.[4] This phenomenon was not further investigated or explained. A blue color also developed in freshly prepared pyridine solutions of I and II and the cause of this color development has been investigated.

The acids were prepared by methods described in the references cited. When the compounds were highly purified by several recrystallizations, I and III melted with decomposition to a red oil but II decomposed to give a blue melt. A potentiometric titration of I demonstrated the presence of two carboxyl groups, one being neutralized at *p*H 8.65 and the other at *p*H 4.50. Anhydrous pyridine solutions of these acids became blue upon standing. The solutions were investigated spectrophotometrically and in every case Beer's law was obeyed and the spectrum resembled that of thiobenzophenone in other solvents.[5] The spectra indicated that the quantity of colored material produced by a mole of acid was also the same in every case. A cursory rate study of the formation of a blue color in pyridine solutions of I at 30° demonstrated that the reaction was complex as the kinetics followed no simple order.

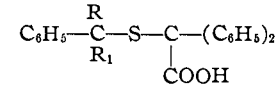
The blue color also developed in other solvents such as quinoline at room temperature and camphor at its melting point. II gave a colorless solution in benzene which became deep blue upon standing 24 hours at 70°. Cryoscopic molecular weight determinations of I, II and III in camphor indicated that in each case the acid might have lost a molecule of carbon dioxide and the resulting sulfide then split into two particles.

Isolation of the products of decomposition of I indicated that the reaction proceeds according to the equation



In order to determine what types of molcules would undergo this reaction, a number of compounds with structures related to I were prepared, dissolved in pyridine, and the development of color noted. The structures and data are shown in Table I.

Triphenylthiodiacetic acid was the only additional compound other than I, II and III found to decompose and form thiobenzophenone. This acid decomposed so slowly that 80% of the starting material was recovered from a pyridine solution which had been kept at room temperature for 5 days. The development of the blue color, however, was shown spectrophotometrically to increase daily, indicating that the decomposition reaction was in progress. The reaction is apparently limited to compounds of the general formula



A diphenylcarboxymethyl group must be attached to the sulfur atom; the sulfide group may be replaced by a disulfide, R must be a phenyl group or a hydrogen atom; and R_1 must be a carboxyl group or a derivative of a carboxyl group. If both R and R_1 were phenyl groups the reaction might possibly proceed but several attempts to prepare triphenylmethylmercaptodiphenylacetic acid (IV) failed.

Any mechanism which would account for the decomposition of I and related compounds to give thiobenzophenone must involve the rupture of the sulfur–carbon bond and the loss of carbon dioxide from the carboxyl group. If the carbon dioxide was lost from I prior to the rupture of the sulfur–carbon bond, the first product formed would be benzhydrylmercaptodiphenylacetic acid. Since this latter compound does not form thiobenzophenone in pyridine solution it is probable that dissociation at the sulfur–carbon bond precedes

(1) Abstracted from a portion of a dissertation submitted by Frank M. Brower to the Graduate School of the University of Kentucky in partial fulfillment of the requirements of the Ph.D. degree, 1954.

(2) P. Panzera, Ph.D. Dissertation, University of Kentucky, 1953.

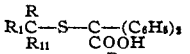
(3) H. Becker and A. Bistrzycki, *Ber.*, **47**, 3154 (1914).

(4) Y. Iskander and R. Tewfik, *J. Chem. Soc.*, 2050 (1951).

(5) A. Burawoy, *Ber.*, **63**, 3156 (1930); G. N. Lewis and N. Kasha, THIS JOURNAL, **67**, 998 (1945).

TABLE I

EFFECTS OF STRUCTURE UPON FORMATION OF THIOBENZOPHENONE IN PYRIDINE SOLUTION

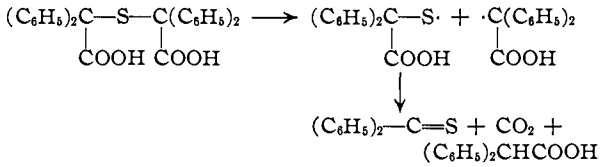


R	R_1	R_{11}	Color	X	Y	Color
C_6H_5	C_6H_5	—COOH	Blue	H	$(C_6H_5)_2C(COOH)$	Colorless
C_6H_5	H	—COOH	Blue	C_6H_5—	$(C_6H_5)_2C(COOH)$	Colorless
H	H	—COOH	Colorless	C_6H_5NHCO	$(C_6H_5)_2C(COOH)$	Colorless
C_6H_5	C_6H_5	$—CONC_2H_5$	Blue	$(C_6H_5)_2C(COOH)S$	$(C_6H_5)_2C(COOH)$	Blue
C_6H_5	C_6H_5	H	Colorless	$(C_6H_5)C(COOCH_3)$	$(C_6H_5)_2C(COOCH_3)$	Colorless
C_6H_5	H	H	Colorless	$(C_6H_5)_2C(O—N(C_2H_5))$	$OC(C_6H_5)_2$	Colorless
C_3H_7	H	H	Colorless			

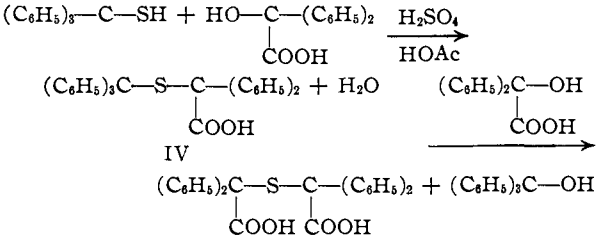
decarboxylation when I decomposes to form thiobenzophenone.

The authors believe that a free radical dissociation of the sulfur–carbon bond is more probable than an ionic one. Evidence substantiating this is as follows. (a) The reaction occurs in solvents which do not normally promote ionization, *i.e.*, pyridine[6] and benzene. (b) The reaction occurs only when the decomposing molecules have a group with a structure approaching that of triphenylmethyl attached to either side of the sulfur atom. (c) Certain sulfides with structures similar to I but which cannot give thiobenzophenone appear to form stable free radicals in hot ethyl benzoate. Phenylmercaptodiphenylacetic acid, like the closely related phenyltriphenylmethyl sulfide,[7] was found to form a colorless ethyl benzoate solution at room temperature which became yellow upon heating above 200°. The color of these solutions faded when cooled and intensified again when heated. This process was repeated several times with the same solution, indicating the possible existence of an equilibrium between stable colored free radicals and undissociated molecules. The dimethyl ester of I behaves similarly in ethyl benzoate solution.

The proposed reaction mechanism, then, involves initially a dissociation into radicals such that the sulfur atom is a part of the radical containing a carboxyl group. This radical then decomposes into thiobenzophenone, carbon dioxide, and a hydrogen atom which unites with the remaining undecomposed radical. It is possible that the decomposition of the sulfur-containing radical is initiated by the abstraction of the hydrogen of the carboxyl group by the radical which does not decompose.



The general reaction by which most of the sulfides described in this work were prepared involves the condensation of benzilic acid with a mercaptan in the presence of sulfuric acid. This reaction does not always proceed satisfactorily when other alcohols are substituted for benzilic acid. Mandelic acid, α-hydroxyisobutyric acid and lactic acid are reported as failing to react with thiophenol.[8] In the present work it was found that benzhydrol reacts readily with mercaptodiphenylacetic acid but triphenylcarbinol failed to react. Benzilic acid, on the other hand, reacts readily with most mercaptans but in one case the desired product was not obtained. When triphenylmethylmercaptan and benzilic acid were used, I and triphenylcarbinol were obtained, indicating the possible existence of the desired IV as an intermediate.



Although this reaction occurs in anhydrous media the result is consistent with the known ease of hydrolysis of triphenylmethyl sulfides under acidic conditions.[9]

Experimental

Dimethyl Tetraphenylthiodiacetate.—To a solution of 6.5 g. (0.140 mole) of tetraphenylthiodiacetic acid in 125 ml. of 5% sodium hydroxide there was added portionwise, with vigorous shaking, 30 ml. of methyl sulfate and sufficient solid potassium hydroxide to keep the solution basic. The rate of addition of these materials was such that the temperature did not rise above 50°. The pale blue precipitate which separated from the basic solution was removed by filtration, triturated with water, allowed to dry, and recrystallized 3 times from Skellysolve B. The yield of white solid melting at 149–150.5° was 2.9 g. (42.9%). *Anal.* Calcd. for $C_{30}H_{26}O_4S$: S, 6.64. Found: S, 6.72.

Preparation of Alkyl- and Arylmercaptodiphenylacetic Acids.—These sulfides were prepared by a general procedure similar to that of Bistrzycki and Risi.[6] To a mixture of the mercaptan (0.01 mole) and the alcohol (0.01 mole) in 8 ml. of glacial acetic acid, 4 ml. of concentrated sulfuric acid was added dropwise, with stirring, at a temperature of 40–60°. The reaction mixture became dark red during this process and a precipitate (occasionally an oil) formed. After stand-

(6) E. J. Corey, THIS JOURNAL, **75**, 1172 (1953).
(7) H. Lecher, *Ber.*, **48**, 535 (1915).
(8) A. Bistrzycki and J. Risi, *Helv. Chim. Acta*, **8**, 584 (1925).
(9) Y. Iskander, *J. Chem. Soc.*, 1549 (1948).

ing at room temperature for one hour, approximately 30 g. of crushed ice was added; the precipitate was filtered off and crystallized from toluene or 50% acetic acid.

Phenylmercaptodiphenylacetic acid: prepared from thiophenol and benzilic acid, 99.3% yield, m.p. 127–129° (lit. 126–128°). *Anal.* Calcd. for $C_{20}H_{16}O_2S$: neut equiv., 320.4. Found: neut. equiv., 324.3.

***n*-Butylmercaptodiphenylacetic acid**: prepared from *n*-butylmercaptan and benzilic acid; crystallized from 50% acetic acid, 48.8% yield, m.p. 106–107.5°. *Anal.* Calcd. for $C_{18}H_{20}O_2S$: S, 10.67; neut. equiv., 300.4. Found: S, 10.71; neut. equiv., 300.0.

Benzylmercaptodiphenylacetic acid: prepared from benzylmercaptan and benzilic acid, 90.8% yield; crystallized from toluene, m.p. 180.5–182°. *Anal.* Calcd. for $C_{21}H_{18}O_2S$: S, 9.59; neut. equiv., 334.4. Found: S, 9.47; neut. equiv., 338.8.

The Decomposition of Tetraphenylthiodiacetic Acid in Anhydrous Pyridine at Room Temperature.—A solution of 0.5194 g. (0.0011 mole) of tetraphenylthiodiacetic acid in 50 ml. of anhydrous pyridine was allowed to stand for 6 hours at room temperature with occasional shaking. A deep blue color slowly developed during the first 1–2 hours. The pyridine was distilled off at approximately 30° (1 mm.), and the oily, blue, solid residue was dissolved in benzene. The benzene solution was extracted with 5% sodium bicarbonate. The aqueous extract, when acidified with dilute hydrochloric acid, yielded 0.2203 g. of a white solid which melted at 144.5–146°. This material, which was thought to be diphenylacetic acid, melted, after one recrystallization from water, at 146.5–147.5° (lit. 148°). The anilide of the acid was prepared in the usual manner, m.p. 181–182° (lit. 180°). The yield of diphenylacetic acid was 90.8%.

The blue benzene solution was evaporated to dryness at room temperature in a stream of air. The residue was converted to the 2,4-nitrophenylhydrazone of thiobenzophenone in the usual manner. The quantity of pure derivative isolated weighed 0.1690 g. (40.8%) and melted at 237–239° (lit. 239°).

The liberation of carbon dioxide in this reaction was proven by dissolving a second 0.5-g. sample of tetraphenylthiodiglycolic acid in 50 ml. of pyridine in a 3-necked flask which had previously been swept out with nitrogen. After standing several hours a nitrogen stream was swept over the surface of the pyridine solution and into a solution of saturated barium hydroxide. A heavy white precipitate of barium carbonate was rapidly formed.

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Thionocarbanilates with Anthelmintic Activity

BY ROBERT P. MULL

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A variety of thionocarbanilates were prepared and characterized. Butyl *p*-allyloxythionocarbanilate manifests exceptional anthelmintic activity in mice against the oxyurid worms, *Aspiculuris tetraptera* and *Syphacia obvelata*.

The use of thionocarbanilates as local anesthetics has been investigated previously[1,2] as has their fungistatic,[3] insecticidal[4] and other biological properties.[5] On the whole, however, these compounds either have failed to manifest sufficient activity or exhibited certain deleterious effects which have precluded their use as effective chemotherapeutics.

The present work describes the synthesis of several new thionocarbanilates which are relatively non-toxic and evince anthelmintic activity. Most of these thionocarbanilates were prepared by condensation of an appropriately substituted phenyl isothiocyanate and sodium alcoholate (method A) in the manner reported by Bost and Andrews.[1] The attempted preparation of butyl *o*-hydroxythionocarbanilate according to this procedure, however, resulted in the formation of 2-benzoxazolethiol.[6] In this and a few other necessary cases, therefore, the synthesis was accomplished by reaction of butyl or phenyl chlorothionoformate with the respective aromatic amine (method B). Both methods avoided excessive heat and prolonged reflux, thus minimizing the likelihood of side product formation; the yields were good. Almost all of the compounds were low melting crystalline solids that could be purified by recrystallization. High vacuum sublimation or distillation in all cases resulted in the decomposition of the product.

Except for the two hydrochlorides, all the thionocarbanilates listed in Table I were moderately soluble in ethanol and difficultly soluble in water. This latter quality is advantageous since the anthelmintic must reach the habitat of the parasite and therefore resist rapid absorption and destruction in the host's organism. Of the numerous compounds investigated, butyl *p*-allyloxythionocarbanilate was found to possess exceptional activity as an anthelmintic when tested in mice against the oxyurid worms, *Aspiculuris tetraptera* and *Syphacia obvelata*, occurring either singly or simultaneously.[7]

Of the three isomeric ethers, it was found that the butyl *m*-allyloxythionocarbanilate was intermediate in activity between the more active butyl *p*-allyloxy and the moderately active butyl *o*-allyloxythionocarbanilates. Maximum enhancement of the anthelmintic properties of this class of compounds was observed in the case of the butyl esters.

Experimental

Substituted Phenyl Isothiocyanates.—These compounds were prepared from the appropriate aromatic amine by the use of thiophosgene[8] according to the general method of Dy-

(1) R. W. Bost and E. R. Andrews, THIS JOURNAL, **65**, 900 (1943).

(2) T. F. Wood and J. H. Gardner, *ibid.*, **63**, 2741 (1941); Y.-T. Huang, Y.-W. Yieh and I. Chang, *Brit. J. Pharmacol.*, **3**, 297 (1948).

(3) W. H. Davies and W. A. Sexton, *Biochem. J.*, **40**, 331 (1946).

(4) W. H. Davies and W. A. Sexton, *ibid.*, **43**, 461 (1948).

(5) W. G. Templeman and W. A. Sexton, *Proc. Roy. Soc.* (*London*), **B133**, 480 (1946); C. Mentzer and D. Molho, *Compt. rend.*, **230**, 406 (1950); H. Nagai, *J. Pharm. Chem.*, **24**, 35 (1952); M. Araki, Y. Yokota, M. Kuga, S. Chin, F. Fujikawa, K. Nakajima, H. Fujii, A. Tokuoka and Y. Hirota, *J. Pharm. Soc. Japan*, **72**, 979 (1952).

(6) G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

(7) Thanks are due to Dr. G. Rawson and his associates of the Microbiology Division of Ciba for the testing of these compounds, the details of which will be published elsewhere.

(8) Rapter Laboratories, Argo, Illinois.