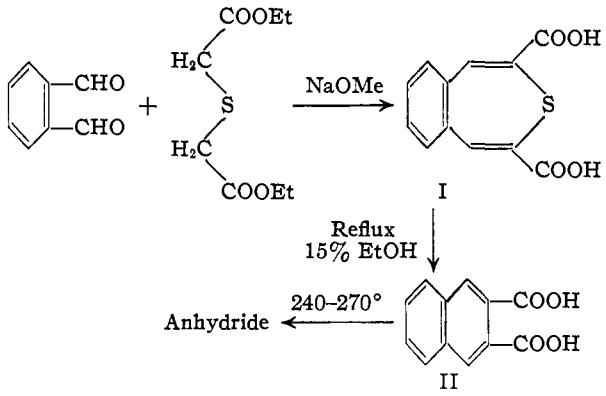

Although the structure of the initial condensation product is not rigorously proven, its method of formation and the result of the decomposition make its identity with structure I exceedingly probable. Its instability with respect to the highly resonant naphthalene derivative is in accord with the observation that a Fisher–Taylor–Hirschfelder model of this structure is somewhat strained and definitely not planar. The ultraviolet absorption spectrum in absolute ethanol showed a peak at 280 mμ; however, the apparent molar absorption coefficient at this wave length decreased continuously indicating decomposition at room temperature. It is planned to study this decomposition further.

Experimental[5]

Condensation of *o*-Phthalaldehyde with Diethyl Thiodiacetate.—A solution of 9.00 g. (0.0437 mole) of the ester and 5.85 g. (0.0437 mole) of the aldehyde in 15 ml. of absolute methanol was run into a solution of sodium methoxide made by dissolving 4.2 g. of metallic sodium in 60 ml. of methanol. The solution was stirred and cooled, and the rate of addition was regulated so that the temperature did not rise above 15°. The mixture was allowed to stand in an ice-bath for an additional two hours and was evaporated at room temperature by suction to a volume of about 40 ml. After dissolving the yellowish precipitate by adding about 90 ml. of cold water, the solution was immediately acidified by dropwise addition of excess cold 18% hydrochloric acid while stirring vigorously in an ice-bath. The orange solid which precipitated amounted to 5.7 g., but it was not completely fusible up to 305° indicating that it contained some unchanged sodium salt.

Recrystallization was accomplished in two equal portions by adding each portion to 200 ml. of boiling 80% ethanol and stirring rapidly for 20 or 30 seconds. Concentrated hydrochloric acid (4 ml.) was then added and the solutions stirred again. Without waiting for the last bits of solid to dissolve, the solutions were poured through fast filter paper (without suction) into flasks cooled in an ice-bath. After allowing the filtrate to stand one-half hour in a refrigerator, the product was collected and dried. It consisted of fine, uniform, orange needles which were soluble in 5% sodium bicarbonate solution. It appeared stable for weeks in a desiccator; however, it was found that further recrystallization tended to produce a less pure product. Upon heating it sintered and turned nearly white at 185–195° and then melted with effervescence at 236.0–237.5°. The total yield was 2.4 g. (22%).

Anal. Calcd. for $C_{12}H_8O_4S$: C, 58.05; H, 3.25; S, 12.92; neut. equiv., 124. Found: C, 58.30; H, 3.46; S, 13.05; neut. equiv., 126.

Decomposition of the Condensation Product.—A sample of the above product (1.001 g.) was refluxed with about 50 ml. of 15% ethanol for two hours. Upon cooling, the solid, which had turned nearly white during the first 20 minutes, was filtered. A small second crop was obtained by evaporating the filtrate to a volume of 5 ml. The combined precipitates were then heated to boiling and agitated with 10 ml. of 10% sodium carbonate solution. After cooling the mixture, a quantity (113 mg.) of nearly white solid was removed by filtration. This evidently contained most of the sulfur; it was soluble in carbon disulfide and burned with a pale blue flame producing sulfur dioxide; however, it appeared to differ from the common crystalline forms of free sulfur (m.p. 115–118).

Acidification of the filtrate yielded 832 mg. of a white, crystalline, sulfur-free acid (m.p. 236.5–237.5° with effervescence). By recrystallization from water–dioxane mixture, the melting point was raised to 237.5–238.5°. Sublimation at atmospheric pressure and 240–270° temperature yielded the anhydride (m.p. 245–246 with some previous sublimation).

Anal. Calcd. for $C_{12}H_6O_3$: C, 72.73; H, 3.05. Found: C, 72.82; H, 3.31.

It produced no depression of the melting point when mixed with 2,3-naphthalenedicarboxylic anhydride prepared from 3-amino-2-naphthoic acid by the method of Waldman and Mathiowetz.[6]

(5) Microanalyses are by Clark Microanalytical Laboratory, Urbana, Illinois. Melting points are corrected.

(6) H. Waldman and H. Mathiowetz, *Ber.*, **64**, 1713 (1931).

DEPARTMENT OF CHEMISTRY
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Alkylation with Long Chain *p*-Toluenesulfonates. VI. Friedel–Crafts Reaction of *n*-Octadecyl *p*-Toluenesulfonate and Benzene[1]

BY DAVID A. SHIRLEY[2] AND JOSEPH R. ZIETZ, JR.

RECEIVED AUGUST 10, 1953

In 1928 Clemo and Walton[3] observed the alkylation of benzene with simple alkyl *p*-toluenesulfonates in the presence of aluminum chloride. A patent was issued to Foldi[4] in 1933 involving this general type reaction.

As a part of a general program of evaluation of the alkylating properties of long chain *p*-toluenesulfonates[5] we examined the reaction of *n*-octadecyl *p*-toluenesulfonate with benzene in the presence of aluminum chloride. An 73% yield of *n*-octadecylbenzene was obtained. The lack of apparent rearrangement in the long chain fragment is in line with an observation of Gilman and Turck[6] in the Friedel–Crafts alkylation of benzene with *n*-octadecyl bromide.

This note concludes our work on alkylation reactions of long chain *p*-toluenesulfonates.

Experimental

Benzene (156 g. or 2.0 moles) was dried by distilling off 39 g. (0.5 mole) and 42.5 g. (0.10 mole) of *n*-octadecyl *p*-toluenesulfonate[7] was added followed by 13.3 g. (0.10 mole) of aluminum chloride. The mixture was stirred at room temperature for 15 hours, for 10 hours at 50–55° and for a final 14 hours at room temperature. The deep orange-colored reaction mixture was poured into excess ice–hydrochloric acid mixture. The organic layer was separated and washed with warm dilute hydrochloric acid, dried over calcium chloride and distilled to remove benzene. The residue

(1) A report of work done under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract was supervised by the Southern Regional Research Laboratory of the Bureau of Agricultural and Industrial Chemistry.

(2) Department of Chemistry, University of Tennessee, Knoxville, Tennessee.

(3) G. R. Clemo and E. Walton, *J. Chem. Soc.*, **133**, 723 (1928).

(4) Z. Foldi, U. S. Patent 1,897,795; *C. A.*, **27**, 2693 (1933).

(5) Preceding paper, D. A. Shirley and J. R. Zietz, Jr., *J. Org. Chem.*, in press.

(6) H. Gilman and J. A. V. Turck, THIS JOURNAL, **61**, 478 (1939).

(7) D. A. Shirley and W. H. Reedy, *ibid.*, **73**, 458 (1951).

was distilled once under a water-pump vacuum and then a second time at 0.25 mm. and the *n*-octadecylbenzene collected at 155–160°. The yield of *n*-octadecylbenzene was 24.2 g. or 73%. The boiling point of this compound has been reported as 249° at 15 mm.[8] and 225–250° at 14 mm.[9]

The product was further identified by conversion to its *p*-sulfonamide derivative, m.p. 100–101°, by chlorosulfonation followed by treatment with ammonia. The melting point is in agreement with values found in the literature.[6,9]

(8) F. Krafft, *Ber.*, **19**, 2982 (1886); V. A. Hetling and V. S. Shchekin, *J. Gen. Chem., U.S.S.R.*, **13**, 717 (1943); *C. A.*, **39**, 693 (1945).

(9) F. Seidel and O. Engelfreid, *Ber.*, **69**, 2567 (1936).

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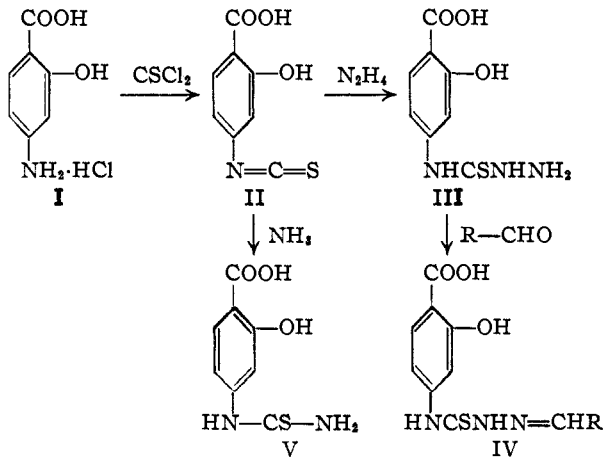
Some Derivatives of *p*-Aminosalicylic Acid[1]

BY R. B. SELIGMAN, R. W. BOST[2] AND R. L. MCKEE

RECEIVED JUNE 11, 1953

Since Lehmann's[3] announcement of the tuberculostatic activity of *p*-aminosalicylic acid (PAS) and Domagk's[4] discovery of the use of the aromatic aldehyde thiosemicarbazones for the same purpose both have enjoyed widespread clinical use. It was our purpose to combine chemically the PAS-fragment with aromatic thiosemicarbazones into one molecule. This necessitated that the N^4-position of the thiosemicarbazone be substituted and such substitution had previously been reported to inactivate biologically the molecule.[5] However, it was hoped that N^4-substitution with the PAS-fragment would enable these compounds to retain their activity or increase it by acting synergistically if *in vivo* cleavage resulted.

The thiosemicarbazones (IV) were produced by the following series of reactions



The aldehydes used for the condensations were benzaldehyde, *p*-nitrobenzaldehyde, nicotinaldehyde, cinnamaldehyde and 5-nitro-2-furaldehyde.

During the course of the investigation these additional derivatives of PAS were also prepared: *p*-thioureidosalicylic acid (V), by treating II with aqueous ammonia; 4-(4-phenyl-2-thiazolyl)-aminosalicylic acid, from V with phenacyl bromide; 2-(4-carboxy-3-hydroxyanilino)-1,3,4-thiadiazole, by treating III with formic acid.

Acknowledgment.—The authors wish to thank Dr. J. D. Thayer of the Venereal Disease Experiment Laboratory, United States Public Health Service, School of Public Health, University of North Carolina for testing these compounds (*in vitro* and *in vivo*) to determine their tuberculostatic activity. His findings will be published at a later date.

Experimental

p-Isothiocyanosalicylic Acid (II).—*p*-Aminosalicylic acid (30.6 g.) was suspended in 350 ml. of water and 67 ml. of concentrated hydrochloric acid added with mechanical stirring. To this suspension another 350-ml. portion of water was added and finally 27 g. of thiophosgene in one portion. After 3 hours of stirring the orange color of the thiophosgene was dissipated indicating completion of the reaction. The solid product was filtered, the filter cake washed many times with water and dried over phosphorus pentoxide. This produced 32 g. (82.4%) of white solid that was recrystallized from benzene and melted from 186–187° (followed by resolidification). The pure product was slightly unstable to light.

Anal. Calcd. for $C_8H_5NO_3S$: N, 7.2; S, 16.4; neut. equiv., 195. Found: N, 7.2; S, 16.3; neut. equiv., 200.

p-Thioureidosalicylic Acid (V).—*p*-Isothiocyanosalicylic acid (5.5 g.) was dissolved in 100 ml. of aqueous ammonia (28%) and the solution stirred overnight. This solution was then heated to boiling, treated with Norite, filtered and acidified with concentrated hydrochloric acid producing 5 g. (83.6%) of white solid. When recrystallized from aqueous ethanol white cubes were obtained that melted at 179–180°.

Anal. Calcd. for $C_8H_8N_2O_3S$: N, 13.2; S, 15.1. Found: N, 13.2; S, 14.8.

4-(4-Phenyl-2-thiazolyl)-aminosalicylic Acid.—*p*-Thioureidosalicylic acid (4 g.) and phenacyl bromide (4 g.) were dissolved in an excess of absolute ethanol and heated on a steam-bath for 14 hours. The excess ethanol was removed under diminished pressure leaving a green-grey residue. This was washed with several portions of petroleum ether (60–90°) to remove any excess phenacyl bromide leaving 5 g. (85%) of the crude product. Recrystallization from aqueous ethanol (Norite) produced an off-white solid that melted from 217–218°.

Anal. Calcd. for $C_{16}H_{12}N_2O_3S$: N, 9.0; S, 10.3. Found: N, 9.0; S, 10.4.

4-(4-Carboxy-3-hydroxyphenyl)-thiosemicarbazide (III).—It was found in this particular preparation that the method of Pulvermacher[6] for making thiosemicarbazides from isothiocyanates produced a low yield of impure product. The method found most desirable was to suspend *p*-isothiocyanosalicylic acid (7.9 g.) in 250 ml. of water, stir mechanically and add hydrazine hydrate (4.8 g.). This was refluxed for 4 hours producing a clear liquid. Norite was added to the boiling liquid, the solution filtered, the hot filtrate stirred and acidified with 10% hydrochloric acid. After cooling slowly, 7.7 g. (84%) of fine white solid was recovered that melted from 198–199° with gas evolution. This could be recrystallized from a very large excess of water without, however, any alteration of the melting point.

Anal. Calcd. for $C_8H_9N_3O_3S$: N, 18.5; S, 14.1. Found: N, 18.6; S, 13.9.

General Method of Preparing the Thiosemicarbazones (IV).—Some 4-(4-carboxy-3-hydroxyphenyl)-thiosemicarbazide (3–7 g.) was suspended in 150 ml. of distilled water and 15 ml. of acetic acid added along with the aldehyde in slight excess. Usually immediate reaction took place as evidenced by the formation of a yellow solid. This mixture was heated to reflux (in the case of 5-nitrofurfuraldehyde decomposition took place at temperatures above 65°) for several hours, the flask cooled and the reaction

(1) Taken from a thesis submitted to the Graduate School of the University of North Carolina by R. B. Seligman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Deceased.

(3) J. Lehmann, *Lancet*, **250**, 15 (1946).

(4) G. Domagk, *et al.*, *Naturwissenschaften*, **33**, 315 (1946).

(5) E. Hoggarth, A. R. Martin, N. E. Storey and E. H. P. Young, *Brit. J. Pharmacol.*, **4**, 248 (1950).

(6) G. Pulvermacher, *Ber.*, **27**, 615 (1894).