coccic activity as compared to the action of sulfanilamide and sulfapyridine. A sulfonamidophenylazopyridine derivative also tested, is included in Table II.

The observations on chemotherapeutic efficacy are of interest and justify a detailed study of the toxicological properties of the most active compounds. The results seem to indicate that heterocyclic amino compounds, other than 2-aminopyridine, may be coupled with the sulfanilyl radical without great change in physiological activity.

Experimental

2-Aminothiazole and 2-amino-4-methylthiazole were prepared by treating thiourea with α,β-dichloroethyl ether, and with chloroacetone, respectively.[4]

The nitro and acetamino sulfonamides were prepared by treating two moles of heterocyclic amine with one mole of the required sulfonyl chloride in ethyl acetate or dioxane solution, as shown in the following preparation.

2 - *p* - Nitrobenzenesulfonamido - 6 - aminopyridine.—Twenty-one and eight-tenths grams of 2,6-diaminopyridine in 200 cc. of ethyl acetate was poured into a solution of 22.1 g. of *p*-nitrobenzenesulfonyl chloride in 75 cc. of ethyl acetate. The solution was kept in cold water for several hours with an occasional shaking and then let stand overnight at room temperature. The solvent was distilled on a steam-bath and the oily residue shaken with 200 cc. of cold water until it crystallized. The product was filtered off and recrystallized from alcohol with the use of a little decolorizing charcoal. The yield was 22 g. It was soluble in dilute alkalies.

2 - Sulfanilamido - 6 - aminopyridine. 1.—Twenty-two grams of the above nitro compound was stirred with 200 cc. of 10% hydrochloric acid and an excess of finely divided tin. The mixture was kept at 50° for half an hour, filtered while still warm and diluted with water. The tin salts were precipitated with hydrogen sulfide and the filtered solution neutralized with sodium bicarbonate to precipitate the sulfanilamide. The crude material was recrystallized from alcohol, yield 15.5 g. (80%). It was soluble in dilute acids and dilute alkali.

2.—Attempts to hydrolyze the acetyl group from 2-N^4-acetylsulfanilamido-6-aminopyridine by refluxing with 10% hydrochloric acid gave chiefly sulfanilic acid. The acetyl group was removed with practically quantitative yields of the desired sulfanilamide by refluxing with ten times its weight of 5–10% sodium hydroxide for forty-five minutes.

Sulfanilamidothiazoles.—Reduction of 2-*p*-nitrobenzenesulfanilamido-4-methylthiazole with tin and hydrochloric acid as described for the pyridine compound gave only 30% of 2-sulfanilamido-4-methylthiazole.

The acetyl group was hydrolyzed from the 2-N^4-acetylsulfanilamidothiazole by refluxing with ten times its weight of 10% hydrochloric acid for half an hour. The yield of 2-sulfanilamidothiazole was about 70%. Longer refluxing gave a much lower yield. The 2-sulfanilamido-4-methylthiazole was also prepared in this manner. The sulfanilamidothiazoles were soluble in dilute acids and dilute alkali.

Summary

Some 2-sulfanilamido thiazoles and pyridines have been prepared and their chemotherapeutic activity against experimental streptococcic and pneumococcic infections in mice has been determined.

Several of the compounds appear to possess anti-streptococcic and anti-pneumococcic efficacy comparable to sulfanilamide and sulfapyridine, respectively.

NEWARK, N. J. RECEIVED APRIL 18, 1939

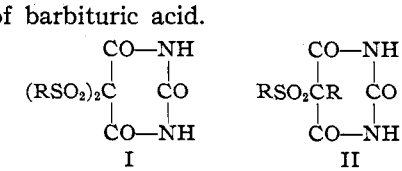
(4) Traumann, *Ann.*, **249**, 36 (1888).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING AT THE UNIVERSITY OF PENNSYLVANIA]

5-Sulfonylbarbituric Acids[1]

BY EDMOND L. D'OUVILLE,[2] FREDERICK J. MYERS AND RALPH CONNOR

α-Sulfonylamides[3] were effective enough as hypnotics to encourage a continued investigation of compounds containing the sulfone group combined with other groups that are present in some of the common hypnotics. Attention was naturally directed toward the synthesis of 5,5-disulfonyl (I) and 5-alkyl-5-sulfonyl (II) derivatives of barbituric acid.



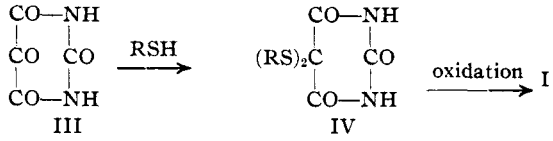
I II

The reactivity of the carbonyl group in alloxan (III) suggested that it might react with thiol compounds to give mercaptols (IV) which could be oxidized to the desired products (I).

(1) A portion of the communication is abstracted from a thesis submitted by Edmond L. d'Ouville in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1937.

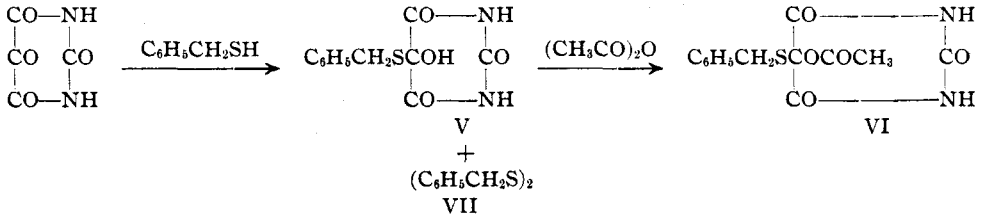
(2) Chemical Foundation Fellow.

(3) d'Ouville and Connor, THIS JOURNAL, **60**, 33 (1938).



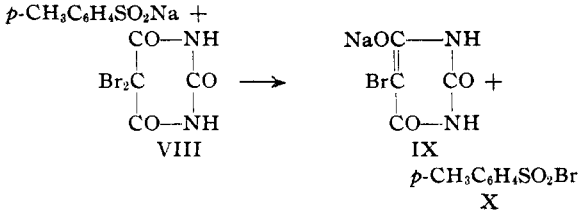
III IV I

With benzyl mercaptan in dry dioxane and using dry hydrogen chloride as a catalyst the product was the hemi-mercaptol, 5-hydroxy-5-(benzylthio)-barbituric acid (V); in glacial acetic acid–acetic anhydride solution 5-acetoxy-5-(benzylthio)-barbituric acid (VI), the acetylation product of V, was formed. Under the conditions tried it was not possible to carry the reaction further to the mercaptol stage. In addition to V, dibenzyl disulfide (VII) was produced; this must involve the reduction of alloxan, presumably to dialuric acid, although the reduction product was not isolated. With *p*-thiocresol in dioxane or glacial acetic acid as solvent and anhydrous hydrogen chloride, sulfuric acid or zinc chloride as catalysts, no condensation with alloxan occurred.



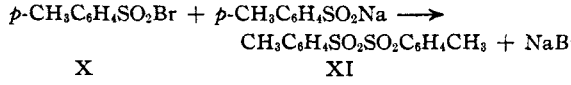
V + $(C_6H_5CH_2S)_2$ VII VI

A second possible synthesis of the disulfonylbarbituric acids was the reaction of 5,5-dibromobarbituric acid (VIII) with salts of sulfinic acid. With sodium *p*-toluenesulfinate a reaction occurred very readily at room temperature but none of the desired product (I, R = *p*-$CH_3C_6H_4$–) was obtained. The reaction appeared to be quite complex and the physical properties of the products made their separation and purification very difficult. The product isolated in the largest amount was the sodium salt of 5-bromobarbituric acid (IX), which was isolated in an amount corresponding to about 40% of the theoretical. The reduction of the dibromobarbituric acid implies that the first step in the reaction is the formation of IX and *p*-toluenesulfonyl bromide (X).



VIII IX X

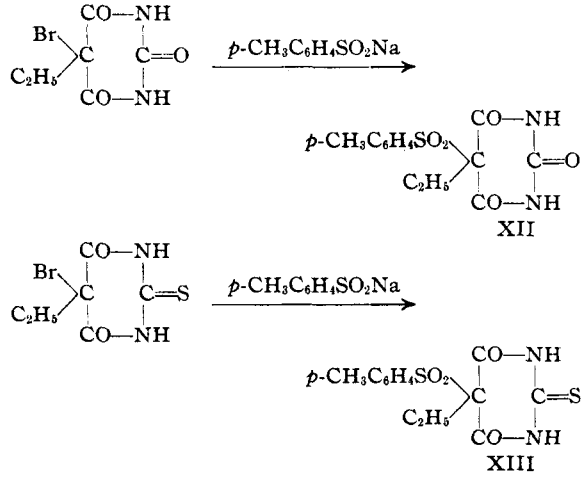
While X was not isolated, di-*p*-tolylsulfone (XI) was obtained; this is evidence for the formation of X since disulfones are readily formed[4] by the reaction of sulfonyl halides with the salts of sulfinic acids. Attempts to avoid the oxidation–re-



X XI

duction reactions in the preparation of disulfonylbarbituric acids were abandoned when the monosulfonyl derivatives (II) had been prepared and found to have properties which indicate that I would probably be very unstable and of no hypnotic value.

5-Ethyl-5-*p*-tolylsulfonylbarbituric acid (XII) and 5-ethyl-5-*p*-tolylsulfonyl-2-thiobarbituric acid (XIII) were prepared by the reaction of sodium *p*-toluenesulfinate with 5-ethyl-5-bromobarbituric acid and with 5-ethyl-5-bromo-2-thiobarbituric acid. Better yields of the metathesis products were obtained when the reactions were carried out without heating; for example, the yield of XII was 20% at 25° as compared with



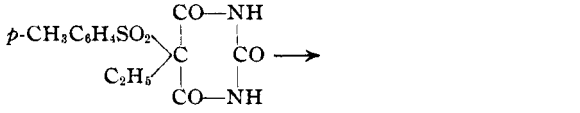
XII XIII

8% at 64°. This influence of temperature has been reported previously[3] and undoubtedly is due to the fact that higher temperatures favor the oxidation–reduction reaction. In the prepara-

(4) Kohler and MacDonald, *Am. Chem. J.*, **22**, 222 (1899).

tion of XII a by-product was the disulfone XI, showing that oxidation–reduction does occur.[5]

The yield of sulfonyl barbituric acid isolated was by no means a true gage of the amount of metathesis. A portion of the metathesis product underwent cleavage to give α-*p*-tolylsulfonyl-*n*-butyramide (XIV).



p-$CH_3C_6H_4SO_2CH(C_2H_5)CONH_2$

XIV

This cleavage of 5-sulfonylbarbituric acids is not surprising in view of other indications that the introduction of a sulfone group into active methylene compounds gives a structure labile to alcoholysis.[7]

It also appears likely that the acidity of the barbituric acids introduces a third complication in these reactions by liberating some of the sulfinic acid from its salt.

The 5-sulfonyl derivatives of the barbituric acids studied were relatively unstable. They dissolved readily in sodium carbonate solution but were slowly converted, even by water alone, to the cleavage product XIV. This, combined with the analytical data, establishes the structures of the products. Of the barbituric acids prepared, XII was the more stable and when pure could be stored satisfactorily in the dark; XIII could not be kept and its melting point was lowered over 35° by standing for three weeks. Preliminary pharmacological tests on XII, carried out through the kindness of Dr. Robert S. Shelton of the Wm. S. Merrell Company, indicated that it was without value as a hypnotic. Because of this report and the instability of the compounds, no further representatives of the series were prepared.

Experimental Part[8]

5-Hydroxy-5-(benzylthio)-barbituric Acid (V).—A mixture of 16 g. (0.1 mole) of alloxan monohydrate, 23 g. (0.19 mole) of benzyl mercaptan and 200 ml. of dioxane was cooled in an ice–salt bath and saturated with dry hydrogen chloride. After standing in the ice–salt bath overnight, the solution was resaturated with hydrogen chloride. White needles began to separate. After two days the solid (22 g., m. p. 135–140 dec.) was removed by filtration and recrystallized successively from alcohol and benzene. The purified product weighed 12.2 g. (46%), m. p. 169–174° dec. It turned deep red if allowed to stand in contact with air.

Anal. Calcd. for $C_{11}H_{10}O_4N_2S$: N, 10.54; S, 11.97. Found: N, 10.51, 10.81; S, 11.88.

Dilution of the mother liquor with water gave 5 g. of dibenzyl disulfide which after one recrystallization from alcohol melted at 70°.

5-Acetoxy-5-(benzylthio)-barbituric Acid (VI).—A mixture of 32 g. (0.2 mole) of alloxan monohydrate, 50 g. (0.4 mole) of benzyl mercaptan, 100 ml. of glacial acetic acid and 40 ml. of acetic anhydride was cooled in an ice–salt mixture and saturated with dry hydrogen chloride. The reaction mixture was kept at 0° for twelve hours and at room temperature for an additional twelve hours; the solid was removed by filtration and washed successively with water, alcohol and ether. The combined washings and mother liquor were diluted to 1.5 liter with water, filtered and the semi-solid residue washed with dilute alcohol. The combined solids weighed 19 g., m. p. 90–100°. Three recrystallizations from alcohol gave 5 g. (9.5%) of a white crystalline solid which turned pink at 190°, later became orange and finally melted with decomposition between 210° and 235°. Dilution of the mother liquors from the recrystallizations gave 4.5 g. of what appeared to be the same product in a less pure state.

Anal. Calcd. for $C_{13}H_{12}O_5N_2S$: N, 9.09; S, 10.39. Found: N, 9.17, 9.34, 9.33; S, 10.25.

Attempted Condensation of *p*-Thiocresol with Alloxan.—Using both glacial acetic acid and dioxane as solvents, reactions were carried out with alloxan hydrate and *p*-thiocresol under conditions similar to those described above. Dioxane was used as a solvent with sulfuric acid and zinc chloride, both alone and together, as catalysts in the cold and at 100°. In all cases no reaction product was isolated and unreacted *p*-thiocresol was obtained.

5,5-Dibromobarbituric Acid with Sodium *p*-Toluenesulfinate.—A suspension of 14.3 g. (0.05 mole) of 5,5-dibromobarbituric acid[9] and 21.4 g. (0.10 mole) sodium *p*-toluenesulfinate dihydrate[10] in 200 ml. of absolute methanol was allowed to stand at room temperature for four days. The crystalline solid (0.8 g.) was removed by filtration and recrystallized from benzene. The purified material became discolored at 200° and melted with decomposition at 207°. An authentic sample of di-*p*-tolyldisulfone[4] behaved similarly, both alone and when mixed with the reaction product.

The methanol filtrate was allowed to stand for seven days at room temperature and the solid that appeared removed by filtration. There was obtained 4.3 g. (38%) of the sodium salt of monobromobarbituric acid. Heating with 40% sulfuric acid solution gave 5-bromobarbituric acid, m. p. 200° (dec.), which was identified by a mixed

(5) Other investigators[6] have reported the formation of sodium benzenesulfonate and the unhalogenated active methylene compound when sodium benzenesulfinate was allowed to react with ethyl α-chloroacetoacetate, ethyl chloromalonate and diacetylchloromethane.

(6) Kohler and MacDonald, *Am. Chem. J.*, **22**, 227 (1899); Otto and Rossing, *Ber.*, **23**, 756 (1890).

(7) For example, the formation[6] of ethyl phenylsulfonylacetate in reactions which should cause the introduction of a phenylsulfonyl group in ethyl malonate and ethyl acetoacetate.

(8) All melting points are corrected.

(9) Biltz and Hamburger, *Ber.*, **49**, 635 (1916).

(10) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 1932, p. 479.

melting point with an authentic sample[11] and by conversion with 1:1 hydrochloric acid[9] to 5-chlorobarbituric acid, m. p. 273° (dec.). The latter gave no depression of the melting point when mixed with a sample of 5-chlorobarbituric acid prepared in a similar manner from 5-bromobarbituric acid.

The filtrate obtained after removal of sodium bromobarbiturate gave additional solid material but it appeared to be a mixture that could not be separated. The presence of an additional quantity of sodium bromobarbiturate was shown by the formation of 5-chlorobarbituric acid when a sample of the solid was heated with 1:1 hydrochloric acid.

5-*p*-Tolylsulfonyl-5-ethylbarbituric Acid (XII).—A mixture of 21 g. (0.10 mole) of sodium *p*-toluenesulfinate dihydrate and 20 g. (0.085 mole) of 5-bromo-5-ethylbarbituric acid[12] in 250 ml. of absolute methanol was allowed to stand for eight days at room temperature. The solvent was then removed by evaporation, the residue washed with ether and the solid remaining treated with dilute sodium hydroxide solution. Recrystallization of the alkali-insoluble material from alcohol gave α-*p*-tolylsulfonyl-*n*-butyramide (XIV).[3] Acidification of the alkaline solution with concentrated hydrochloric acid gave a bulky white precipitate which was filtered, dried and recrystallized from alcohol. The yield of pure XII was 5.5 g. (20%), m. p. 200.5–203.5° (dec.).

Anal. Calcd. for $C_{13}H_{14}O_6N_2S$: mol. wt., 310; N, 9.03; S, 10.32. Found: mol. wt., 316, 312; N, 9.08, 9.24; S, 10.25, 10.50.

After the removal of XII, evaporation of the acidic solution gave 12 g. of solid. The material was extremely soluble in water and on ignition charred and gave an alkaline ash. A small portion was refluxed with thionyl chloride[13] but the product was impure, m. p. 58–61°. With *p*-toluenesulfonyl chloride (m. p. 69°) the mixed melting point was 67°.

In another experiment the solid precipitated in the reaction mixture was separated by filtration, washed with water, dried and recrystallized from benzene. The product weighed 2.3 g. (18%), m. p. 204–208° (dec.), and was identified as di-*p*-tolyldisulfone by a mixed melting point.

(11) Back, *Ber.*, **55B**, 3400 (1922).

(12) Aspelund, *J. prakt. Chem.*, [2] **136**, 329 (1933).

(13) Smiles and Hilditch, *J. Chem. Soc.*, **90**, 522 (1907); Sutherland and Shriner, THIS JOURNAL, **58**, 63 (1936).

5-*p*-Tolylsulfonyl-5-ethyl-2-thiobarbituric Acid (XIII).—Twenty-eight grams (0.13 mole) of sodium *p*-toluenesulfinate dihydrate was added to 250 ml. of absolute methanol, the mixture cooled to 5° and 25.6 g. (0.1 mole) of 5-bromo-5-ethyl-2-thiobarbituric acid[14] added. The solution was stirred vigorously and kept below 5° for one and one-half hours. The solution was allowed to come to room temperature and stand for eight days. It was then poured over ice, filtered and the solid washed with water. The product was almost entirely soluble in sodium carbonate solution. This solution was filtered, acidified with concentrated hydrochloric acid and the product recrystallized from dilute alcohol. The yield of pure XIII was 6.5 g. (20%), m. p. 179.9–180°. The product decomposed on standing three weeks, m. p. 141–145°.

Anal. Calcd. for $C_{13}H_{14}O_4N_2S_2$: mol. wt., 326; N, 8.59. Found: mol. wt., 320; N, 8.75, 8.77.

Summary

Attempts to synthesize 5,5-disulfonyl derivatives of barbituric acid were unsuccessful. *p*-Thiocresol did not react with alloxan while benzyl mercaptan gave 5-hydroxy-5-(benzylthio)-barbituric acid in dioxane as a solvent and 5-acetoxy-5-(benzylthio)-barbituric acid in acetic acid–acetic anhydride. Sodium *p*-toluenesulfinate with 5,5-dibromobarbituric acid gave sodium 5-bromobarbiturate, accompanied by oxidation products of the sulfinate.

The reaction at room temperature of sodium *p*-toluenesulfinate with 5-ethyl-5-bromobarbituric acid and with 5-ethyl-5-bromo-2-thiobarbituric acid gave 5-*p*-tolylsulfonyl-5-ethylbarbituric acid and 5-*p*-tolylsulfonyl-5-ethyl-2-thiobarbituric acid. The by-products show that the yields of metathesis products are lowered by oxidation–reduction reactions and by the ease of alcoholysis of the product.

PHILADELPHIA, PENNA. RECEIVED MAY 15, 1939

(14) Prepared by the method of Aspelund[12] for 5-bromo-5-ethylbarbituric acid.