[CONTRIBUTION FROM THE SCHOOL OF PHARMACY OF THE UNIVERSITY OF MARYLAND]

Some Unsymmetrical Aryl Sulfides[1]

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It has been shown by Johnson and his coworkers,[3] by Dunning, Dunning and Drake,[4] and others,[5] that substituted aryl sulfides have considerable germicidal property. The present investigation is concerned with the preparation of ureido-diphenyl sulfides of the general formula NH_2CONHSR, where R is represented by the *p*-hydroxyphenyl, resorcyl, *m*-cresyl and thymyl radicals. These compounds were examined with regard to their germicidal properties and their use as urinary antiseptics.

The new derivatives were chemically characterized by the preparation of their acetates and bromine substitution products. The azo dyes resulting from the coupling of the diazotized amines with R-salt were also prepared.

The general method of preparation consisted in preparing *p*,*p*′-dinitrodiphenyl disulfide according to the method of Bogert and Stull[6] by the action of sodium disulfide on *p*-nitrochlorobenzene. *p*-Nitrophenyl-sulfurchloride was prepared by allowing chlorine to react on the *p*,*p*′-dinitrodiphenyl disulfide by the method of Zincke and Lenhart[7] and subsequently condensed with the respective phenols. The nitro compounds were reduced catalytically to the amino compounds by the Adams platinum catalyst method.[8] The amines were converted into the ureides by condensation with cyanic acid. The reactions with phenol are presented by the scheme

$$2NO_2C_6H_4Cl + Na_2S_2 \longrightarrow NO_2C_6H_4SSC_6H_4NO_2 \xrightarrow{Cl_2} 2NO_2C_6H_4SCl$$

$$NO_2C_6H_4SCl + C_6H_5OH \longrightarrow NO_2C_6H_4SC_6H_4OH \xrightarrow{H_2} NH_2C_6H_4SC_6H_4OH$$

$$NH_2C_6H_4SC_6H_4CH + HCNO \longrightarrow NH_2CONHC_6H_4SC_6H_4OH$$

Experimental Part

Condensation of *p*-Nitrophenylsulfurchloride with Phenols.—A slow current of chlorine is passed into a suspension of one mole of *p*,*p*′-dinitrodiphenyl disulfide in ice-cold chloroform until a clear solution is obtained. The excess of chlorine is removed by aspiration, and the orange colored solution of *p*-nitrophenylsulfurchloride thus obtained slowly added to a cooled solution of the respective phenol in dry ether. The reaction mixture is then refluxed for six hours on a water-bath. Most of the solvent is distilled off and the concentrated solution left to crystallize overnight in an ice-box. The crude product is purified by recrystallizing several times from an ether–petroleum ether mixture and finally from dilute alcohol. Table I shows the condensation products prepared.

TABLE I

	Condensation with	Formula of nitro compound	M. p., °C.	% Sulfur Found	% Sulfur Calcd.
I	Phenol	$NO_2C_6H_4SC_6H_4OH$[7]	150–151	13.01	12.95
II	Resorcinol	$NO_2C_6H_4SC_6H_3(OH)_2$[7]	184–185	12.20	12.16
III	*m*-Cresol	$NO_2C_6H_4SC_6H_3(CH_3)(OH)$	193–193.5	12.25	12.29
IV	Thymol	$NO_2C_6H_4SC_6H_2(CH_3)(C_3H_7)(OH)$	116–117	10.63	10.59

The yield of nitrophenylsulfurchloride with resorcinol and *m*-cresol was 80–90%, whereas the yield with phenol and thymol was plus or minus 20%. In the two latter instances a large amount of oil which could not be identified was obtained.

Acetylization.—The nitrosulfides are acetylated by refluxing for six hours with ten parts of acetic anhydride and 0.4 part of anhydrous sodium acetate. The pale yellow acetyl derivatives are precipitated with water and recrystallized from dilute alcohol, and finally from a benzene petroleum ether mixture. The acetates prepared are listed in Table II.

Bromination.—The calculated amount of bromine dissolved in some glacial acetic acid is slowly added to a glacial acetic acid solution of the nitrosulfide. In some cases gentle heating is necessary to complete the reaction. On removing the hydrobromic acid by aspiration, the brominated sulfide crystallizes. It is recrystallized from dilute alcohol and subsequently from a benzene–petroleum ether solution. Table III contains the bromo derivatives prepared in this manner.

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(1) Taken in part from a thesis presented by N. E. Foss in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of Maryland, and presented before the Meeting of the American Chemical Society in Washington, D. C., March, 1933.

(2) The Dunning Fellow.

(3) Johnson and Hilbert, THIS JOURNAL, **51**, 1526 (1929); Johnson and Bass, *ibid.*, **52**, 1146 (1930).

(4) Dunning, Dunning and Drake, *ibid.*, **53**, 3466 (1931).

(5) Moness, Bracker and Christiansen, *J. Am. Pharm. Assn.*, **21**, 557 (1932); Suter and Hanson, THIS JOURNAL, **54**, 4100 (1932); Miller and Read, *ibid.*, **55**, 1224 (1933).

(6) Bogert and Stull, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 64.

(7) Zincke and Lenhart, *Ann.*, **400**, 1 (1924).

(8) Adams, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

TABLE II

	Acetyl compound	M. p., °C.	Sulfur, % Found	Sulfur, % Calcd.
I	Mono-acetate[7]	80.5- 81.5	11.15	11.09
II	Di-acetate[7]	110 -111	9.25	9.19
III	Mono-acetate	98 - 99	10.61	10.56
IV	Mono-acetate	77 - 78	9.30	9.27

TABLE III

	Bromine compound	M. p., °C.	% Sulfur Found	% Sulfur Calcd.	% Bromine Found	% Bromine Calcd.
I	Di-bromo	155–156	8.09	8.00	39.36	39.50
II	Di-bromo	179–180	7.76	7.60	38.01	37.98
III	Di-bromo	204–205	7.59	7.60	37.86	38.10
IV	Mono-bromo	126–127	8.42	8.38	21.17	20.95

Reduction to Amines.—One part of nitrosulfide dissolved in ten parts of 95% ethyl alcohol is reduced by hydrogen with 0.01 part of Adams platinum black as catalyst. The yields were from 80–90%. Table IV includes the amines prepared.

TABLE IV

	Amine where R = $Na_2C_6H_4S$—	M. p., °C.	% Sulfur Found	% Sulfur Calcd.	% Nitrogen Found	% Nitrogen Calcd.
I	R-C_6H_4OH	151 -152	14.80	14.75	6.36	6.45
II	R-$C_6H_3(OH)_2$	151 -152	13.80	13.73	6.11	6.01
III	R-$C_6H_3(CH_3)(OH)$	149.5–150	13.90	13.85	6.12	6.06
IV	R-$C_6H_2(CH_3)(C_3H_7)(OH)$	112.5–113	11.85	11.73	5.12	5.04

Hydrochlorides of the Amines.—The hydrochlorides are prepared by heating the amines with concentrated hydrochloric acid, cooling, filtering, and washing with cold alcohol.

Acetylization of the Amino Compounds.—The amino compounds are acetylated in the usual manner by refluxing with acetic anhydride and anhydrous sodium acetate. By this method both the hydroxyl and amino groups were acetylated. Table V contains the acetates prepared in this manner.

TABLE V

	Acetyl compound	M. p., °C.	Sulfur, % Found	Sulfur, % Calcd.
I	Di-acetate	158.5–159	10.68	10.63
II	Tri-acetate	158 -158.5	8.84	8.91
III	Di-acetate	128 -128.5	10.30	10.22
IV	Di-acetate	90 - 91	8.16	8.17

The Amines Coupled with R-Salt.—The azo dyes are prepared by diazotizing the amines and coupling the resulting diazonium salts with 2-hydroxynaphthalene-3,6-disulfonic acid in acid solution. The dyes are red in color and readily soluble in alkaline solution, but insoluble in acid solution. Table VI contains the azo dyes prepared.

TABLE VI

	Formula of azo dye	Sulfur, % Found	Sulfur, % Calcd.
I	$C_{22}H_{17}O_8N_2S_3$	15.42	17.94
II	$C_{22}H_{17}O_9N_2S_3$	17.31	17.51
III	$C_{23}H_{19}O_8N_2S_3$	13.81	17,58
IV	$C_{26}H_{25}O_8N_2S_3$	13.60	16.27

Conversion of the Amine to the Ureide.—An excess of potassium cyanate dissolved in water and cooled to 0° is dropped into a solution of the amine dissolved in ten parts of 50% acetic acid and cooled in an ice–salt bath. The solution is rapidly stirred for a few minutes and suddenly a mass of white crystals appears. The mixture is heated slightly to complete the reaction and the mass is recrystallized from dilute alcohol. The yield is 60–80%. Table VII lists the ureides prepared.

Properties.—The nitrosulfides, as well as their bromine derivatives and acetates, are yellow. The amino and ureide derivatives are colorless. In the nitro compounds two bromine atoms may be substituted in the two ortho positions of the hydroxy group, except in the case of the thymyl radical, where only one bromine is introduced, the second ortho position already being occupied. All the compounds with a free hydroxy group give a deep purple color with ferric chloride in alcohol solution. The amines are only weak bases and form the hydrochlorides with difficulty.

Bacteriological and Pharmacological Results.—Due to the extreme insolubility of these compounds, it was difficult to obtain any definite bacteriological data. All the phenolic sulfur ureides were soluble in water in less than 1:10,000 concentration, except the resorcyl compound, which was soluble in about 1:1000 concentration. In 30% alcohol, the same degree of insolubility persisted, and only in 50% ethylene glycol solutions were 1:1000 dilutions obtained. The thymyl derivative was the only ureide which showed any activity when tested against *Staphylococcus aureus* and *Bacillus typhosus* by the technique of the United States Department of Agriculture. More favorable results were obtained against *Staphylococcus aureus* by using the cup-plate method of the United States Hygienic Laboratories. By this procedure, the thymyl derivative showed the largest zone, only the resorcyl derivative failing to show any

TABLE VII

	Ureide where R = $NH_2CONHC_6H_4S$—	M. p., °C.	Sulfur, % Found	Sulfur, % Calcd.	Nitrogen, % Found	Nitrogen, % Calcd.
I	R-C_6H_4OH	228–229	12.25	12.29	10.76	10.75
II	R-$C_6H_3(OH)_2$	178–178.5	11.59	11.59	10.03	10.14
III	R-$C_6H_3(CH_3)(OH)$	201–201.5	11.63	11.67	10.30	10.21
IV	R-$C_6H_2(CH_3)(C_3H_7)(OH)$	177–177.5	10.35	10.13	8.62	8.86

activity. It was also observed that the thymyl derivative exhibited a greater germicidal activity against *Bacillus typhosus* than *Staphylococcus aureus.*

The pharmacological results were somewhat more noteworthy. The cat and rabbit were used as test animals. It was found that the ureides were eliminated in the urine and that they were non-toxic in any concentration in which they might appear in the blood. It is significant to note that these ureides, when introduced into the femoral vein of the cat in the form of their sodium salts, produced no effect on respiration or blood pressure as recorded by the carotid blood pressure, provided that the rate of administration was not too rapid.

All of these ureides showed a very low toxicity. Five hundred milligrams, given in suspension by a stomach tube to rabbits, produced no toxic effect, no purgation, no diuresis, no hypnosis, no anesthesia and no excitement. The phenolsulfonphthalein test was not affected.

Summary

Twenty-eight compounds have been prepared. They are of the general nature  where R may be NO_2, NH_2, or NH_2CONH, and R_2 may be the phenyl, resorcyl, *m*-cresyl or thymyl radical. Some bromo derivatives and acetates have been made. The diazotized amines were coupled with certain intermediates to form azo dyes. Twenty-four of these compounds have not been previously described in the literature.

The ureide derivatives have been tested bacteriologically. Only the thymyl ureide has been found to have any germicidal activity.

The ureides have also been tested pharmacologically, and it was shown that they were promptly excreted by way of the urinary tract.

BALTIMORE, MD. RECEIVED JUNE 4, 1934

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 134]

The Tautomerism of 1,4-Diphenylbutane-1,2,4-trione Enol

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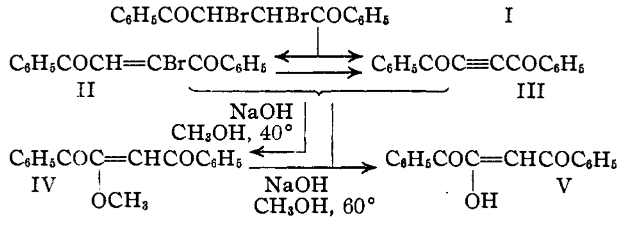
The 1,2,4-triketones and their enols are of interest because they combine the properties of α-, β- and γ-diketones, and because in the enolic forms they react like unsaturated 1,4-diketones. 1,2-Di-(trimethylbenzoyl)-ethenol has been prepared in both keto and enol forms by the action of alcoholic sodium acetate on di-(trimethylbenzoyl)-dibromoethane,[1a] but the analogous reactions in the dibenzoyl series[1] give materials which are not easily characterized and which have proved to be complex mixtures of secondary products. Diphenylbutanetrione, $C_6H_5COCOCH_2COC_6H_5$, has not as yet been isolated in the keto form, but the enol, which we regard as dibenzoylethenol V, may be prepared in good yield by the action of alcoholic sodium hydroxide on dibenzoyldibromoethane I, dibenzoylacetylene III, or dibenzoylmethoxyethylene IV.



The chain of reactions involved in this synthesis, starting with dibenzoyldibromoethane, possibly proceeds as indicated in the above diagram; in any case, each compound cited has been isolated under controlled conditions and reacts further as indicated to give the enol.[2] Sodium methylate, or sodium hydroxide in 92% methanol, reacts in the cold with dibenzoyldibromoethane or with dibenzoylacetylene to give dibenzoylmethoxyethylene IV even when an excess of alkali is used; however, the methyl ether is hydrolyzed to the enol by the excess of alkali when the mixtures are heated at 60° for five minutes. It is noteworthy that, even in the 92% methanolic solution, sodium methylate appears to be the primary reactant rather than sodium hydroxide, since the elements of methanol and not of water are involved and the enol arises from hydrolysis of the first formed methyl ether. Other enol ethers, including the phenyl, are hydrolyzed to the enol

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[1] (a) Lutz, THIS JOURNAL, **48**, 2905 (1926); (b) Conant and Lutz, *ibid.*, **47**, 881 (1925).

[2] For the isolation of dibenzoylbromoethylene and dibenzoylacetylene, see Ref. 1.