[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Preparation of Some Sulfanilamide Derivatives of *s*-Triazine[1]

G. F. D'ALELIO AND HARRY J. WHITE, JR.[2]

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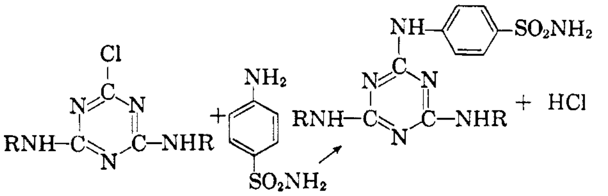
A general procedure for the synthesis of N^4-sulfanilamide derivatives of *s*-triazine from chloro-*s*-triazines and sulfanilamide is described. A series of new compounds was prepared using this method.

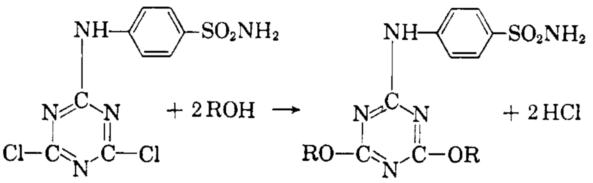
The reaction of cyanuric chloride with aliphatic[3] and aromatic[4] amines is well known. Thurston[5] used this method to prepare a number of amino-chloro-*s*-triazines. Kaiser[6] prepared a variety of substituted melamines by the reaction of chloro-*s*-triazines with amines. However, little attention has been given to the reaction of sulfanilamide with cyanuric chloride, and only two of these derivatives have been reported.[7] Since some of these sulfanilamide derivatives may have useful drug properties, it was considered worthwhile to prepare an assortment of these compounds for broad screening.[8]

It has been found in this work that the reaction of sulfanilamide with substituted chloro-*s*-triazines constitutes a good general method for the preparation of substituted (4-sulfamoylanilino)-*s*-triazines. Water is a convenient solvent for this reaction since sulfanilamide is soluble in hot water and the chloro-*s*-triazines are at least partially soluble in this solvent. There was no evidence of hydrolysis of the chloro-*s*-triazines in the aqueous medium. Since the (4-sulfamoylanilino)-*s*-triazines are insoluble in water, the products are isolated in good yields. Sodium hydroxide is the most efficient hydrogen chloride acceptor for these reactions.



Cyanuric chloride reacts with one mole of sulfanilamide at 0–5° to form 2,4-dichloro-6-(4-sulfamoylanilino)-*s*-triazine. The product is isolated in good yield from acetone solution.

2,4-Dichloro-6-(4-sulfamoylanilino)-*s*-triazine reacts with alcohols and amines to form 2,4-dialkoxy- and 2,4-diamino-6-(4-sulfamoylanilino)-*s*-triazines. The reaction with amines was found to run smoothly in water at 100°. Aqueous sodium hydroxide is the most suitable hydrogen chloride acceptor, although excess amine may be used. The reaction with alcohols was run at reflux temperature in the presence of sodium hydroxide using excess alcohol as the solvent.



The two chlorine atoms of 2,4-dichloro-6-(4-sulfamoylanilino)-*s*-triazine are readily hydrolyzed to yield 2,4-dihydroxy-6-(4-sulfamoylanilino)-*s*-triazine. The most satisfactory procedure is to reflux the chloro-*s*-triazine in glacial acetic acid. Since the product is insoluble in the reaction medium, a quantitative yield is obtained. The hydrolysis may also be carried out using aqueous sodium hydroxide, but this procedure was not preferred since the yield was lower.

Sulfanilamide replaces the three chlorine atoms of cyanuric chloride at 100°. The reaction is carried out in water using sodium hydroxide as the hydrogen chloride acceptor.

The sulfanilamide derivatives of *s*-triazine prepared in this work are described in Table I and the analytical data is given in Table II.[9]

EXPERIMENTAL

2,4-Dichloro-6-methoxy-s-triazine and 2-chloro-4,6-dimethoxy-6-triazine were prepared according to the method of Dudley.[10] 2-Chloro-4,6-diamino-*s*-triazine and 2,4-dichloro-6-(2-hydroxyethylamino)-*s*-triazine were prepared using the method described by Thurston.[5]

2,4-Dichloro-6-(4-sulfamoylanilino)-s-triazine(I). A solution of 17.2 g. (0.1 mole) of sulfanilamide in 100 ml. of ace-

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[1] Abstracted from a portion of the Ph.D. dissertation of Harry J. White, Jr., University of Notre Dame, 1957.

[2] Miles Laboratories Fellow 1955–57.

[3] W. M. Pearlman and C. K. Banks, *J. Am. Chem. Soc.*, **70**, 3726 (1948).

[4] C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

[5] J. T. Thurston, J. R. Dudley, D. W. Kaiser, I. Hechenkleikner, F. C. Schaefer, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2981 (1951).

[6] D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer, I. Hechenkleikner and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2984 (1951).

[7] G. F. D'Alelio, U. S. Patent **2,312,698** (1943).

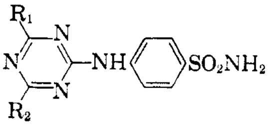
[8] Pharmacological testing is being carried out by Miles Laboratories, Elkhart, Ind.

[9] Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. and Midwest Microlab, Indianapolis, Ind.

[10] J. R. Dudley, J. T. Thurston, F. C. Schaefer, D. Holm-Hansen, C. J. Hull and P. Adams, *J. Am. Chem. Soc.*, **73**, 2986 (1951).

TABLE I

4-Sulfamoylanilino-s-triazines,



Compound	R_1	R_2	Yield, %	M.P., °C.
I	Cl	Cl	94	Infusible
II	NH_2	NH_2	89	308–309 (dec.)
III	OC_2H_5	OC_2H_5	71[a]	210–211
IV	OC_6H_5	OC_6H_5	93[a]	207–208
V	OCH_3	OCH_3	74	214–218 (dec.)
VI	NHC_6H_5	NHC_6H_5	57[a]	216–217
VII	p-$NHC_6H_4SO_2Na$	p-$NHC_6H_4SO_3Na$	56[a]	Infusible
VIII	$NHCH_2CO_2Na$	$NHCH_2CO_2Na$	68[a]	Infusible
IX	OH	OH	99[a]	295–296 (dec.)
X	p-$NHC_6H_4SO_2NH_2$	OCH_3	93	307 (dec.)
XI	p-$NHC_6H_4SO_2NH_2$	$NHCH_2CH_2OH$	90	297–298 (dec.)
XII	p-$NHC_6H_4SO_2NH_2$	p-$NHC_6H_4SO_2NH_2$	92	Infusible

[a] Prepared from I.

TABLE II

Analytical Data

Compound	Formula	N	S	N	S
		Calculated		Found	
I	$C_9H_7Cl_2N_5O_2S$[a]		10.00		10.24
II	$C_9H_{11}N_7O_2S$		11.36		11.12
III	$C_{13}H_{17}N_5O_4S$	20.64	9.44	20.37	9.22
IV	$C_{21}H_{17}N_5O_4S$	16.08	7.36	15.82	7.14
V	$C_{11}H_{13}N_5O_4S$	22.43	10.28	22.11	10.62
VI	$C_{21}H_{17}N_7O_2S$	22.61	7.38	22.22	7.02
VII	$C_{21}H_{17}N_7O_8S_3Na_2.4H_2O$[b]				
VIII	$C_{13}H_{13}N_7O_6SNa_2.2H_2O$[c]				
IX	$C_9H_9N_5O_4S.2H_2O$	21.94	10.03	21.92	9.66
X	$C_{16}H_{17}N_7O_5S_2$	21.74	14.10	21.65	13.96
XI	$C_{17}H_{20}N_8O_5S_2$	23.36	13.32	23.14	12.87
XII	$C_{21}H_{21}N_9O_6S_3$	21.30	16.51	20.96	16.48

[a] *Anal.* Calcd.: Cl, 22.18. Found: Cl, 21.70. [b] *Anal.* Calcd: C, 35.55; H, 3.53. Found: C, 35.12; H, 3.90. [c] *Anal.* Calcd: C, 32.68; H, 3.55. Found: C, 32.44; H, 3.10.

tone was dropped into a solution of 18.5 g. (0.1 mole) of cyanuric chloride in 100 ml. of acetone. The temperature was maintained at 0–5°. The mixture was stirred for 0.5 hr. and then a solution of 4.0 g. (0.1 mole) of sodium hydroxide in 60 ml. of water was added dropwise. Stirring was continued for an additional 0.5 hr. Ice water (200 ml.) was added and the solid was filtered. The product was washed with ice water until free of chloride ion. The yield was 30 g. (94%) of an infusible white solid.

The product was purified by dissolving in hot acetone and precipitating with ice water.

Reaction of chloro-s-triazines with sulfanilamide. One mole of the chloro-s-triazine was added to a solution of sulfanilamide (1 mole for each chlorine atom to be replaced) in hot water. The mixture was heated to reflux and a stoichiometric amount of aqueous sodium hydroxide was dropped in over a period of 1 hr. Refluxing was continued for 2–3 hr. The mixture was cooled and the product was filtered and washed with water. The products were recrystallized from 50% aqueous acetone or 50% aqueous dioxane.

Reaction of I with amines. One mole of I was added to a solution or suspension of 2 moles of amine in water. The mixture was heated to reflux and 2 moles of aqueous sodium hydroxide was slowly added. Refluxing was continued for 2–4 hr. The insoluble products were easily isolated by filtration. In the case of sodium salts, the products were isolated by precipitation with ethanol.

Reaction of I with alcohols. One mole of I was added to a solution or suspension of 2 moles of sodium hydroxide in the appropriate alcohol. The mixture was refluxed for 4–5 hr. The products were isolated by precipitation with water.

2,4,6-Tris-(4-sulfamoylanilino)-s-triazine. Cyanuric chloride (9.5 g., 0.05 mole) was added to 29.3 g. (0.17 mole) of sulfanilamide in 100 ml. of water. The mixture was heated to reflux and a solution of 6.0 g. (0.15 mole) of sodium hydroxide in 50 ml. of water was added. Refluxing was continued for 10 hr. The mixture was cooled and the solid was filtered off and washed with water. Yield was 27 g. (92%). The infusible product was recrystallized from 50% aqueous acetone.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, IND.