Sulfonyl Isocyanates from Sulfonamides.—A three-neck round-bottom flask was flushed with nitrogen and was charged with a mixture of 0.1 mole of a suitable sulfonamide, 0.5 ml. of boron trifluoride etherate, and 150 ml. of 1,2-dichloroethane. A gas outlet adapter at the top of the reflux condenser leading to a trap partially filled with water prevented excessive amounts of HCl from escaping into the hood. With efficient stirring, 14.0 g. (9.4 ml., 0.11 mole) of oxalyl chloride was added to the mixture dropwise. Evolution of gases began immediately, and, after the addition of oxalyl chloride was complete, the mixture was heated under reflux with stirring from 1–8 hr. After the reaction mixture cooled to room temperature, the mixture was treated with Supercel and filtered through a sintered-glass funnel to give a clear red-brown solution. The solvent was removed from the filtrate by distillation at atmospheric pressure, and the residue was then distilled at reduced pressure to give the desired sulfonyl isocyanate as a clear colorless oil. For examples of products obtained by this method see Table II.

Owing to the extreme reactivity of the sulfonyl isocyanates, elemental analyses of these compounds were not obtained; however, that these products are indeed sulfonyl isocyanates is shown by their characteristic infrared spectra.

Isolation of N,N'-Bis(sulfonyl)oxamides.—The mixtures of Supercel and crystalline by-products from the above procedures were each slurried in a hot solvent of recrystallization and filtered. Upon cooling, colorless crystals of the N,N'-bis(sulfonyl)oxamide formed. In each case the product was characterized by its melting point and infrared spectrum and was analyzed. For examples of compounds isolated by this process see Table III. No attempt was made to recover quantitatively these and other possible by-products.

Sulfonylureas from Sulfonyl Isocyanates.—A round-bottom flask was charged with a solution of 0.01 mole of the appropriate sulfonyl isocyanate in 10 ml. of dry benzene. With cooling in an ice bath and stirring, the solution in the flask was treated slowly with a solution of 0.01 mole of the appropriate amine in 10 ml. of dry benzene. After the addition was complete the reaction mixture was allowed to warm to room temperature; the volatile components were then evaporated under reduced pressure to give usually an oil. The oil was taken up in methylene chloride and washed successively with 1 *N* HCl and water. The organic phase was then dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallized to give the product as colorless crystals. For examples of products obtained by this procedure see Table IV.

N-Sulfonylcarbamate Esters.—The procedure was essentially the same as that above except that 0.01 mole of the appropriate alcohol was substituted for the amine, and the wash with 1 *N* HCl was omitted. See Table V for N-sulfamylcarbamates made by this method.

Acknowledgments.—The technical assistance of Messrs. Richard B. James and Frederic Smith is gratefully acknowledged. The authors also wish to thank Professor E. J. Corey for helpful discussions during the course of this work.

Sulfanilamido-*s*-triazines. I. Synthesis of 2-Sulfanilamido-4,6-diethyl-*s*-triazine and Related Compounds

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A series of 2-sulfanilamido-4,6-disubstituted *s*-triazines was prepared by nucleophilic displacement of methoxy groups from 2-methoxy-4,6-disubstituted *s*-triazines with sulfanilamide anion. 2-Sulfanilamido-4,6-diethoxy-*s*-triazine was only obtainable by acid-catalyzed nucleophilic substitution of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine. 2-Sulfanilamido-4,6-diethyl-*s*-triazine has high antibacterial activity, good aqueous solubility, and other properties suitable to its use as a medicinal agent.

Previous attempts to prepare sulfanilamido-*s*-triazine *via* sulfonylation of 2-amino-*s*-triazine have been unsuccessful,[2,3] although one derivative, 2-sulfanilamido-4,6-diamino-*s*-triazine, has been obtained[2] by such a reaction. Although the latter had no antibacterial activity,[2] it was not considered to be a satisfactory criterion of activity of the triazine series.[4] In this relatively unexplored class of sulfanilamido heterocycle, the solubility desired in a sulfanilamide drug was expected on the basis of the high aqueous solubility of *s*-triazine[5] and various substituted *s*-triazines[6,7] and of 2-sulfanilamido-4,6-diamino-*s*-triazine.[2,8] No alkyl derivatives of 2-sulfanilamido-*s*-triazine have been reported and, in considering their possible synthesis at the initiation of this work, our attention was directed to methoxytriazines for two reasons. Preparation of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine from trimethyl cyanurate had been reported,[9] and direct ring syntheses of 2-methoxy-4,6-dialkyl-*s*-triazines[10] and of 2-methoxy-*s*-triazine[11] had just been developed in our laboratories.

2-Sulfanilamido-*s*-triazine (IV) and its 4,6-dimethoxy (IX) and 4,6-dimethyl (V) derivatives were prepared

(1) Central Research Division, American Cyanamid Co., Stamford, Conn.

(2) G. W. Anderson, H. E. Faith, H. W. Marson, P. S. Winnek, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 2902 (1942).

(3) H. Bretschneider and W. Klötzer, U. S. Patent 2,774,756 (Dec. 18, 1956). Unpublished results of their own and of other laboratories are summarized by the authors in the public file on this patent: the synthesis of 2-sulfanilamido-*s*-triazine claimed in Swiss Patent 244,348 (1947) could not be repeated by the Swiss patentees or by others.

(4) Amino derivatives of several sulfanilamido heterocycles display poor activity: E. H. Northey, "The Sulfanilamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, pp. 69, 79, 89, 93, etc.

(5) C. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 5646 (1954). *s*-Triazine dissolves readily in water, as a result of hydrogen-bonded solvation, prior to its relatively rapid decomposition.

(6) D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer, I. Hechenbleikner, and D. Holm-Hansen, *ibid.*, **73**, 2984 (1951).

(7) V. P. Wystrach, D. W. Kaiser, and F. C. Schaefer, *ibid.*, **77**, 5915 (1955).

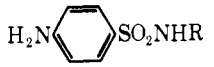
(8) The aqueous solubility here is the result of hydrogen-bonded solvation of the acidic sulfanilamido heterocycle (*cf.* triazine itself[5]) as well as of the anion formed at physiological pH. This diamino derivative is highly soluble in spite of the presence of the amino groups which, in heterocycles, decrease solubility (W. Pfleiderer in "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p. 182) due to hydrogen bonding in the solid state. In this case, the amino groups would decrease solubility also by decreasing the acidity of the sulfanilamidotriazine as a result of their electron-donating character.

(9) H. Bretschneider and W. Klötzer, *Monatsh. Chem.*, **87**, 120 (1956).

(10) F. C. Schaefer, *J. Org. Chem.*, **27**, 3808 (1962).

(11) F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

TABLE I
PROPERTIES OF 2-SULFANILAMIDO-s-TRIAZINES AND REFERENCE SULFA DRUGS



R	R_f[a]	Soly.[b] at 37°, mg./100 ml. (pH 5.6)	Rel. activ. against *S. pyogenes*[c,d]	Rel. activ. against *S. aureus*[c,d] 6 hr. before infect.	Rel. activ. against *S. aureus*[c,d] 1 hr. after infect.
2-s-Triazinyl, Na salt	0.12	...	0.1	I[e]	I[f]
2-(4,6-Me_2-s-triazinyl)	0.24	1300-2000 (5.2)	0.3	I[e]	*Ca.* 0.06
2-(4,6-Me_2-s-triazinyl), N^4-Ac	0.35	250-500	...	...	...
2-(4,6-Me_2-s-triazinyl), N^4-benzylidene	...	...	0.25	I[e]	*Ca.* 0.1
2-(4,6-Me_2-s-triazinyl), N^4-benzyl	...	...	...	0.5	0.2
2-(4,6-Et_2-s-triazinyl)	0.44	100 (5.9)[g]	2-3	5	2
2-(4,6-Et_2-s-triazinyl), N^4-Ac	0.67	200-400[h]	...	...	...
2-[4,6-(*n*-$Pr)_2$-s-triazinyl]	0.69	100-200	1	2	0.5
2-[4,6-(*n*-$Pr)_2$-s-triazinyl], N^4-Ac	0.64	100-200	...	...	...
2-(4-CH_3O-6-*n*-Pr-s-triazinyl)	0.59	250-500 (5.7)	...	I[e]	I[i]
2-[4,6-$(CH_3O)_2$-s-triazinyl][j]	0.30	250-500	0.08	I[e]	I[f]
2-[4,6-$(CH_3O)_2$-s-triazinyl], N^4-Ac[k]	...	250-500	...	...	...
2-[4,6-$(CH_3O)_2$-s-triazinyl], N^4-benzylidene	...	...	I[i]	I[e]	I[l]
2-[4,6-$(CH_3O)_2$-s-triazinyl], N^4-benzyl	...	...	...	I[e]	I[l]
2-[4,6-$(EtO)_2$-s-triazinyl]	0.52[m]	125-250 (5.8)	I[n]	*Ca.* 0.1	I[l]
5-(3,4-Me_2-isoxazolyl)[o]	...	109 (5.5)	1.0 (std.)[c]	1.0 (std.)[c,p]	1.0 (std.)[c]
5-(3,4-Me_2-isoxazolyl), N^4-Ac	...	80 (5.5)	...	...	...

[a] The paper chromatogram was developed with the top phase of a 9:1:8 butanol–concentrated ammonia–water system.[15] Sulfanilamide drugs are detected by diazotization and coupling with spray reagents[15] or by their quenching of the paper's ultraviolet fluorescence; the N^4-acetyl derivatives fluoresce more strongly than the paper. [b] Solubility in 0.1 *M* acetate buffer (initial pH 6.0) was determined by the rough visual method described previously.[15] The final pH, if other than 5.6, is given in parentheses. [c] Activity is relative to that of 5-sulfanilamido-3,4-dimethylisoxazole taken as unity. [d] We wish to thank G. S. Redin, M. E. McCoy, E. Ewald, and N. A. Kuck for permission to quote this portion of their data[12] obtained by published procedures: *Streptococcus pyogenes* C203, drug-diet administration, H. J. White, B. C. Wadsworth, G. S. Redin, and A. J. Gentile, *Antibiot. Chemotherapy*, **2,** 659 (1952); *Staphylococcus aureus*, strain Smith, dosage by single oral tubing, G. S. Redin and M. E. McCoy, *Chemotherapia*, **4,** 386 (1962). [e] Inactive at the very high dosage (1280–2560 mg./kg.) required to demonstrate activity of the standard under these conditions. [f] Inactive at 12 times the ED_{50} of the standard. The activity observed on oral dosage of sulfanilamido-s-triazine is at least partly due to its decomposition to sulfanilylguanidine. [g] In normal human urine, solubility[18] is 200 mg. % at pH 6 and >1000 mg. % at pH 7. [h] In normal human urine, solubility[18] is 650 mg. % at pH 6 and >5000 mg. % at pH 7. [i] Inactive at four times the ED_{50} of the standard. [j] Prepared in 65% yield in 18 hr. by the reaction in Chart I; anhydrous m.p. 163–164° (cor.) *vs.* lit.[9] 169–170°; hydrate m.p. 138–140° (cor.) *vs.* lit.[9] 140–142°. [k] Acetylation by the method described for the diethyl analog; m.p. 216–217° (cor.) *vs.* lit.[9] m.p. 210–212°. [l] Inactive at eight times the ED_{50} of the standard. [m] Sulfanilamide and this compound have essentially the same R_f in the usual system[a] so a system (18:1:1:16 butanol–ammonia–acetic acid–water) was devised to distinguish them: sulfanilamide, R_f 0.51; 2-sulfanilamido-4,6-diethoxy-s-triazine, R_f 0.87; dimethoxy analog, R_f 0.82. [n] Inactive at two times the ED_{50} of the standard. [o] R. J. Schnitzer, R. H. K. Foster, N. Ercoli, G. Soo-Hoo, C. N. Mangieri, and M. D. Roe, *J. Pharmacol. Exptl. Therap.*, **88,** 47 (1946); H. M. Wuest and M. Hoffer, U. S. Patent 2,430,094 (1947); *Chem. Abstr.*, **42,** 1610 (1948). [p] The ED_{50} of the standard is a rough estimate since doses in the 1280–2560-mg./kg. range are required to obtain significant but less than 100% survival.

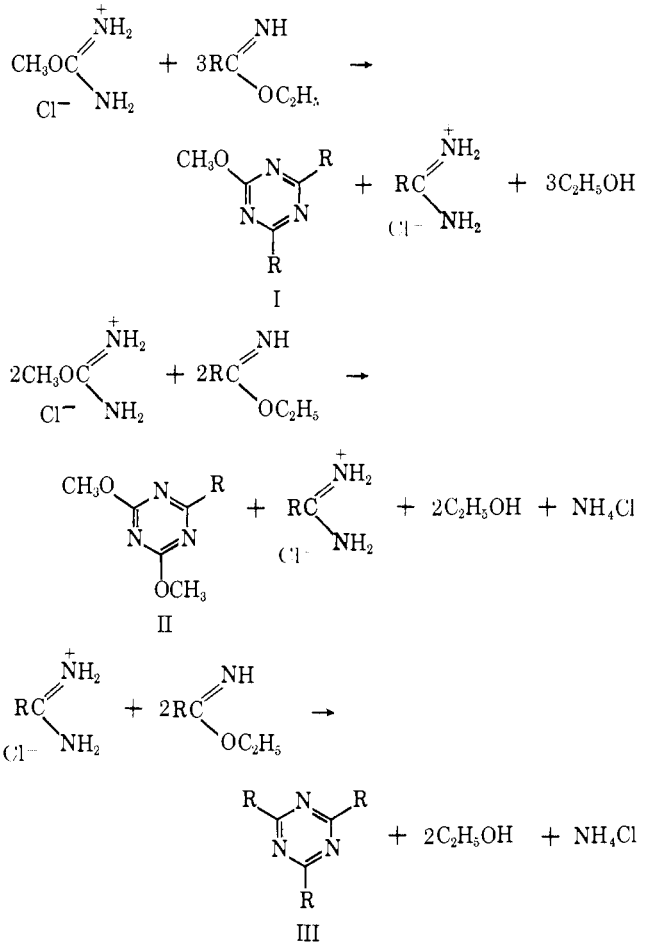
first and were found[12] to have low activity against streptococcal, staphylococcal, and pasturella infections in mice when administered orally as a single dose or in a drug–diet mixture. To ascertain whether this low oral activity was due to poor absorption and/or rapid excretion or, alternatively, was due to low intrinsic activity of sulfanilamido-s-triazines, the activity was measured[13] on the basis of attained blood concentration. The activity of IX was about one-half that of 2-sulfanilamidopyrimidine on the basis of concentration in the blood, while V had activity equal to or greater than that of this standard. This high intrinsic activity coupled with the exceptionally high solubility of these sulfanilamido-s-triazines and their N^4-acetyl derivatives encouraged further work designed to increase blood concentrations following oral administration. Alteration of the pharmacological properties so as to achieve higher and better maintained blood levels was then sought in three ways: lengthening the alkyl chains, increasing the size of the alkoxy groups, and formation of regenerable derivatives such as N^4-benzal and N^4-benzyl. Of these three types of modification, only the first produced analogs with more desirable properties (Table I).

The methoxydialkyl-s-triazine intermediates (I) were prepared as shown in Chart I from 3 moles of alkanoic acid imidate and 1 mole of O-methylisourea hydrochloride. The rate of ring closure decreased with increased size of the alkyl group, occurring spontaneously at 20° when R was methyl and in a few hours at 78–95° with the ethyl and *n*-propyl analogs. Formation of some dimethoxymonoalkyl-s-triazine (II) was observed in each case (*cf.* Table III) and is thus a more general side reaction in these cyclizations than indicated by earlier results.[10] The amount of this by-product was substantially greater (*ca.* 15% of the total) when R was *n*-propyl than when R was methyl or ethyl (4–5% of the total). In all three cases, the trialkyl-s-

(12) Results kindly furnished by G. S. Redin, E. McCoy, E. Ewald, and N. A. Kuck of the Experimental Therapeutics Research Section of these laboratories. The group of gram-negative and gram-positive infections studied included *Streptococcus pyogenes* C203, *Pasteurella multocida* 310, *Staphylococcus aureus* (Smith), *Klebsiella pneumoniae* AD, *Diplococcus pneumoniae* SVI, and *Escherichia coli* UC311.

(13) Determined by Mrs. N. A. Kuck of the Experimental Therapeutics Research Section of these laboratories. The maintained blood concentration required for 50% survival was ascertained for comparison with 2-sulfanilamidopyrimidine.

Chart I



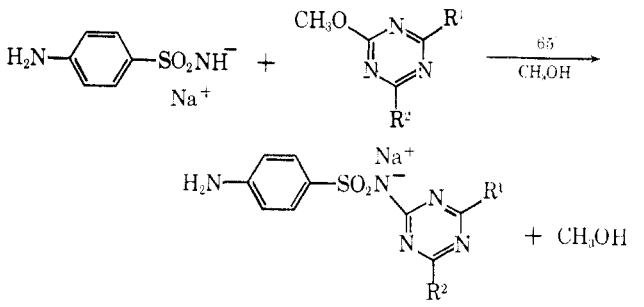
triazine (III) comprised 20–25% of the material isolated and characterized. Variations in the cyclization conditions were made in attempts to form either 4,6-diethyl-2-methoxy-*s*-triazine or 2,4-dimethoxy-6-ethyl-*s*-triazine preferentially. A temperature of 65° (16 hr.) compared with 95° (1.5 hr.) favored the mono relative to the dimethoxy derivative. A 1:2 molar ratio of imidate–isourea did not change the ratio of mono to dimethoxy derivative but increased the yield of both at the expense of triethyl-*s*-triazine. The trialkyltriazines (III) can be formed by intervention of the by-product amidine, as indicated in Chart I, or by trimerization of the imidate catalyzed by the isourea or amidine salts.

Ethoxytriazine by-products from alkoxy exchange in the O-methylisourea or in the methoxytriazines could be formed by the ethanol produced, acting under the influence of the unreacted basic imidate. However, gas–liquid partition chromatography of the cyclization mixture (Chart I) failed to detect 4,6-diethyl-2-ethoxy-*s*-triazine. Alkoxy exchange in 4,6-diethyl-2-methoxy-*s*-triazine does occur in stronger base: sodium ethoxide readily produced the 4,6-diethyl-2-ethoxy-*s*-triazine needed as a standard.

2-Methoxy-*s*-triazine (I, R = H) was obtained by the ring-opening and reclosure reaction[11] of *s*-triazine with O-methylisourea hydrochloride.

The series of monomethoxytriazines shown in Chart II was found to react in boiling methanol with equimolar amounts of sodium sulfanilamide to produce sulfanilamido-*s*-triazines (Table II) as indicated. The

Chart II



IV, $R^1 = R^2 = H$
V, $R^1 = R^2 = CH_3$
VI, $R^1 = R^2 = C_2H_5$
VII, $R^1 = R^2 = n\text{-}C_3H_7$
VIII, $R^1 = CH_3O$; $R^2 = n\text{-}C_3H_7$
IX, $R^1 = R^2 = CH_3O$

reaction was rather slow when anhydrous solvent was distilled directly into the reaction flask. However, the product was formed much more rapidly, though in lower yield because of hydrolytic side reactions, when a small amount of water was present.[14] The sulfonamide salts crystallized in high yield from the reaction mixtures or were directly converted to the sulfonamides with dilute acid. A small amount of N^1- and N^4-methylation of sulfanilamide occurred in the case of trimethyl cyanurate and the amount increased in reactions carried out above 65°. Such methylation was inappreciable with the methoxydialkyl-*s*-triazines at 65°. This type of side reaction and effect of temperature had been previously observed[15] in nucleophilic displacements by sulfanilamide anion of various substituents on pyrimidines and pyridazines bearing methoxy groups. No polysubstitution by sodium sulfanilamide was observed with trimethyl cyanurate or 2,4-dimethoxy-6-alkyl-*s*-triazines.

The methoxy-dialkyl-*s*-triazines (I), isolated by vacuum distillation for use in these reactions, were shown by g.l.p.c. (*cf.* Table III) to contain appreciable amounts of the by-products (II and III). The trialkyl-*s*-triazines (III) do not react with sodium sulfanilamide but the dimethoxymonoalkyl by-products (II) yield 2-sulfanilamido-4-methoxy-6-alkyl-*s*-triazines (*e.g.*, VIII in Chart II). However, only in the case of the *n*-propyl compounds was chromatographic separation of the unsymmetrical sulfonamide by-product VIII from the main product VII required.

Another suitable starting material for synthesis of 2-sulfanilamido-4,6-diethyl-*s*-triazine (VI) was 4,6-diethyl-2-trichloromethyl-*s*-triazine.[10] It reacted with sodium sulfanilamide in refluxing methanol but not in dimethyl sulfoxide. The reaction is indirect and proceeds through the more reactive 2-methoxy derivative formed rapidly *in situ*. A similar competitive displacement by the very small amount[16] of more nucleophilic methoxide ion in equilibrium with sodium sulfanilamide in boiling methanol occurred with 2-chloro-4,6-di-

(14) The next paper in this series will report further work on this accelerative effect and a proposed mechanism.

(15) R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, **26**, 2764 (1961).

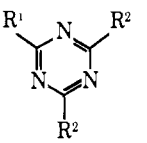
(16) The acid ionization constants in water at 25° are 4×10^{-11} for sulfanilamide [P. H. Bell and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 2905 (1942)] and 3×10^{-16} for methanol [P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960)]. The ratio of sulfanilamide anion to methoxide is about 10,000:1 when one corrects for the 10-fold greater molarity of methanol.

TABLE II
2-SULFANILAMIDO-s-TRIAZINES

Substituent	Yield, %	M.p., °C. (cor.)	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
H, Na salt[a]	49	326–327° dec.	$C_9H_8N_5NaO_2S$	39.6	3.0	25.6	11.7	39.2	3.4	25.4	11.3
4,6-Me_2, Na salt·$2H_2O$	87[b,c]	*d*	$C_{11}H_{12}N_5NaO_2S\cdot 2H_2O$	39.2	4.8	20.8	9.5	39.2	4.9	20.9	9.6
4,6-Me_2	83[e]	194–195[f]	$C_{11}H_{13}N_5O_2S$	47.3	4.7	25.1	11.5	47.4	4.9	24.9	11.6
4,6-Me_2, N^4-Ac	48[e,g]	272–273	$C_{13}H_{15}N_5O_3S$			21.8				22.1	
4,6-Et_2	70	190–190.5	$C_{13}H_{17}N_5O_2S$	50.8	5.6	22.8	10.4	50.6	5.8	22.7	10.3
4,6-Et_2, Na salt	76	292 dec.	$C_{13}H_{16}N_5NaO_2S$	47.4	4.9	21.3	9.7	47.0	5.0	21.2	9.9
4,6-Et_2, N^4-Ac	71[g]	209–211	$C_{15}H_{19}N_5O_3S$	51.6	5.5	20.0	9.2	51.7	5.7	20.1	9.1
4,6-(*n*-Pr)$_2$	28	119.0–119.5[h]	$C_{15}H_{21}N_5O_2S$	53.7	6.3	20.9	9.6	53.4	6.6	20.7	9.8
4,6-(*n*-Pr)$_2$, N^4-Ac·H_2O	53[e,g]	163.0[h]	$C_{17}H_{23}N_5O_3S\cdot H_2O$	51.6	5.9	17.7		51.8	6.0	17.5	
4,6-Me_2, N^4-benzylidene	92	168.5–169.5	$C_{18}H_{17}N_5O_2S$	58.8	4.9	19.1	8.7	58.0	5.0	19.0	8.8
4,6-Me_2, N^4-benzyl	26	187.5–189.5	$C_{18}H_{19}N_5O_2S$	58.5	5.2	19.0		58.5	5.3	18.6	
4,6-(MeO)$_2$, N^4-benzylidene	96[i]	170–172	$C_{18}H_{17}N_5O_4S$	54.1	4.3	17.5	8.0	54.0	4.7	17.2	7.9
4,6-(MeO)$_2$, N^4-benzyl	42[i,j]	172.0–172.5	$C_{18}H_{19}N_5O_4S$	53.9	4.8	17.5		53.6	4.9	17.1	
4,6-(EtO)$_2$	28	134.5–136.0	$C_{13}H_{17}N_5O_4S$	46.0	5.1	20.6	9.5	46.3	5.2	20.5	9.2
4-MeO-6-*n*-Pr	15	110–127	$C_{13}H_{17}N_5O_3S$	48.3	5.3	21.7	9.9	47.9	5.6	21.7	10.2

[a] Hygroscopic. [b] Prepared by the procedure used for the diethyl analog except that a reflux time of 52 hr. was used. Titration indicated 80% completion after 1.8 hr. and 98% after 52 hr., paper chromatography showing only a small increase in product during this period. A preparation heated for 16 hr. gave a 70% yield of isolated salt. [c] Unless special precautions were taken in handling of the reagents and the products, the hygroscopic salt was obtained as the monohydrate (obtained by drying at 100° at 10 mm. or recrystallization from anhydrous ethanol) or dihydrate (by equilibration of the product with air at 65°). [d] The melting point varies from 180–215° for the dihydrate to 260–270° for the anhydrous salt (obtained by drying at 140°, oil pump vacuum). [e] Prepared by the procedures described for the diethyl analog. [f] Isolated initially as a monohydrate (m.p. 100°) which can be dehydrated *in vacuo* (125°) or by recrystallization from ethanol (3.5 ml./g.). [g] The N^4-acetyldipropyl compound was isolated from aqueous solution; the dimethyl and diethyl analogs also form hydrates. [h] With gas evolution. [i] Prepared by the procedures described for the dimethyl analog. [j] Recrystallized from acetonitrile (2 ml./g.).

TABLE III
s-TRIAZINE INTERMEDIATES AND BY-PRODUCTS



Compd. R[1]	Compd. R[2]	Yield, %	B.p. (mm.) or m.p., °C.	G.c. retention[a] time, min.	Infrared (max.),[b] cm.$^{-1}$	Formula	Calcd., % OCH_3	N	Found, % OCH_3	N
C_2H_5	C_2H_5	9	25–26	4.5	1435, 1320[c,d]	$C_9H_{15}N_3$		25.4		24.6
CH_3O	C_2H_5	39	205–210 (760)	16.5	1490, 1365, 1115[d]	$C_8H_{13}N_3O$	9.0	25.1	8.9	24.7
C_2H_5	CH_3O	2.6	51	30	1490, 1360, 1310, 1125[d]	$C_7H_{11}N_3O_2$		24.8		24.5
C_2H_5O	C_2H_5[e]	20	87 (2)	12.5[f]	1485, 1345, 1115[d]	$C_9H_{15}N_3O$	16.0[g]	23.2	15.7[g]	22.8
n-C_3H_7	*n*-C_3H_7	12	220 (760)	10.5[h]	1435, 1335[c,d]	$C_{12}H_{21}N_3$		20.3		19.8
CH_3O	*n*-C_3H_7	34	95–97 (2)	28.5[h]	1485, 1360, 1120[d]	$C_{10}H_{17}N_3O$	7.7	21.5	7.7	21.7
n-C_3H_7	CH_3O	8	220 (760)	45[h]	1490, 1355, 1120[d]	$C_8H_{13}N_3O_2$	16.4	22.9	15.7	22.7
CH_3	CH_3	17	155 (760)	2.5[i,j]	1435, 1340[d]	$C_6H_9N_3O$				
CH_3O	CH_3	62	47–49[k]	5.5[i]	1490, 1370, 1115[d,l]	$C_6H_9N_3O$	10.8		10.6	
CH_3	CH_3O	3.3		9.5[i]	1505, 1360, 1130[d]	$C_6H_9N_3O_2$		27.1		27.6

[a] Determined in a Wilkens Aerograph Master A-100 on a polyethylene glycol column (available commercially as Carbowax 20-M) with a column temperature of 173°, helium flow of 48 cc./min. [b] Measured as films or melts in a Perkin-Elmer Infracord 137 spectrophotometer except for 4,6-dimethoxy-2-methyl-*s*-triazine (solution in CCl_4) and 2,4,6-trimethyl-*s*-triazine (KBr disk). [c] No absorption maximum at 1565 cm.$^{-1}$. [d] The following assignments of absorption maxima also present are made on the basis of published correlations for azines (A. R. Katritzky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p. 274 ff; N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p. 233 ff): ring stretching at 1565, 1550, 1490 (or 1435 in the trialkyls), 1465, 1390; ring breathing at 1060–1080 and 995; ring bending at 815–845 cm.$^{-1}$. Stretching of the triazine–O linkage absorbs at 1360 and of the alkyl–O bond at 1115–1130 cm.$^{-1}$. Alkyl vibration modes lead to absorption at 3050–2900 (triplet), 1465, 1390, 1200, 1030, and 930 cm.$^{-1}$. [e] Prepared by refluxing a solution of the 2-methoxy analog in ethanolic sodium ethoxide for 2 hr. [f] With helium flow of 52 cc./min.; retention time of 2-methoxy analog was 10.5 min. in the same run. [g] OC_2H_5 value. [h] Column temperature 172°, helium flow 48 cc./min. [i] A silicone column at 174° was used with helium flow of 46 cc./min.; this column gave poor resolution of the mixtures in the case of the ethyl and *n*-propyl homologs. [j] Identical in infrared spectrum with 2,4,6-trimethyl-*s*-triazine prepared[18] by trimerization of ethyl acetimidate. [k] B.p. 80° (3 mm.). [l] No absorption maximum at 1465 cm.$^{-1}$.

methoxy-*s*-triazine, forming sulfanilamide and trimethyl cyanurate. Since these products do not react under these conditions, 2-sulfanilamido-4,6-dimethoxy-*s*-triazine was formed in a second reaction step only when additional methoxide was added to regenerate sulfanilamide anion.

In contrast to the facile reaction of sodium sulfanilamide with methoxy-*s*-triazines in methanol, displacement of an ethoxy group from triethyl cyanurate failed in refluxing ethanol (120 hr.) in spite of the higher temperature. In order to determine the effect of the much lower solubility of sodium sulfanilamide in ethanol on the decrease in reactivity, more concentrated reactions in the more effective solvents dimethyl sulfoxide and N,N-dimethylacetamide were tried under various conditions (60–120° for 45–95 hr.) but without success.

Reactions of sodium sulfanilamide were attempted with 4,6-diethoxy-2-methoxy-*s*-triazine formed *in situ* from triethoxy-*s*-triazine and 1 mole of methanol in dimethyl sulfoxide, N,N-dimethylacetamide, or ethanol. However, formation of the desired 2-sulfanilamido-4,6-diethoxy-*s*-triazine was slow and substantial amounts of the products from 2,4-dimethoxy-6-ethoxy- and 2,4,6-trimethoxy-*s*-triazines were also produced. When the reaction solvent was methanol, the sulfanilamides corresponding to these two triazines were formed rapidly and in considerable amounts. Alkoxy exchange in 2-sulfanilamido-4,6-dimethoxy-*s*-triazine (IX) failed in refluxing ethanol or ethanolic ethoxide (50 hr.) but was effected successfully under acid catalysis (*p*-toluenesulfonic acid). Similar acid-catalyzed reactions of IX in 1-propanol at 98° and in 1-butanol at 118° proceeded more slowly and resulted in extensive side reactions.

The sulfanilamido-*s*-triazines show a remarkable variation of stability with 4,6-disubstitution. 2-Sulfanilamido-*s*-triazine was decomposed immediately upon adjusting an aqueous solution of the sodium salt to pH 2 (80% decomposed at 0° and 100% at 20°) while the sodium salt was stable in water at 20° and at 100°. In contrast, the 4,6-diethyl analog can be precipitated without decomposition by acidification of an aqueous solution of its sodium salt. However, this analog also showed susceptibility to acid-catalyzed decomposition. An aqueous solution of 2-sulfanilamido-4,6-diethyl-*s*-triazine was about 90% decomposed at the prevailing pH of 4 by 8-hr. boiling. After 20 hr. its sodium salt was only slightly decomposed by boiling in water at pH 7 or 10 and only a trace was decomposed in anhydrous or aqueous methanol at the boiling point. The sodium salt of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine was stable for 20 hr. in boiling methanol or water, in contrast to an earlier report.[9] The nature of the products of acid-catalyzed ring cleavage and its mechanism will be discussed in a subsequent publication. The rapid decomposition of 2-sulfanilamido-*s*-triazine in dilute acid makes it likely that all or part of its antibacterial activity after oral dosage is due to its decomposition products. The stability of 2-sulfanilamido-4,6-diethyl-*s*-triazine is quite adequate for oral dosage without occurrence of decomposition.

Comparison of 2-sulfanilamido-4,6-diethyl-*s*-triazine with its close relatives can be summarized as follows. The dimethyl analog is less active, more soluble, and gives poorer maintenance of blood level. The di-*n*-propyl compound is less active, less soluble, and gives reasonably good maintenance of blood level. The dimethoxy analog shows less activity and poorer maintenance of blood levels and is somewhat more soluble. The closely related 4-ethyl-6-methoxy and 4-ethyl-6-methyl analogs[17] were both only one-sixteenth as active as the 4,6-diethyl compound against the staphylococcal infection in mice.[12]

2-Sulfanilamido-4,6-diethyl-*s*-triazine (generic name, sulfasymazine) is more active than any of the other sulfanilamido-*s*-triazines (Table I) against lethal bacterial infections in mice.[12] Its solubility in buffers at urinary pH (Table I) and in urine[18] is high and its even more soluble N^4-acetyl derivative has a greater solubility than this derivative of other sulfa drugs. In tests[12,19] designed to estimate relative speed of elimination in mice and in dogs, both 4,6-dimethyl- and 4,6-dimethoxy-2-sulfanilamido-*s*-triazine had rapid rates of excretion relative to the diethyl analog. In both species and in man, persistence of therapeutic blood levels for 24 hr. is achieved with a single dose of sulfasymazine. If desired, its rate of excretion can be drastically increased[19] by administration of bicarbonate to alkalinize the urine. 2-Sulfanilamido-4,6-diethyl-*s*-triazine (VI) is acidic[20] ($pK_a = 5.4$) due to the strong electron-attracting character of the heterocyclic ring and, consequently, 20% solutions of its sodium salt in water are almost neutral. This sulfanilamido heterocycle is suitable for use in liquid pharmaceutical preparations since it is tasteless. Curiously, the dimethyl analog was bitter to half the members of a taste panel and tasteless to the other half. Sulfasymazine is well absorbed after oral dosage in dogs and in man and only a small fraction is inactivated by metabolism to N^4-acetyl and glucuronide derivatives.[21] 2-Sulfanilamido-4,6-diethyl-*s*-triazine thus possesses a new and especially favorable combination of properties desirable in a sulfanilamide drug. Detailed reports on the antibacterial and pharmacological properties of 2-sulfanilamido-4,6-diethyl-*s*-triazine are being published separately.

Experimental Section

All melting points are corrected and were determined in a modified Hershberg apparatus.

2,4-Diethyl-6-methoxy-*s*-triazine.—A mixture of 225 g. (1.85 moles) of ethyl propionimidate[22,23] (80% pure by alkalimetric titration) and 68.3 g. (0.618 mole) of methylisourea hydrochloride[24] was heated at reflux with stirring for 1.5 hr. On cooling the reaction mixture overnight, white propionamidine hydrochloride (45 g.) crystallized. Distillation of the filtrate gave 53.9 g. of a mixture of 2,4-diethyl-6-methoxy-*s*-triazine and by-products (see chromatographic analysis in Table III) boiling at 58–64° (0.75 mm.). This was used directly for reaction with sodium sulfanilamide.

The distillation residue (50 g.) was mainly propionamidine hydrochloride.[25] The two crops were combined and recrystallized from isopropyl alcohol to yield 37 g. of white by-product which melted at 141–142° after recrystallization from 60% acetic acid.

Anal. Calcd. for $C_5H_{11}ClN_2$: C, 33.2; H, 7.4; N, 25.8. Found: C, 33.5; H, 8.4; N, 25.6.

4,6-Di-*n*-propyl-2-methoxy-*s*-triazine was prepared on a 1 *M* scale in the same manner using ethyl butyrinidate [b.p. 41° (20 mm.)[23,26]] and a reflux time of 6.5 hr., after which time alkalimetric titration indicated 98% completion. Chromatographic analysis is given in Table III.

Sodium 2-Sulfanilamido-4,6-diethyl-*s*-triazine.—A solution of 50 g. (0.22 mole) of 2,4-diethyl-6-methoxy-*s*-triazine (75% pure by g.l.p.c.) and 48.5 g. (0.25 mole) of anhydrous sodium sulfanilamide in 250 ml. of anhydrous methanol was refluxed for 70 hr. Titrations with 0.02 *N* HCl (phenolphthalein) indicated 84%

(17) Paper by Dr. F. Markley and associates, Organic Chemicals Division, American Cyanamid Co., Bound Brook, N. J., in preparation.

(18) Data kindly furnished by H. A. Floyd of the Experimental Therapeutics Research Section of these laboratories.

(19) These data were obtained by Dr. R. R. Roepke and associates of the Experimental Therapeutics Research Section of these laboratories.

(20) Determined in 30% acetone by L. Brancone and associates; the N^4-acetyl derivative has a pK_a of 5.1.

(21) For permission to quote their data, we are indebted to Dr. R. D. Schaefer of the Clinical Research Department and to Dr. R. R. Roepke of the Experimental Therapeutics Research Section of these laboratories.

(22) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

(23) S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **64**, 1827 (1942).

(24) R. H. McKee, *Am. Chem. J.*, **26**, 244 (1901); an alternative salt is the *p*-toluenesulfonate [J. W. Janus, *J. Chem. Soc.*, 3551 (1955)].

(25) A. Pinner, *Ber.*, **17**, 178 (1884), reported m.p. 129°.

(26) A. Pinner in "Die Imidoaether und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, 1892, p. 30.

completion after 22.5 hr. and 91% after 70 hr. On concentrating to half-volume and cooling, the white sodium salt was obtained (55.0 g., anhydrous after 4 hr. *in vacuo* at 80°, m.p. 292° dec.), containing a trace of sodium sulfanilamide by paper chromatography.

Paper chromatography[15] of aliquots of a refluxing solution of 4,6-diethyl-2-trichloromethyl-*s*-triazine (0.42 g., 1.7 mmoles) and sodium sulfanilamide (0.97 g., 5.0 mmoles) in 5 ml. of reagent grade methanol demonstrated the formation of 2-sulfanilamido-4,6-diethyl-*s*-triazine. The amount steadily increased with time, about 50% being formed in 12 hr.

2-Sulfanilamido-4,6-diethyl-*s*-triazine.—A solution of 55.0 g. (0.167 mole) of sodium 2-sulfanilamido-4,6-diethyl-*s*-triazine in 175 ml. of water was taken to pH 3 by the dropwise addition of 25 ml. of 6 *N* HCl. The white precipitate (49.1 g., 96%), melting at 186.5–187.5°, was recrystallized from ethanol (11 ml./g.).

Chromatographic purification, which was performed on the dipropyl reaction product, was not required for the dimethyl and diethyl analogs since the amount of 2,4-dimethoxy-6-alkyl-*s*-triazine by-product present in the triazine reagent was substantially lower.

2-(N^4-Acetylsulfanilamido)-4,6-diethyl-*s*-triazine.—Acetic anhydride (43.9 g., 0.430 mole) was added quickly with vigorous stirring to a finely powdered slurry of 22.0 g. (0.072 mole) of 2-sulfanilamido-4,6-diethyl-*s*-triazine in 220 ml. of glacial acetic acid. The mixture was heated on the steam bath for a few minutes to give a colorless solution, which was diluted with 2 vol. of water and chilled to yield white crystals (29.0 g., m.p. 164–166° raised to about 190° by vacuum drying). On recrystallization from 170 ml. of 1-butanol, a solvate (m.p. 164–168° raised to 196° by vacuum drying) was apparently formed by the product, which melted at 209–211° after boiling 30 min. with water and drying. Material melting at 165–170° was obtained by recrystallization from methanol, ethanol, acetonitrile, or ethylene dichloride.

2-Sulfanilamido-4,6-diethoxy-*s*-triazine.—A solution of 15.6 g. (0.05 mole) of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine and 0.3 g. (0.0016 mole) *p*-toluenesulfonic acid monohydrate in 500 ml. of absolute ethanol was refluxed for 264 hr. According to paper chromatographic examination (see footnote *m*, Table I) after 72 hr., the reaction had attained approximately 65% completion. Paper chromatograms after 240 and 264 hr. both showed that 65% conversion to the diethoxy compound had been achieved. Also present was 15% of material (R_f 0.42) which was a major component after 24–52 hr. and is therefore presumed to be the intermediate 2-sulfanilamido-4-ethoxy-6-methoxy-*s*-triazine. About 20% decomposition to sulfanilamide had occurred at 264 hr. The reaction mixture was concentrated under vacuum to one-half volume and added with stirring to 750 ml. of water to precipitate 6.2 g. of product which melted at 135–136° after recrystallization from 31 ml. of 1:1 ethanol-hexane.

An experiment using ten times as much acid catalyst gave a complex mixture of products; one carried out at 20° (96 hr., 0.2 *N* HCl) produced no reaction.

2-Sulfanilamido-4,6-di-*n*-propyl-*s*-triazine and 2-sulfanilamido-4-methoxy-6-*n*-propyl-*s*-triazine were prepared in the same manner as the 4,6-diethyl analog using starting material which contained 14% of 2,4-dimethoxy-6-*n*-propyl-*s*-triazine and 61% of 4,6-di-*n*-propyl-2-methoxy-*s*-triazine. After acidification, the mixture was separated with a 2:3:3:2 heptane–ethyl acetate–methanol–water system on a column of diatomaceous earth.

2-(N^4-Benzylidenesulfanilamido)-4,6-dimethyl-*s*-triazine.—A solution of 21.6 g. (0.204 mole) of benzaldehyde in 20 ml. of ethanol was added with stirring to 19.0 g. (0.068 mole) of 2-sulfanilamido-4,6-dimethyl-*s*-triazine in 190 ml. of boiling ethanol. After refluxing for 15 min., the solution was evaporated to a yellow crystalline residue (23.1 g.) melting at 168.5–169.5°, unchanged by recrystallization from acetonitrile.

2-(N^4-Benzylsulfanilamido)-4,6-dimethyl-*s*-triazine.—A solution of 8.5 g. (0.0232 mole) of 2-(N^4-benzylidenesulfanilamido)-4,6-dimethyl-*s*-triazine in 135 ml. of dioxane together with 4.0 g. of 10% palladium on charcoal was placed in a Parr hydrogenator under hydrogen pressure of 3 kg./cm.^{2}. When the theoretical amount of hydrogen was absorbed (about 8 min.), the mixture was filtered, diluted with 3 vol. of water, and chilled. The solid (5.5 g.) was recrystallized from 33 ml. of boiling 1-butanol. Debenzylation results if the reduction is not interrupted.

Sodium 2-Sulfanilamido-*s*-triazine.—A solution of 85.5 g. (0.44 mole) of sodium sulfanilamide and 49.0 g. (0.44 mole) of 2-methoxy-*s*-triazine[11] in 325 ml. of methanol was refluxed for 3 hr. The mixture was seeded with a small amount of sodium 2-sulfanilamido-*s*-triazine to effect crystallization of the product which was filtered hot, washed, and dried at 110° (58 g., m.p. 310–315° dec.) and then recrystallized from methanol (4 ml./g.).

Stability of 2-Sulfanilamido-*s*-triazines.—The extent of decomposition was estimated by paper chromatography. Sodium 2-sulfanilamido-*s*-triazine was unchanged in aqueous solution at 20° at or 100° for 1 hr. Isolation or neutralization *immediately* after acidification to pH 2 gave material which was 80% decomposed if acidification was at 0° and 100% decomposed if at 20°. The nature of the decomposition will be reported shortly.

Refluxing a methanolic 0.05 *M* solution of sodium 2-sulfanilamido-4,6-diethyl-*s*-triazine for 20 hr. produced 1% or less of decomposition, and in aqueous or in ammoniacal (pH 10) solution about 5% decomposition occurred. Boiling an aqueous 0.025 *M* solution (pH 4) of the sulfonamide itself produced about 60% decomposition in 1.5 hr., 85% in 5 hr., and about 95% in 8 hr.

The decomposition of 2-sulfanilamido-4,6-dimethoxy-*s*-triazine in acidic ethanol is described above in the preparation of the 4,6-diethoxy analog. The sodium salt, after 20-hr. boiling in water or in methanol, showed only a trace of decomposition.

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