being on the side of the cyclopropane ring remote from these protons.

anti-**2′-Aminospiro(1,4-benzodioxan-2,1′-cyclopropane) (9c).**—The *anti* acid above was converted *via* the mixed carboxylic–carbonic anhydride procedure[3a] to the azide, which on pyrolysis gave the isocyanate. Alkaline hydrolysis[3a] of the isocyanate gave the amine (45%), isolated as the hydrochloride, mp 211–213° (from 2-propanol).

Anal. Calcd for $C_{10}H_{11}NO_2 \cdot HCl$: C, 56.20; H, 5.62; Cl, 16.60. Found: C, 56.27; H, 5.67; Cl, 16.45.

N,N′-Bis[2′-*syn*-spiro(1,4-benzodioxan-2,1′-cyclopropyl)]-urea.—The *syn* acid was converted *via* the mixed carboxylic–carbonic anhydride procedure[3a] to the azide. This was pyrolyzed to give the crude isocyanate, which was hydrolyzed with alkali.[3a] When cold, the reaction mixture was filtered. From the filtrate, the amine hydrochloride (6%) was isolated by extraction with dilute HCl. The solid filtered from the reaction was recrystallized from ethanol to give the urea (53%): mp 213–216°; ν_{max} 3370, 1645 cm^{-1}.

Anal. Calcd for $C_{21}H_{20}N_2O_5$: N, 7.37. Found: N, 7.40.

syn-**2′-Aminospiro(1,4-benzodioxan-2,1′-cyclopropane) (8c).**

A.—The N,N′-disubstituted urea above was treated with 2 equiv of phthalic anhydride according to Manske.[10] After trituration with aqueous $NaHCO_3$, the product was recrystallized from ethanol to give *syn*-**2′-N-phthalimidospiro(1,4-benzodioxan-2,1′-cyclopropane)** (69%): mp 164–167°; ν_{max} 1790, 1745, 1730 cm^{-1}.

A suspension of this derivative in ethanol was treated under reflux with an equimolar quantity of hydrazine for 15 min. The hot reaction mixture was acidified with HCl and, when cold, it was filtered. The filtrate was basified and extracted with ether, and the ether extract was treated with gaseous HCl to precipitate the amine hydrochloride (79%), mp 220–222°.

B.—Alternatively, the crude isocyanate obtained on pyrolysis of the azide derived from the *syn* acid was hydrolyzed with concentrated HCl[3] to give in one step the amine hydrochloride (62% from the acid), mp 220–222°.

Anal. Calcd for $C_{10}H_{11}NO_2 \cdot HCl$: C, 56.20; H, 5.66; Cl, 16.60. Found: C, 56.35; H, 5.61; Cl, 16.44.

anti-**2′-Guanidinospiro(1,4-benzodioxan-2,1′-cyclopropane) Sulfate (2b).**—The free *anti* amine, isolated from the hydrochloride, mp 211–213°, was heated at 90° for 5 hr with 1-amidino-3,5-dimethylpyrazole sulfate[1] (1 equiv) in water. The product (13%) was obtained by filtration from the cooled reaction mixture and subsequent recrystallization from water. It had mp 288–290°.

Anal. Calcd for $C_{11}H_{13}N_3O_2 \cdot 0.5H_2SO_4$: C, 49.25; H, 5.26; N, 15.67. Found: C, 49.52; H, 5.59; N, 15.58.

syn-**2′-Guanidinospiro(1,4-benzodioxan-2,1′-cyclopropane) Tosylate (2a).**—The *syn* amine hydrochloride (mp 220–222°) was converted to the tosylate salt by treatment of an aqueous solution of the hydrochloride with 1 equiv of *p*-toluenesulfonic acid. The tosylate salt was refluxed in 95% ethanol with cyanamide (10 equiv) for 16 hr. The mixture was concentrated under vacuum and treated with ether. The precipitated material was recrystallized from water to give the product (80%), mp 175–177°.

Anal. Calcd for $C_{11}H_{13}N_3O_2 \cdot C_7H_8O_3S$: C, 55.23; H, 5.37; N, 10.73. Found: C, 55.09; H, 5.07; N, 10.51.

Acknowledgment.—We wish to thank our colleagues in the Pharmacology Department of Pfizer Ltd. for supplying us with the biological results reported in this paper, Mr. P. R. Wood for the microanalyses, and Mr. J. Zoro for his competent assistance. Also, we acknowledge the help of Dr. J. Feeney of Varian Associates in obtaining a confirmatory 100-Mc/sec spectrum on compound **3** (R = CH_3).

as-Triazines. I. 5-Sulfanilamido Derivatives and Intermediates[1]

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A series of *as*-triazines bearing 6-alkyl (or hydrogen) and 3- and/or 5-chloro, -methoxy, -methylthio, -oxo, or -thioxo groups has been prepared. The 5 position has been established as more reactive than the 3 toward nucleophilic substitution with sulfanilamide anion. The 5-sulfanilamido-*as*-triazines have good solubility but have little or no oral antibacterial activity against infections in mice.

Until the present study, exploration of the sulfanilamido-*as*-triazine series was extremely limited, only two examples of this series having been recorded.[3,4] These were 3-sulfanilamido-*as*-triazines bearing benzo[3] or phenyl[4] substituents in the 5 and 6 positions. Simpler sulfanilamido-*as*-triazines appeared accessible through 3-amino-,[5] 3-amino-5-methyl-,[6] and 3-amino-5,6-dimethyl-*as*-triazines.[5] However, attempts to couple these amines with *p*-nitro- or *p*-acetylaminobenzenesulfonyl chloride gave complex mixtures which yielded none of the desired products. Although 3-amino-5,6-diphenyl- and 3-aminobenzo-*as*-triazines have been used successfully in such reactions, the alkyl analogs are unstable to these conditions and yield water-soluble products, presumably as a result of ring cleavage.

A possible alternative route appeared to be the reaction of a methoxy- or methylthio-*as*-triazine with sodium sulfanilamide, a route which had been employed in the *s*-triazine series.[7] Furthermore, a displacement reaction had been effected with ammonia on 6-methyl-*as*-triazine-3,5-dithione.[8] During the course of our work, examples of methylthio displacements from *as*-triazines by hydrazine[9] and by ammonia were reported.[10] A suitable intermediate for such a reaction appeared to be 5,6-dimethyl-3-methylthio-*as*-triazine, accessible through the corresponding 3-thione. Repetition of

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(3) F. J. Wolf, K. Pfister, 3rd, R. M. Wilson, Jr., and C. A. Robinson, *J. Am. Chem. Soc.*, **76**, 3551 (1954).

(4) G. W. Raiziss, L. W. Clemence, and M. Freifelder, *ibid.*, **63**, 2739 (1941).

(5) J. G. Erickson, *ibid.*, **74**, 4706 (1952).

(6) Prepared by the method of ref 3 by Drs. J. Semb and R. B. Angier of these laboratories; mp 180°. *Anal.* Calcd for $C_4H_6N_4$: N, 51.0. Found: N, 51.1.

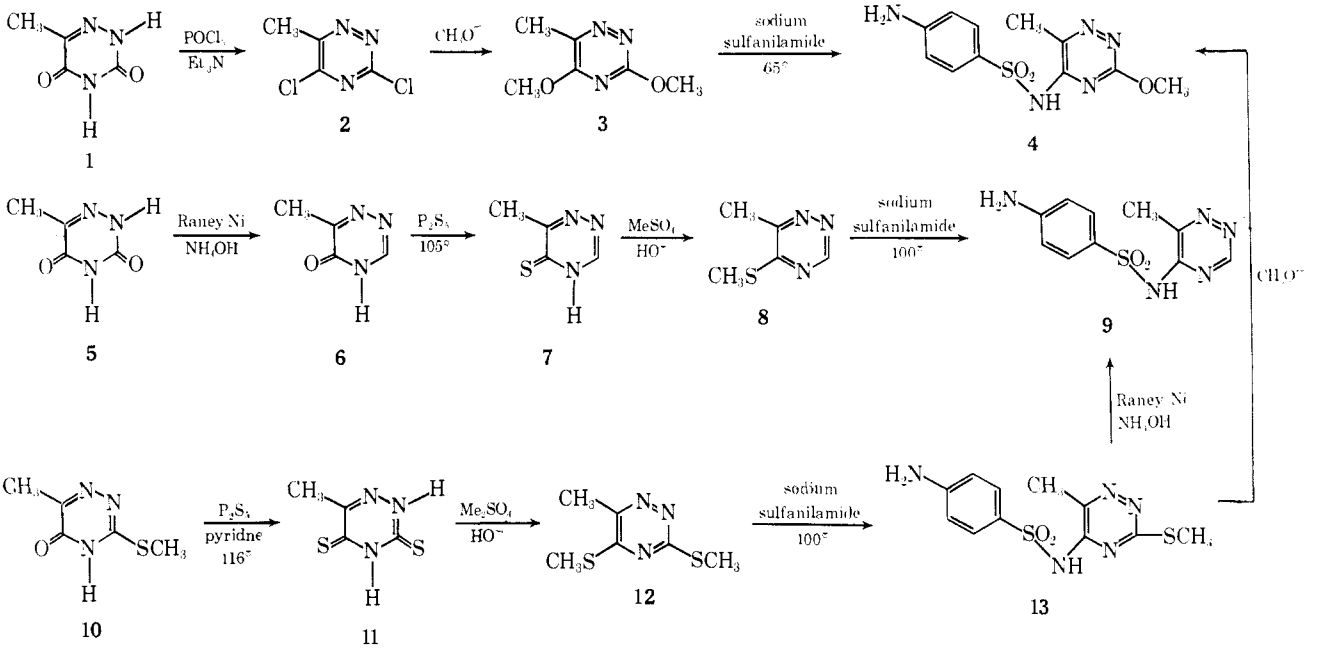
(7) (a) H. Bretschneider and W. Klötzer, *Monatsh.*, **87**, 120 (1956); (b) W. E. Taft, H. M. Krazinski, F. C. Schaefer, and R. G. Shepherd, *J. Med. Chem.*, **8**, 784 (1965).

(8) E. A. Falco, E. Pappas, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 1938 (1956).

(9) D. Libermann and R. Jacquier, *Bull. Soc. Chim. France*, 383 (1961).

(10) Burroughs Wellcome and Co., British Patent 802,122 (1958); *Chem. Abstr.*, **53**, 7216e (1959).

Scheme I



two reported preparations[11,12] of the latter gave products which had somewhat similar properties to those reported, but which proved to be the mono- and bis-thiosemicarbazones of biacetyl. Refluxing the monothiosemicarbazone in aqueous potassium carbonate, or heating it to 180° at atmospheric pressure and under vacuum, failed to effect the desired cyclization.[13]

On completion of these experiments, the first reported preparation[14] of 3,5-dichloro-*as*-triazine appeared. This compound was obtained in low yield from *as*-triazine-3,5-dione and "aged" $POCl_3$ in the presence of triethylamine. We effected a similar transformation with 6-methyl-*as*-triazine-3,5-dione[15] (**1**, see Scheme I) and fresh reagent grade $POCl_3$ to obtain 3,5-dichloro-6-methyl-*as*-triazine (**2**) in a yield of 35%. Methoxylation of **2** yielded 3,5-dimethoxy-6-methyl-*as*-triazine (**3**), which, upon treatment with sodium sulfanilamide in refluxing methanol, underwent facile methoxy displacement to yield 5-sulfanilamido-3-methoxy-6-methyl-*as*-triazine (**4**).[16]

Since **4** might well have had the alternative structure, 3-sulfanilamido-5-methoxy-6-methyl-*as*-triazine, its orientation was established through two sequences, both originating with 6-methyl-*as*-triazin-5-one-3-thione[15] (**5**, see Scheme I). Dethiation of **5** to yield 6-methyl-*as*-triazin-5-one (**6**) is apparently the first successful transformation of this type in the *as*-triazine series. A reported[17] attempt to dethiate the corresponding 6-benzyl derivative caused hydrolysis to 6-benzyl-*as*-triazine-3,5-dione instead. A similar attempt to dethiate *as*-triazine-3,5-dithione led to products which were not characterized.[14] Thionation of **6** was effected in pyridine at 105° to yield 6-methyl-*as*-triazine-5-thione (**7**). When this reaction was attempted at reflux, extensive decomposition resulted in a low yield of the desired product. Methylation of **7** gave 6-methyl-5-methylthio-*as*-triazine (**8**), which, on reaction with sodium sulfanilamide, yielded 5-sulfanilamido-6-methyl-*as*-triazine (**9**).

The latter was also prepared by an alternative sequence. Thionation of **10**[8] (or of **5**[15]) yielded 6-methyl-*as*-triazine-3,5-dithione (**11**),[8,9] which, on methylation, gave the 3,5-bis(methylthio) derivative (**12**).[9] Reaction of **12** with sodium sulfanilamide yielded 5-sulfanilamido-6-methyl-3-methylthio-*as*-triazine (**13**). Hydrogenolysis of the methylthio group in **13** gave a sulfanilamido-6-methyl-*as*-triazine identical in all respects with **9**, prepared through the previous unequivocal sequence, thus confirming the orientation of **13**, as shown. Methoxylation of **13** gave mainly a product of the same R_f value as the previously prepared **4**, whose structure was in doubt. A comparison of this product with **4** through their infrared and ultraviolet spectra and R_f values confirmed that they were identical. Thus, higher reactivity of the 5 position over the 3 position in **3** and **12** is established.

Preferential substitution at the 5 position of the *as*-triazines, demonstrated in this work and also in the amination[8] of 6-methyl-*as*-triazine-3,5-dithione, casts doubt[18] on the structure assignments of Grundmann, *et al.*,[14] in their reactions of 3,5-dichloro-*as*-triazine with various nucleophiles. These authors assumed preferential displacement of the 3-chloro rather than the 5-chloro substituent by a fallacious analogy with the reactivity of 2,4-dichloropyrimidine toward nucleophiles.[19]

(11) Ng. Ph. Buu-Hoï, Ng. D. Xuong, and F. Binon, *J. Chem. Soc.*, 713 (1956).

(12) J. Klosa, *Arch. Pharm.*, **288**, 465 (1955).

(13) We wish to thank Miss H. M. Krazinski for performing these experiments.

(14) C. Grundmann, H. Schroeder, and R. Rätz, *J. Org. Chem.*, **23**, 1522 (1958).

(15) J. Bougault and L. Daniel, *Compt. Rend.*, **186**, 1216 (1928).

(16) Reaction of **2** directly with sodium sulfanilamide resulted in formation of a complex mixture.

(17) J. Bougault, E. Cattelain, and P. Chabrier, *Compt. Rend.*, **208**, 657 (1939).

(18) One of the assigned structures, 5-ethoxy-3-methylthio-*as*-triazine, is probably correct since a two-step preferential substitution at the 5 position has been postulated by R. G. Shepherd and J. L. Fedrick, *Advan. Heterocyclic Chem.*, **4**, 298 (1965).

(19) Reaction of 2,4-dichloropyrimidine with NH_3 yields a *mixture* of the two possible aminochloro derivatives and with 1 mole of methoxide yields only 2-chloro-4-methoxypyrimidine. See D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp 188, 201; also see ref 18, p 293.

The structures of the tautomeric oxygen- and sulfur-containing *as*-triazines herein described are the oxo and thioxo forms, rather than the hydroxy and mercapto forms. This is to be expected on the basis of the structure of *as*-triazine-3,5-dione,[20] 2- and 4-pyrimidinones,[21] and 2- and 4-pyrimidinethiones.[22] These *as*-triazin-5-ones display strong absorption due to ring-carbonyl stretching in the 1650-cm^{-1} region. Our *as*-triazine-5-thiones show strong absorption in the 1193–1200-cm^{-1} region, slightly higher than the region reported by Spinner[23] to be characteristic of a number of α- and γ-thioxo azines and diazines and assigned by him to thiocarbonyl stretching.

Data on the new *as*-triazine intermediates are compiled in Table I. The 6-alkyl homologs of **9** and **13** in Table II were prepared by routes completely analogous to those outlined in Scheme I. Orientation of the 6-alkyl homologs of **13** was assumed to be the same as in the 6-methyl series.

These new 5-sulfanilamido-*as*-triazines had little or no oral antibacterial activity as tested (Table II);[24] one showed activity just below the lethal dose. Four compounds exhibited blood concentrations so low that the intrinsic activity based on attained blood level is uncertain. Great variation is apparent in the solubility of these sulfonamides, from those of extremely low solubility to the very soluble 5-sulfanilamido-3-methoxy-6-methyl-*as*-triazine (1000–1500 mg %, see Table II).

Although the data are limited, the pK_a values of these 5-sulfanilamido-*as*-triazines are consistent with the *meta*-substituent constants[25] of the R_3 substituents: H, $\sigma_m = 0$; OCH_3, $\sigma_m = 0.115$; SCH_3, $\sigma_m = 0.144$.

Experimental Section[26]

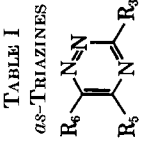
3,5-Dichloro-6-methyl-*as*-triazine (2).—Triethylamine (65.8 g, 0.650 mole) was added slowly with stirring to 199 g (1.30 moles) of ice-cooled $POCl_3$. 6-Methyl-*as*-triazine-3,5-dione[15] (41.3 g, 0.325 mole) was added to the resulting slurry and the mixture was refluxed with stirring for 15 min. After cooling, the dark brown solution was extracted with ten 200-ml portions of hexane. Concentration of the extracts left a brown crystalline residue, which was vacuum sublimed at 80–90° (1.0 mm) to yield light yellow crystals (12.1 g) melting at 41.5–44°. Continuous extraction of the reaction mixture with hexane for 3 days yielded 6.7 g of additional material. A second sublimation yielded very pale yellow crystals for analysis.

Lower yields (9–15%) resulted with twice as much $POCl_3$ or twice the reaction time.

3,5-Dimethoxy-6-methyl-*as*-triazine (3).—A solution of **2** (4.35 g, 0.0265 mole) in 20 ml of methanol was treated by slow addition, with stirring, of a solution prepared by dissolving 1.22 g (0.053 g-atom) of Na in 50 ml of methanol. After removal of NaCl, the filtrate was concentrated to dryness. The residue was extracted with 60 ml of hexane and the filtered extract was cooled to 0°.

5-Sulfanilamido-3-methoxy-6-methyl-*as*-triazine (4). Method 1.—Sulfanilamide (1.68 g, 9.78 mmoles) was dissolved in a solution of 0.225 g (9.78 mg-atoms) of Na in 10 ml of dry methanol.

Table I
as-Triazines



R_5	R_3	R_6	Yield, %	Purifn[a]	Mp[b] or bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S	Uv absorption[c] λ_{max}^{MeOH}, mμ	Uv absorption[c] ε
Cl	Cl	CH_3	35	Subl	44.5–45.5	$C_4H_3Cl_2N_3$	29.3	1.8	25.6	43.2[d]	29.4	2.1	25.2	43.0[d]		
OCH_3	OCH_3	CH_3	63	A (27)	107–108	$C_6H_9N_3O_2$	46.4	5.8	27.1		46.7	6.0	27.3		273	5400
H	Oxo	CH_3	84	Subl	211–212	$C_4H_5N_3O$	43.2	4.5	37.8		43.3	5.0	37.7		236	9400
H	Thioxo	CH_3	90	B (50)	180.5 dec	$C_4H_5N_3S$	37.8	4.0	33.0	25.2	38.5	4.1	32.6	25.0	288, 330	6000, 8600
H	SCH_3	CH_3	27	A (50)	56.5–57.5	$C_5H_7N_3S$	42.5	5.0	29.8	22.7	42.7	5.0	29.1	22.5	219, 253, 297	3500, 5500, 7900
H	Oxo	C_2H_5	59	C (10)	154.5–155.5	$C_5H_7N_3O$	48.0	5.6	33.6		48.3	5.5	33.6		237	9800
H	Thioxo	C_2H_5	80	C (30)	184–185	$C_5H_7N_3S$	42.5	5.0	29.8	22.7	42.7	5.2	29.6	23.0	290 (sh), 331	6350, 9600
H	SCH_3	C_2H_5	36	Subl 50° (0.05 mm)	36–37.5	$C_6H_9N_3S$	46.4	5.8	27.1	20.7	46.4	5.7	27.3	20.8	216, 253, 297	3200, 5300, 7900
H	Oxo	*n*-C_3H_7	60	C (6)	144.5–145.5	$C_6H_9N_3O$	51.8	6.5	30.2		52.1	6.6	29.9		238	9900
H	Thioxo	*n*-C_3H_7	94	C (16)	152.5–153.5	$C_6H_9N_3S$	46.4	5.8	27.1	20.7	46.6	5.8	26.8	20.7	290 (sh), 330	5800, 8800
H	SCH_3	*n*-C_3H_7	53		105–107 (1.2)	$C_7H_{11}N_3S$	49.7	6.5	24.8	18.9	49.7	6.8	24.8	18.8	218, 253, 299	2700, 4700, 7400

[a] Subl signifies vacuum sublimation; crystallization solvent: A, hexane; B, 4:1 heptane–ethanol; C, methanol; milliliters per gram is given in parentheses. [b] Melting points were determined in a modified Hershberg apparatus and are corrected. [c] Measured on a Cary Model 11 recording spectrophotometer. [d] Chlorine.

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(23) E. Spinner, *ibid.*, 1237 (1960).

(24) We are indebted to Mr. G. S. Redin and Miss M. E. McCoy of our Experimental Therapeutics Research Section for these results.

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(26) Melting points were determined in a modified Hershberg apparatus and are corrected. Infrared spectra were determined in KBr disks in a Perkin-Elmer Model 21 spectrophotometer.

Table II
5-Sulfanilamido-*as*-triazines

R_3	R_6	Yield, %	Purifn[a]	Mp, °C (cor)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S	R_f[b]	pK_a[c]	Rel act.[d]	Soly,[e] mg/100 ml at pH 6
CH_3O	H	52	A (1000)	196–196.5	$C_{10}H_{11}N_5O_3S$	42.7	3.9	24.9	11.4	43.2	4.1	24.7	11.1	0.30	5.3	<1/64	...
CH_3S	H	53	A (130)	206–207 dec	$C_{10}H_{11}N_5O_2S_2$	40.4	3.7	23.6	21.6	40.4	4.0	23.7	21.2	0.38	4.6	<1/32	...
H	CH_3	53	B (50)	251.5 dec	$C_{10}H_{11}N_5O_2S$	45.3	4.2	26.4	12.1	45.7	4.4	26.5	12.0	0.26	5.6	<1/32	190–250
CH_3O	CH_3	40	C (20)	172–173	$C_{11}H_{13}N_5O_3S$	44.7	4.4	23.7	10.8	45.0	4.7	23.9	10.6	0.33	5.8	<1/16	1000–1500
CH_3S	CH_3	42	D (60)	207–208	$C_{11}H_{13}N_5O_2S_2$[f,g]	43.7	5.4	19.6	17.9	43.0	5.5	19.5	18.4	0.39	5.1	<1/32	250–330
H	C_2H_5	37	E (97)	232–233	$C_{11}H_{13}N_5O_2S$	47.3	4.7	25.1	11.5	47.1	4.6	25.0	11.5	0.35	5.6	<1/32	40–80
CH_3S	C_2H_5	22	A (45)	198–199	$C_{12}H_{15}N_5O_2S_2$[g,h]	45.3	5.7	18.9	17.3	45.0	5.6	18.6	17.3	0.51	5.3	Tᵢ	170–330
H	n-C_3H_7	42	E (47)	235–236	$C_{12}H_{15}N_5O_2S$	49.1	5.1	23.9	10.9	49.3	5.0	24.2	10.9	0.44	5.8	<1/16	60–120

[a] Recrystallized from the following solvents: A, ethanol; B, 3:1 ethanol–water; C, 3:1 ethanol–hexane; D, 4:1 ethanol–hexane; E, methanol; millilitres per gram is given in parentheses. [b] See Experimental Section. [c] Determined by potentiometric titration in 30% acetone. [d] Approximate relative antibacterial activity of the compound against a lethal infection with *Staphylococcus aureus* Smith in mice is based on comparison of per cent survival using graded (twofold) doses given by single oral tubing (immediately after infection) with per cent survival produced by graded doses of sulfadiazine. The designation "<1/64" means that the compound was inactive at 64 times the minimal effective doses of the standard. The authors are indebted to Mr. G. S. Redin and Miss M. E. McCoy of our Experimental Therapeutics Research Section for these data. [e] Determined in pH 6, 0.1 *M* acetate buffer; see R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, **26**, 2764 (1961), for details. [f] Contains 1 mole of ethanol based on relative integrated areas in the nmr spectrum (dimethyl-4/6 sulfoxide solution) of the methyl groups of the ethanol and the *as*-triazine ring. [g] Calculated values are for the mono ethanolates. [h] The nmr spectrum indicated about 1 mole of ethanol based on a comparison of the methylene protons of ethanol with the phenyl protons adjacent to the sulfonamide group. [i] Toxic; saved part of the mice at 160 mg/kg; all of the mice were killed by the drug at 640 mg/kg.

After addition of 1.52 g (9.78 mmoles) of **3**, the solution was refluxed for 20 hr. Paper chromatographic examination indicated about 80% reaction after 1.5 hr and 95% after 17 hr, the product appearing at R_f 0.39 compared with R_f 0.59 for sulfanilamide. After evaporation, the residue was dissolved in H_2O (20 ml) and adjusted to pH 4 by dropwise addition of 1 *N* HCl to give a light yellow precipitate weighing 1.75 g. This was recrystallized from 35 ml of 3:1 ethanol–hexane (charcoal).

Method 2.—A 357-mg (1.00 mmole) sample of **13** in a solution of 61 mg (3.7 mg-atoms) of Na in 4.0 ml of methanol was refluxed for 340 hr. Paper chromatography indicated about 60% conversion after 196 hr and almost quantitative conversion after 340 hr. Concentration of the reaction mixture to dryness under an oil pump left a pale yellow solid (394 mg) which was dissolved in 2 ml of water. This solution was adjusted to pH 4 with 1 *N* HCl and the initial gum was transformed by prolonged stirring into a pale yellow solid (122 mg). Recrystallization from hexane–ethanol failed to give material suitable for a melting-point identification due to the presence of minor by-products, so spectral and chromatographic comparisons were carried out. The material consisted of a major component with R_f 0.32 and three minor arylamine components, compared with the previously prepared sample of this compound having R_f 0.33. The infrared spectrum of this material was essentially identical with that of the product from method 1 and distinctly different from that of the starting material. The same is true of the ultraviolet spectrum shown in Table III.

6-Methyl-*as*-triazin-5-one (6).—A mixture of 7.16 g (0.050 mole) of 6-methyl-*as*-triazin-5-one-3-thione,[15] 25 g of wet Raney nickel, 6 ml of NH_4OH, and H_2O (144 ml) was refluxed with stirring for 3 hr (1.5 hr for ethyl and *n*-propyl homologs). The filtrate was concentrated to dryness and the residue was recrystallized from 100 ml of ethanol (charcoal), yielding pale green crystals (0.95 g) which melted at 205.5–207.5°. Concentration of the filtrate to 15 ml gave 3.73 g of similar material, total 4.68 g (84%). A portion (100 mg) was sublimed at 140° (0.05 mm) to yield 42 mg of white solid, ν_{max} 1656 (C=O stretching) cm^{-1}.

6-Methyl-*as*-triazine-5-thione (7).—A powdered mixture of 6.67 g (0.060 mole) of **6** and 8.13 g (0.0366 mole) of P_2S_5 in 348 ml of pyridine was stirred at 105° for 3 hr. The clear red solution was concentrated at 50° under vacuum to a syrup which soon crystallized. The solid was slurried in 100 ml of cold water, filtered, washed, and dried to give 4.63 g of orange-brown solid melting at 107° dec. Concentration of the filtrate, as above, to 25 ml yielded an additional 2.24 g of similar material, total 6.87 g (90%). A portion (0.48 g) was recrystallized from 50 ml of 4:1 heptane–ethanol (charcoal) to give fine orange needles (191 mg), ν_{max} 1197 (C=S stretching) cm^{-1}.

6-Methyl-5-methylthio-*as*-triazine (8).—Compound **7** (6.36 g, 0.050 mole) was dissolved in 55 ml of 2 *N* NaOH. The ice-cooled solution was treated by rapid addition of 6.94 g (0.055 mole) of dimethyl sulfate with vigorous stirring. The solution was stirred for 20 min, then was saturated with salt and extracted with four 100-ml portions of $CHCl_3$. The extracts were dried over Drierite and concentrated at 40° under an aspirator to a brown, oily solid which was vacuum sublimed (60°, 0.05 mm) to yield 1.94 g (27%) of pale yellow solid melting at 51–53°.

The 6-ethyl homolog, which separated as a solid from a similar reaction mixture, displayed proton peaks in its nmr spectrum at τ 0.71 (3 position), 7.13 (CH_2), 7.38 (SCH_3), and 8.67 (CH_3 of ethyl group).

5-Methylthio-6-*n*-propyl-*as*-triazine, collected by CH_2Cl_2 extraction, had $n^{20}D$ 1.5585.

5-Sulfanilamido-6-methyl-*as*-triazine (9). Method 1.—A mixture of compound **8** (1.11 g, 7.85 mmoles) and 1.53 g (7.85 mmoles) of sodium sulfanilamide in 15.7 ml of dimethylformamide (DMF) was maintained at 95–110° for 17–20 hr to form a clear, medium brown solution. This was concentrated at 50° with an oil pump to yield a viscous, brown residue which was dissolved in 25 ml of water, and the solution was adjusted to pH 4 (no precipitate at pH 7) by dropwise addition of 6 *N* HCl. The granular, yellow precipitate (1.11 g, 53%), melting at 242°, was recrystallized from 60 ml of 3:1 ethanol–water (charcoal). The pale yellow crystals (687 mg, 33%) melted at 251.5° dec; the melting point of the product from method 2 (see below) was also 251.5° dec; the mixture melting point was undepressed. The ir spectra of these two samples were essentially identical. Both samples displayed an R_f value of 0.26.

Method 2.—Raney nickel (W-2, 2 g) was added to a partial solution of 311 mg (1.00 mmole) of **13** in 10 ml of water and 1 ml

Table III

	λ, mμ (ε)		
	CH_3OH	0.1 *N* NaOH	0.1 *N* HCl
Compd **4** by method 2	260, 290 sh (19,800, 12,100)	255, 293 (18,300, 12,900)	281 (12,100)
5-Sulfa-3-methoxy-6-methyl-*as*-triazine (**4**)	260, 290 sh (21,600, 13,000)	254, 293 (17,500, 12,100)	282 (12,700)
5-Sulfa-6-methyl-3-methylthio-*as*-triazine (**13**)	257 (28,300)	253, 308 sh (26,500, 8200)	264 (19,800)

of NH_3. The mixture was refluxed with stirring for 2 hr. Paper chromatography indicated total disappearance of starting material (R_f 0.40) and formation of a major product with R_f 0.23. The supernatant was decanted and centrifuged. The centrifugate was concentrated almost to dryness and the residue was dissolved in 2.5 ml of 0.5 *N* NaOH and the mixture was centrifuged. The centrifugate was adjusted to pH 3 by dropwise addition of 6 *N* HCl. The pale yellow precipitate (87 mg, 33%) melted at 243° dec. A portion (77 mg) was recrystallized from 6 ml of ethanol (charcoal) to yield off-white spears (35 mg) melting at 251.5–252.5° dec.

5-Sulfanilamido-3-methoxy-*as*-triazine.—A solution of 1.72 g (5.79 mmoles) of 5-sulfanilamido-3-methylthio-*as*-triazine in 13.5 ml of 1 *N* $NaOCH_3$ in methanol was refluxed for 92 hr. The solution was concentrated to dryness and the residue was dissolved in H_2O (25 ml). The solution was adjusted to pH 4.5 and the precipitate (1.10 g) obtained was recrystallized from 1100 ml of boiling ethanol (charcoal).

5-Sulfanilamido-6-methyl-3-methylthio-*as*-triazine (**13**) was prepared by method 1 for **9** except for a 2-hr reaction time.

5-Sulfanilamido-6-ethyl-3-methylthio-*as*-triazine.—A mixture of 6.04 g (30.0 mmoles) of 6-ethyl-3,5-bis(methylthio)-*as*-triazine and 6.12 g (31.5 mmoles) of sodium sulfanilamide in 60 ml of DMF was stirred at 105–110° for 7 hr. After the solution was concentrated at 60° under an oil pump, the resulting syrup was dissolved in 80 ml of water. The solution was ice cooled and adjusted to pH 3. The yellow precipitate (7.98 g, mp 127–180°) was recrystallized from 75 ml of methanol (charcoal) to give orange crystals (3.72 g) melting over a range. Recrystallization from 170 ml of ethanol (charcoal) yielded pale yellow leaflets (2.43 g, 22%) which melted at 134° if plunged into bath at this temperature, resolidified, and remelted at 198–199°.

Biacetyl Monothiosemicarbazone.—A mixture of 9.1 g (0.10 mole) of thiosemicarbazide and 86 g (1.0 mole) of biacetyl was stirred for 48 hr. Ethanol (100 ml) was added and the yellow solid was filtered, washed, and dried, 6.9 g (43%), mp 177–178° (gas evolution). The filtrate, on chilling, yielded 1.6 g of similar material (total, 53%). Recrystallization from ethanol (21 ml/g, charcoal) yielded light yellow crystals melting at 180.5–181° (lit.[27] 185°); ν_{max} 1686 (C=O stretching), 1595 and 1505 cm^{-1}.

Anal. Calcd for $C_5H_9N_3OS$: C, 37.7; H, 5.7; N, 26.4. Found: C, 37.9; H, 5.8; N, 26.1.

Biacetyl Mono- and Bis(thiosemicarbazone).—The conditions reported to give 5,6-dimethyl-3-thioxo-*as*-triazine gave instead the following results. Under the conditions of Klosa,[12] equimolar (0.010 mole) amounts of biacetyl and thiosemicarbazide in 100 ml of refluxing ethanol gave 56% of bis(thiosemicarbazone) and, from the filtrate, 12% of the monothiosemicarbazone. Both were identified by melting point and ir spectral comparisons with authentic samples.

Under the conditions of Bnu-Hoï, *et al.*,[11] using refluxing acetic acid, there resulted a 34% yield of bis(thiosemicarbazone) (variable mp 270° dec, lit.[28] mp 255° and 272°; ν_{max} 1495, 1595 cm^{-1}; C, H, N, and S analyses).

Biacetyl S-Methylthiosemicarbazone.—A mixture of 23.3 g (0.100 mole) of S-methylthiosemicarbazide and 86.0 g (1.00 mole) of biacetyl was stirred at room temperature for 2 hr. The solution was stirred with an equal volume of ethyl ether with cooling to effect separation of a brown viscous oil. The ether layer was decanted and the oil was stirred with 112 ml of a 5% sodium carbonate solution. The resulting light yellow solid (12.4 g, 72%) melted at 139.5–141.5°. A portion (1.00 g) was dissolved in 20 ml of a 4:1 mixture of 90–100° petroleum ether–ethanol (charcoal), giving light yellow crytals (0.47 g, mp 141–142°).

Anal. Calcd for $C_6H_{11}N_3SO$: C, 41.6; H, 6.4; N, 24.2. Found: C, 42.1; H, 6.6; N, 24.2.

6-Methyl-*as*-triazine-3,5-dithione (**11**).[9]—A powdered mixture of **10**[8] (15.7 g, 0.100 mole) and 22.2 g (0.100 mole) of P_2S_5 in 80 ml of pyridine was stirred at reflux for 2 hr. The solution was concentrated to about half-volume at 50° under an oil pump and the residue was drowned in 300 ml of water with stirring. The precipitate was filtered and dissolved (mostly) in 100 ml of 1 *N* NaOH. The filtrate on cooling and acidifying to pH 3 with 6 *N* HCl, yielded an orange-yellow solid, 14.7 g (85%), mp 204° dec. A portion (0.32 g) was recrystallized from 10 ml of 50% ethanol (charcoal) to yield orange-yellow crystals (90 mg) melting at 221° dec (lit.[9] 215–217°), ν_{max} 1115, 1224 cm^{-1}.

Anal. Calcd for $C_4H_3N_3S_2$: C, 30.2; H, 3.2; N, 26.4, S, 40.3. Found: C, 30.9; H, 3.3; N, 26.3; S, 40.3.

Paper Chromatography.—The chromatograms were run on Whatman No. 1 paper in descending fashion, using for development the top layer of a 9:1:8 BuOH–NH_3–H_2O system. The dried sheets were examined under an ultraviolet lamp for quenching or fluorescence. The sheets were sprayed with 5:1:6 BuOH–AcOH–BuONO followed (after 2 min) by a 0.1% butanol solution of N-(1-naphthyl)ethylenediamine dihydrochloride. The presence of a primary arylamino group was indicated by a purple color.

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