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Keyphrases

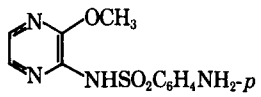
Prodrugs—acetaminophen carbonate esters
4-Acetamidophenyl 2,2,2-trichloroethyl carbonate
Particle size, effect—absorption, excretion, toxicity
LD_{50} values—acetaminophen carbonate esters
Plasma levels—acetaminophen
Urinary excretion—acetaminophen

Selective Acid-Catalyzed Hydrolyses of Methoxysulfanilamidodiazines

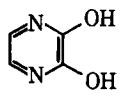
By VINCENT S. VENTURELLA*

The dilute acid hydrolysis of 3-methoxy-6-sulfanilamidopyridazine and several methoxysulfanilamidopyrimidines has been studied. Experiments show that in cases where an intermediate 2-pyrimidone is a possible postulation, further hydrolysis usually leads to the formation of sulfanilamide and the corresponding hydroxypyrimidine. A multistage route for the acidic degradation of 3-methoxy-6-sulfanilamidopyridazine, 2,4-dimethoxy-6-sulfanilamidopyrimidine, and 2-methylthio-4-methoxy-6-sulfanilamidopyrimidine is proposed.

RECENTLY, during a routine evaluation of the acidic degradation of the sulfanilamidopyrazine (I), it was found that the normally expected dilute acid cleavage to sulfanilic acid and 2-amino-3-methoxypyrazine did not occur (1), but that the products formed were sulfanilamide and 2,3-dihydroxypyrazine (II). Such a result



(I)



(II)

is in part unexpected, due to the fact that a 60% HBr solution is routinely used to effect the cleavage of difunctional methoxypyrazines (2), although there is a report (3) that 2,3-disulfanilamidopyrazine forms II under similar conditions. Since the result obtained with (I) may be due to the activation of the CH_3O position by the p-$H_2NC_6H_4SO_2NH$ group, it was desirable to test the mutual activation of these groups on the other substituent in similar sulfanilamidodiazines, such as those with the pyridazine and pyrimidine rings. The hydrolyses (except where noted) were carried out in refluxing 2 *N* HCl.

Hydrolysis of 3-methoxy-6-sulfanilamidopyridazine (III) (sulfamethoxypyridazine)[1] gave the expected sulfanilic acid, but activation of the ether position occurred forming 3-hydroxy-6-aminopyridazine. This result is surprising, even though Jacobs (4) states that the pyridazine ring is susceptible to substitution by nucleophilic reagents, because the present study has shown that a CH_3O group in the 3 position is not susceptible to nucleophilic displacement under the reaction conditions employed. In 2 *N* HCl solutions, neither 3-methoxy nor 3-methoxy-6-aminopyridazine (IV) formed more than a nominal amount of hydrolyzed material (3-hydroxypyridazine; 3-hydroxy-6-aminopyridazine, respectively) after several hours reflux followed by standing in solution for 24–72 hr. This seemingly anomalous result demands further study although a partial explanation can be made on the basis of an induced increase in the basicity of N^2 in the substituted pyridazine. The basicity increase is probably lacking or very weak in 3-methoxy- and 3-methoxy-6-aminopyridazine; a *point which*

Received September 28, 1966, from Temple University School of Pharmacy, Philadelphia, PA 19140
Accepted for publication March 8, 1968.
The author wishes to acknowledge the technical assistance of Dr. Edward J. Watson, Jr., Misses B. Narducci and Cathy Roberts, and the valuable comments of Dr. L. Bauer of the University of Illinois, College of Pharmacy.
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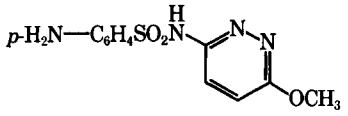
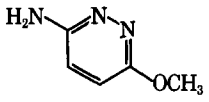
[1] Kynex, which was kindly supplied through the courtesy of Dr. S. Kushner, Lederle Laboratories, Pearl River, N. Y.

would account for the lack of acid-catalyzed aqueous nucleophilic displacement.



(III)

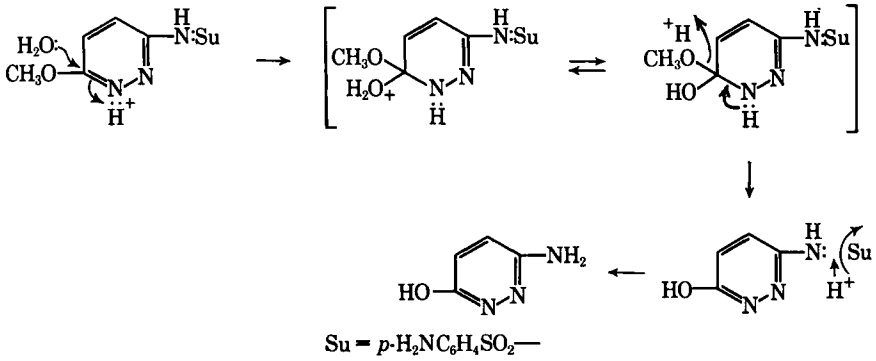


(IV)

A partial explanation which is then possible for the acid hydrolysis of III may be represented by Scheme I. In this scheme, an S_NAr attack is presumed to occur at the methoxyl position. This attack is aided by the induced electrophilic center produced by an electron migration promoted by the protonation of N^2.

hr. with 3.6 *N* HCl and 64.4% after 5.5 hr. with 3.6 *N* H_2SO_4.

Similar dilute acid hydrolysis of 4-methoxy-6-sulfanilamidopyrimidine, 4,6-dimethoxy-2-sulfanilamidopyrimidine, and 2-methylthio-4-methoxy-6-sulfanilamidopyrimidine (V) formed sulfanilic acid and the corresponding hydroxyaminopyrimidine (2-methylthio-4-hydroxy-6-aminopyrimidine with V). The 6 sulfanilamido compounds presumably hydrolyze by a nucleophilic alkoxy displacement *via* the S_NAr mechanism. This can then be followed by either normal SO_2NH bond cleavage or a second S_NAr nucleophilic displacement. In order for hydrolytic displacement of the sulfanilamido group to occur, the results of this study suggest that a 2-pyrimidone intermediate is needed, although there is no definitive proof of requirement. An incomplete hydrolysate of 4-methoxy-6-sulfanilamidopyrimidine was subjected to thin-layer



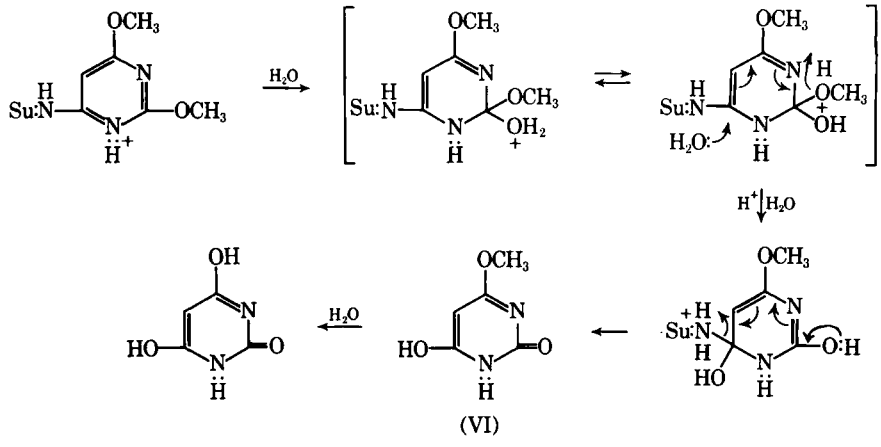
Su = *p*-$H_2NC_6H_4SO_2$—

Scheme I

Of the pyrimidines tested, 2,4-dimethoxy-6-sulfanilamidopyrimidine (sulfadimethoxine)[2] gave a novel result, yielding sulfanilamide and barbituric acid. The novelty of this result rests in the nucleophilic displacement of the sulfanilamido group, whereas one normally would expect nucleophilic displacement of the OCH_3 groups on the basis of the known S_NAr reaction which occurs at the 2,4, or 6 pyrimidyl alkoxy centers in acid solution (5, 6). By comparison with the experimental work of Daniels *et al.*, who used 2-methoxypyrimidine (7), there was a greater amount of reaction completed in a comparable period of time in the current study thereby indicating that CH_3O displacement in the hydrolysis of sulfadimethoxine is indeed accelerated by the presence of the sulfanilamido group. In the present study, essentially quantitative results were obtained after 4 to 6 hr. reflux, whereas the Daniels report (7) showed 40% completion in 1.5 chromatography (Silica Gel G, 0.5 mm., 70 Me_2CO; 30 *n*-BuOH; 30 NH_4OH) and showed an extra spot at R_f 0.52. This substance was isolated from an identical macrobatch and was shown to be 4-methoxy-5-aminopyrimidine [m.p. 148.5–150°; lit. (8), 150–151°]. The appearance of this compound thus points to the fact that when normal sulfa cleavage occurs, CH_3O^- displacement is more resistant.

However, when V was subjected to incomplete hydrolysis in 6 *N* HCl, 2-hydroxy-4-methoxy-6-sulfanilamidopyrimidine was isolated along with 2,6-dihydroxy-4-methoxypyrimidine as the intermediate hydrolytic products. This result was expected in view of the lability of 2-SR substituents of pyrimidines toward 6 *N* HCl (9). Either of the two intermediates then upon further reaction proceed along the sulfadimethoxine pathway since 2,6-dihydroxy-4-methoxypyrimidine (or its 2-pyrimidone tautomer) can be shown to be an intermediate during the sulfadimethoxine hydrolysis (Scheme II). This route is logical since the

[2] Madribon, kindly supplied through the courtesy of Dr. W. E. Scott, Hoffmann-La Roche Inc., Nutley, N. J.



(VI)

Su = p-$H_2NC_6H_4SO_2$—

Scheme II

2 position is more reactive in acid solution than either the 4 or 6 position in the absence of a retarding group such as the 2-methylthio group which is known to be unreactive in compounds similar to V in 2 *N* HCl (9).

Considering the results of the hydrolyses obtained with sulfadimethoxine and with V (2 *N* HCl and 6 *N* HCl) together with the established fact that a structure such as VI is favored in aqueous solution, a possible stepwise reaction for the hydrolysis of sulfadimethoxine can be represented by Scheme II. Alternately one might propose protonation of the other ring nitrogen first in the structure in Scheme II to give an incipient cross-conjugated cation. This alternative however is unlikely since neither 4-methoxy-6-sulfanilamidopyrimidine, 4,6-dimethoxy-2-sulfanilamidopyrimidine, nor V showed nucleophilic displacement of the sulfonamido group in 2 *N* HCl.

It is noteworthy that in neither of the other pyrimidines tested can an intermediate such as VI be postulated, the absence of which promotes normal SO_2NH bond cleavage and S_NAr attack at the CH_3O center (6).

In an effort to determine what normally might be expected to occur in the nonetheric sulfanilamidopyrimidines, 4-sulfanilamidopyrimidine, sulfadiazine, sulfamerazine, and sulfamethazine were subjected to similar hydrolytic experiments. In each of these four compounds the absence of a CH_3O function or the absence of a group that would yield a 2-pyrimidone (or 2-hydroxypyrimidine) function, based upon the present experimental results, would suggest that normal p-NH_2-$C_6H_4SO_2NH$ cleavage should occur. The lack of formation of sulfanilamide during the 2 *N* hydrolysis of 4-sulfanilamidopyrimidine, sulfadiazine, sulfamerazine, and sulfamethazine lends further support to the argument that the net effect of the CH_3O group is to promote the nucleophilic displacement of the p-NH_2-C_6H_4-SO_2NH group. In all the cases concerning the nonetheric sulfanilamidopyrimidines tested in this study, sulfanilic acid and the corresponding aminopyrimidine was isolated indicating the need for the CH_3O substituent in order to effect S_NAr displacement of the sulfanilamido group. It is also worthy of note that even CH_3 substitution, as in sulfamerazine and sulfamethazine, will not promote an S_NAr effect, and a CH_3O group in either the 4 or 6 position alone does not exhibit the unusual S_NAr sulfonamido displacement effect noted with sulfadimethoxine.

EXPERIMENTAL[3]

Isolated compounds were authenticated by comparison with physical constants appearing in the literature or with authentic samples (m.p., UV, IR spectra), mixture melting points, TLC comparison and/or by elemental analysis.

The procedure used for the hydrolysis of III, and the isolation of products is typical of that followed for all of the pyridazines and pyrimidines tested except V in 6 *N* HCl. The results of the hydrolytic experiments are collected in Tables I and II along with pertinent analytical data.

Hydrolysis of 3-Methoxy-6-sulfanilamidopyridazine (III)—Twenty grams (0.071 mole) of III was dissolved in 125 ml. of 2 *N* hydrochloric acid and was heated to reflux for 4 hr. The mixture was cooled and filtered, the solid washed with 50 ml. of cold 2 *N* hydrochloric acid, and suction dried to give a light yellow solid which crystallized from boiling water as white plates, m.p. 280–285° (decomposition); m.p. undepressed on admixture with sulfanilic

[3] All melting points were taken on a Thomas-Hoover apparatus and are corrected. UV spectra were obtained by use of the B. and L. Spectronic 505 or Cary model 15 (courtesy of George Irwin, SKF Laboratories). IR spectra were recorded on Perkin-Elmer model 137 spectrometer.

TABLE I—HYDROLYTIC PRODUCTS OF TESTED PYRIDAZINES

Substituents (wt. used; mole)	Vol. 2 *N* HCl; Reaction Time, hr.	Product(s) Isolated	Yield	M.p.	Supporting Anal. Data
3-Methoxy-6-sulfanilamido (20 Gm.; 0.071)	125 ml.; 4	Sulfanilic acid	11.4 Gm., 93%	280–285° (dec.)[a]	λ_{max}. pH 10 = 258 mμ[b]; IR identical to commercial sample[c]; analysis for $C_6H_8N_2O_2S$: C, 41.61; H, 4.07; N; 8.09. Found: C, 41.43; H, 4.04; N, 8.32.
		3-Hydroxy-6-amino-pyridazine	7.2 Gm., 91.5%	243–244.5° (dec.)[d]	ν(cm.$^{-1}$) 3440, 3315, 1685 (KBr); *p*-AcNHC$_6$H$_4$SO$_2$-NH-deriv. m.p. 198–199.2°[e]
3-Methoxy- (5 Gm.; 0.045)	90 ml.; 2	3-Methoxy-pyridazine	4.1 Gm., 84.4%	—	TLC R_f 0.67 (0.25 mm., Silica Gel G, AcOH, *n*-BuOH, Me_2CO; 40; 40; 20)[f]
	90 ml.; 6	3-Hydroxy-pyridazine hydrate	0.17 Gm., 3.4%	72–73.5°[g]	R_f 0.55 (3-methoxypyridazine TLC parameters)
3-Methoxy-6-amino-[h] (10 Gm., 0.08)	70 ml.; 5	3-Hydroxy-6-amino-pyridazine	0.13 Gm., 1.5%	235–237° (dec.)[d]	m.p. undepressed with hydrolysis product of III; 9.6 Gm. (0.077 mole) of starting material isolated

[a] Mixed m.p. showed no depression. [b] Repressed at pH 2 (9). [c] Distillation Products Ind., Rochester, N. Y. [d] Lit. (10) reports m.p. 245–246°. [e] Lit. (10) reports m.p. 200–202°. [f] R_f for starting material. [g] Lit. (11) reports 70–71°. [h] Aldrich Chem. Corp., Milwaukee, Wis.

TABLE II—HYDROLYTIC PRODUCTS OF TESTED PYRIMIDINES

Substituents (wt. used; moles)	Vol. of HCl; Reaction Time, hr.	Product(s) Isolated	Yield	M.p.	Supporting Anal. Data
2,4-Dimethoxy-6-sulfanilamido- (20 Gm., 0.065)	150 ml. (2 *N*); 5	Barbituric acid	10.8 Gm., 98.6%[a]	242–243.5°	λ_{max}. 256 mμ, log ϵ 4.34 (pH 3.2), pH − $\Delta\epsilon$ analysis positive.[b] Calcd. for $C_4H_4N_2O_3$: C, 37.50; H, 3.12; N, 21.92. Found: C, 38.05; H, 3.36; N, 22.26
		Sulfanilamide	7.9 Gm., 65%[c]	162–163.5°[d]	λ_{max}. 255, 312 mμ (H_2O). Calcd. for $C_6H_8N_2O_2S$: C, 41.84; H, 4.68; N, 16.27. Found: C, 41.91; H, 4.96; N, 15.38
4-Methoxy-6-sulfanilamido- (10 Gm., 0.036)	120 ml. (2 *N*); 6	Sulfanilic acid[e]	3.43 Gm., 56%	286–288° (dec.)	Calcd. for $C_6H_8N_2O_2S$: C, 41.61; H, 4.07; N, 8.09. Found: C, 41.94; H, 4.22; N, 8.00
		4-Hydroxy-6-amino-pyrimidine	2.05 Gm., 52%	261–262°[f]	*g*
4-Methoxy-6-sulfanilamido- (5.6 Gm., 0.02)	75 ml. (2 *N*); 1	4-Methoxy-6-amino-pyrimidine	0.9 Gm., 36%	148.5–150°[h]	R_f 0.52 (Silica Gel G, 0.5 mm., Me_2CO, *n*-BuOH; NH_4OH: (70:30:30)
		Sulfanilic acid[e]	1.1 Gm., 32.1%	284–287° (dec.)	3.3 Gm. of starting material isolated
4,6-Dimethoxy-2-sulfanilamido- (15 Gm., 0.054)	125 ml. (2 *N*); 4	Sulfanilic acid[e]	6.7 Gm., 70%	283–287° (dec.)	
		2-Amino-4,6-dihydroxy-pyrimidine	5.0 Gm., 72.4%	300°	Mixed m.p., IR, UV, qualitatively identical to authentic sample. R_f 0.33; Silica Gel G, 0.5 mm[i], Me_2CO; *n*-BuOH; NH_4OH (70:30:30): Authentic sample[i] gave the same R_f
2-Methylthio-4-methoxy-6-sulfanilamido- (10 Gm., 0.031)	120 ml. (2 *N*); 5	Sulfanilic acid[e]	4.0 Gm., 75%	280–284° (dec.)	
		2-Methylthio-4-hydroxy-6-amino-pyrimidine	3.5 Gm., 72%	261–263° (dec.)[j]	1.1 Gm. (11%) of starting material isolated. 4-Chloro-analog, m.p. 129–130°[k]
(12.6 Gm., 0.038)	150 ml. (6 *N*); 6	Barbituric acid	3.7 Gm., 59%[a]	241–243°	Spectroscopically similar to that isolated from 2,4-dimethoxy-6-sulfanilamido-pyrimidine
		Sulfanilamide	4.3 Gm., 65%	163–164°[d]	2.2 Gm. (21.5%) starting material isolated

(*Continued on next page.*)

TABLE II—(*Continued.*)

Substituents (wt. used; moles)	Vol. of HCl; Reaction Time, hr.	Product(s) Isolated	Yield	M.p.	Supporting Anal. Data
(4.9 Gm., 0.015)	65 ml. (6 *N*); 0.75	Barbituric acid	0.10 Gm., 40%[a]	243–244.5°	
		2-Hydroxy-4-methoxy-6-sulfanilamidopyrimidine	0.82 Gm., 18.5%	166–167.5°	Analysis for $C_{11}H_{12}N_4O_4S$: C, 46.16; H, 4.23; N, 19.57. Found: C, 45.80; H, 4.10; N, 20.18
		2,6-Dihydroxy-4-methoxypyrimidine[l]	0.21 Gm., 9.9%	204–206°	Analysis for $C_5H_6N_2O_3$: C, 42.26; H, 4.25; N, 19.70. Found: C, 42.00; H, 4.19; N, 19.41; 2.4 Gm. (49%) of starting material isolated
4-Sulfanilamido- (5.0 Gm., 0.02)	45 ml. (2 *N*); 5	Sulfanilic acid[e]	1.1 Gm., 32.1%	282–285° (dec.)	
		4-Aminopyrimidine	0.84 Gm., 46.5%	147–148°[m]	$\lambda_{max.}$ H_2O 233 mμ (ε 10,950), 264 mμ (ε 3802).[n] 2.6 Gm. of starting material isolated.
2-Sulfanilamido- (20 Gm., 0.08)	190 ml. (2 *N*); 4	Sulfanilic acid[e]	5.0 Gm., 36.1%	284–287° (dec.)	8.6 Gm. of sulfadiazine remaining in hydrolysis mixture
		2-Aminopyrimidine hydrochloride[o]	4.2 Gm., crude, 40.1%	221–222° (dec.)	ν (cm.$^{-1}$) (KBr) 2710–2720 (salt), 1580, 1610 (aromatic-atypical of 2-hydroxypyrimidine); no carbonyl absorption (as shown by 2-hydroxypyrimidine) (see *Ref. 17*); free base from aq. K_2CO_3 extracted with EtOAc, m.p. 121–122.5° (commercial[i] material melted at 124–126°); 2-acetylamino-deriv., m.p. 149–151° [Lit. (18) reports 145–146.5°]
Sulfamerazine (10 Gm., 0.038)	150 ml. (2 *N*); 7	Sulfanilic acid[e]	6.2 Gm., 94.5%	282–285° (dec.)	
		2-Amino-4-methylpyrimidine	3.5 Gm., 85%	155–157.1°	Lit. (18) reports m.p. 156.5–157.5°; analysis for $C_5H_7N_3$: C, 55.11; H, 6.41; N, 38.48. Found: C, 55.39; H, 6.19; N, 38.02
Sulfamethazine (10 Gm., 0.036)	135 ml. (2 *N*); 6	Sulfanilic acid[e]	5.9 Gm., 94.7%	283–285° (dec.)	
		2-Amino-4,6-dimethylpyrimidine	3.8 Gm., 87%	149–151°	Lit. (19) reports m.p. 152–154°; analysis for $C_6H_9N_3$: C, 58.40; H, 7.31; N, 34.18. Found: C, 58.10; H, 7.22; N, 33.97

[a] As the dihydrate. [b] Reported $\lambda_{max.}$ 257 mμ (pH 3.0); log ε 4.04 (*Ref. 12*). [c] An additional 2.1 Gm. (19%) of impure product was obtained from the recrystallization liquor. [d] Undepressed when admixed with authentic sulfanilamide (Distillation Products Industries, Rochester, N. Y.). [e] Identical to that obtained from the hydrolysis of 3-methoxy-6-sulfanilamidopyridazine (Table I). [f] Lit. (14) reports m.p. 263–264°. [g] 3.1 Gm. of 4-methoxy-6-sulfanilamidopyrimidine recovered. [h] Lit. (8) reports m.p. 150–151°. [i] Aldrich Chem. Co., Milwaukee, Wisc. [j] Lit. (15) reports m.p. 260–263° (dec.). [k] Prepared according to Baker *et al.* (15); reported m.p. 125–128°. [l] 2,6-Dichloro analog, m.p. 51–53° prepared according to Baddiley and Topham (16) (see experimental part). [m] Lit. (17) reports m.p. 150–151°. [n] Lit. (14) reports $\lambda_{max.}$ 232 mμ (ε 11,300) and 265 mμ (ε 3780). [o] The rust colored solid was extensively hydrated as isolated giving a higher melting product than reported. Confirmation of the product was obtained by drying for 10 hr. at 85° *in vacuo* over P_2O_5 yielding a product which melted at 205–208° (dec.); m.p. 173–175° (dec.) when admixed with authentic 2-hydroxypyrimidine.HCl.

acid.[4] The weight of crude material was 11.4 Gm. (93%), calculated as sulfanilic acid.

The filtrate after isolation was carefully neutralized with solid potassium carbonate, cooled in an ice bath, and filtered to give a 91.5% yield of the bland colored 3-hydroxy-6-aminopyridazine (7.2 Gm.), m.p. 243–244.5° (decomposition) after recrystallization from ethanol–water [lit. (11), m.p. 245–246°].

3-Methoxypyridazine—Twenty-five grams (0.17 mole) of 3,6-dichloropyridazine was treated with 1.05 equivalents of sodium methoxide in methanol according to the procedure described by Druey (21) and gave 11.6 Gm. (0.08 mole; 47%) of 3-methoxy-6-chloropyridazine (from boiling hexane, m.p. 87.9–89°; reported 90°). The product was dissolved in 120 ml. of anhydrous methanol and hydrogenated over 0.8 Gm. of Pd/C (22) for 4.5 hr., the dark reaction solution filtered, the filtrate evaporated under reduced pressure to a moist residue, the mixture neutralized with a saturated solution of potassium carbonate, and extracted with 380 ml. of methylene chloride. The extract was dried over

[4] Distillation Products Industries, Rochester, N. Y.

anhydrous magnesium sulfate, the solvent was removed *in vacuo*, and the product distilled to give 4.1 Gm. (0.037 mole) (46%) of a light yellow oil, b.p.$_8$ 76–79° (Druey reports 86–87°, 13 mm.).

4-Chloro-6-sulfanilamidopyrimidine—Twenty-five grams (0.168 mole) of 4,6-dichloropyrimidine,[5] 68.5 Gm. of sodium sulfanilamide, and 68.5 Gm. of acetamide were heated in the absence of solvent and the mixture worked up to yield 14.3 Gm. (0.05 mole; 29.5%) of product as the hydrochloride, m.p. 330–334° (decomposition), in the manner described by Shepherd (23), by acidifying the final solution to pH 3 rather than pH 4, followed by overnight refrigeration.

4-Sulfanilamidopyrimidine—Fourteen grams (0.047 mole) of 4-chloro-6-sulfanilamidopyrimidine was hydrogenated at 3 atm. in 82 ml. of 1.7 *N* sodium hydroxide for 75 min. (H_2 uptake complete) over 2.45 Gm. of 10% Pd/C catalyst (23). The filtered solution was neutralized with 1 *N* hydrochloric acid, refrigerated overnight, and filtered. The yellow solid was crystallized from hot acetonitrile to give 6.8 Gm. (0.031 mole; 63.5%) of 4-sulfanilamidopyrimidine as white microcrystals, vacuum dried at 55°, m.p. 225–227° [lit. (23), m.p. 232–232.5°].

4,6-Dimethoxy-2-sulfanilamidopyrimidine—The general methods described by Braker *et al.* (24) were used with some modifications in the preparation of this compound in 21% overall yield.

Fifty grams (0.392 mole) of 4,6-dihydroxy-2-aminopyrimidine was treated with 200 ml. of phosphorus oxychloride, added all at once, the mixture diluted with 20 ml. of dimethylaniline, stirred mechanically, and refluxed for 3 hr. The mixture was cooled in an ice bath and poured slowly onto 800 Gm. of cracked ice moistened with 50 ml. of ether. After all the ice had melted, the mixture was brought to pH 6 with concentrated ammonia and extracted continuously with ether for 36 hr. The ether extract was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated to dryness, *in vacuo*. The solid was crystallized from a 1:1 ether–hexane mixture and recrystallized from the same solvent to give 34.2 Gm. (0.21 mole; 53%) of 4,6-dichloro-2-aminopyrimidine, m.p. 220–223° (reported by Braker as 223–225°).

The purified dichloro compound (0.20 mole; 32.8 Gm.) was suspended and stirred in 250 ml. of absolute methanol and treated with 3.5 molar equivalents (37.1 Gm.) of solid sodium methoxide and the mixture refluxed for 10 hr. The suspension was cooled to 5°, filtered, the filtrate evaporated to dryness, and the residue triturated with 50 ml. of water. The solid was filtered, washed with three 10-ml. portions of cold water, and vacuum dried at 45° over calcium chloride to yield 30.1 Gm. (0.19 mole; 97%) of 4,6-dimethoxy-2-aminopyrimidine, m.p. 95–97° [lit. (24) m.p. 94–95°] after recrystallization from hot hexane.

The purified dimethoxy compound (29.5 Gm., 0.18 mole) was mixed with 65 ml. of pyridine and 20 ml. of cyclohexane. The mixture was cooled in an ice salt bath, stirred, and treated portionwise with 52.4 Gm. (0.22 mole) of acetylsulfanilylchloride. The mixture was stirred for 3 hr. at room temperature after an initial 30-min. reaction time at 0°. The solvent was evaporated *in vacuo*, the residue treated with 150 ml. of water, the water evaporated under vacuum to give a solid which was crystallized from hot acetone. The yield of 2-(N^1-acetylsulfanilamido)-4,6-dimethoxypyrimidine was 58.2 Gm. (0.16 mole; 91%); m.p. 242–244° (decomposition) [lit. (24) m.p. 240–241° (decomposition)]. The *N*-acetyl sulfonamide was boiled with 180 ml. of 10% aqueous sodium hydroxide solution for 2 hr., the mixture cooled, and acidified with acetic acid to pH 4. The resulting suspension was refrigerated at 5° for 48 hr., filtered, the precipitate washed with 150 ml. of ice water, and suction dried. The white solid obtained was recrystallized from hot methanol–water and vacuum dried at 45° for 12 hr. to give 23.6 Gm. (0.076 mole; 47%) of 4,6-dimethoxy-2-sulfanilamidopyrimidine, m.p. 177–178° (*Reference 24* reports the same m.p.) as white microcrystals.

2-Methylthio-4-methoxy-6-sulfanilamidopyrimidine (V)—This compound was prepared in a manner substantially similar to that reported by Budesinsky *et al.* (25). Twenty-five grams (0.143 mole) of 2-methylthio-4-chloro-6-aminopyrimidine was suspended in 200 ml. of methanol containing 8.65 Gm. (0.16 mole) of sodium methoxide, and the mixture refluxed for 12 hr. The hazy solution was cooled to −10°, the mixture was filtered, the filtrate evaporated to dryness under reduced pressure, the solid suspended, and macerated with 250 ml. of water. The solid was removed by suction filtration and dried in air overnight to give 18.3 Gm. (0.107 mole) (74.8%) of the white microcrystalline 2-methylthio-4-methoxy-6-aminopyrimidine which melted at 106.2–108° after recrystallization from 50% aqueous methanol [lit. (16), m.p. 110°].

Anal.—Calcd. for $C_6H_9N_3OS$: C, 42.08; H, 5.29; N, 24.54. Found: C, 41.77; H, 5.06; N, 24.81.

Reaction of the isolated methoxy compound with acetylsulfanilylchloride in pyridine (24) followed by alkaline hydrolysis gave 23.1 Gm. (66.2%) of V, m.p. 171.5–173°, after recrystallization from ethanol–water [lit. (23), m.p. 171°].

Anal.—Calcd. for $C_{12}H_{14}N_4O_3S_2$: C, 44.15; H, 4.32; N, 17.16. Found: C, 44.70; H, 4.12; N, 17.45.

2,6-Dichloro-4-methoxypyrimidine—One-hundred sixty mg. (0.0011 mole) of 2,6-dihydroxy-4-methoxypyrimidine (isolated from the incomplete 6 *N* hydrochloric acid hydrolysis of 2-methylthio-4-methoxy-6-sulfanilamidopyrimidine) and 1.5 ml. of phosphorus oxychloride were diluted with 2 ml. of dimethylaniline and the mixture refluxed for 1.5 hr. The cooled mixture was poured onto 25 Gm. of cracked ice and extracted with seven 10-ml. portions of ether. The ether extracts were washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure to give 110 mg. (0.00062 mole) (56%) of the 2,6-dichloro derivative, b.p.$_5$ 132–135°. The oil solidified on standing and was crystallized from hot methanol, m.p. 51–53° [reported (26) to melt at 51°].

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Keyphrases

Methoxysulfanilamidodiazines—hydrolyses
Hydrolyses—acid catalyzed
TLC—identity
IR spectrophotometry—structure
UV spectrophotometry—structure

Crystal and Molecular Structure of 6-Thiopurine Riboside

By ELI SHEFTER

The molecular structure of 6-thiopurine riboside (commonly known as 6-mercaptopurine riboside) has been determined by X-ray crystallographic analysis. The material crystallizes from water as orthorhombic needles (space group $P2_12_12_1$) with unit cell dimensions of $a = 8.622$ Å., $b = 13.624$ Å., and $c = 20.262$ Å. There are two unique molecules in the asymmetric unit of the cell. The structure was solved by the heavy atom technique and refined by block diagonal least squares. The final R index is 0.067. In general, the bond lengths and angles agree with those found in other nucleoside structures. The C6-S distances of the two molecules (average 1.669 ± 0.002 Å.) together with the presence of a hydrogen on each of the N1 atoms indicates that the molecules are in the thiolactam configuration rather than the mercapto form. The glycosidic torsion angles (ϕ_{CN}) are +135° and +144° for the two molecules. The *syn* conformation about each of the CN bonds is stabilized by O5′-H...N3 intramolecular hydrogen bonds. The furanose rings are puckered; C2′ being displaced *endo* in both molecules. Each of the unique sulfurs is involved in a C-H...S interaction, while one is also participating in an O-H...S hydrogen bond.

6-Thiopurine (commonly known as 6-mercaptopurine) has been well established as an effective antineoplastic agent. It has been postulated that the compound exerts its effect at an enzymatic level., *i.e.*, through the purine metabolic pathway (1). In order to act as an inhibitor, it must first be converted to its active form, the ribonucleotide. In the hope of providing information on the electronic and steric configuration of this active species, the crystal and molecular structure of the riboside has been investigated.

Received January 18, 1968, from the Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214
Accepted for publication March 5, 1968.
Presented to Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, April 1968.
This research was supported in part by grant No. CA 10104 from the National Cancer Institute, U. S. Public Health Service, Bethesda, Md.
The author is indebted to the Computing Center at this University for a generous gift of computing time, and to Mrs. Phyllis Sackman for her technical assistance.

EXPERIMENTAL

The compound was obtained from Sigma Chemical Co. (St. Louis, Missouri) and crystallized from water. Orthorhombic needles so derived have the following data:

$a = 8.622 \pm 0.002$ Å. $D_M = 1.589 \pm 0.005$ Gm./-cm.^{3} (by flotation)

$b = 13.624 \pm 0.002$ Å. $D_{calcd.} = 1.586$ for $Z = 8$

$c = 20.262 \pm 0.004$ Å. Space group $P2_12_12_1$