Journal of Heterocyclic Chemistry

Volume 1, Number 1 Midwest Research Institute February, 1964

Problems Related to the Synthesis of 3-Aziridinyl-6-chloropyridazine (1)

Wayne H. Nyberg and C. C. Cheng

The correct structure of the reported 3-aziridinyl-6-chloropyridazine was found to be 3-[β-(1-aziridinyl)ethylamino]-6-chloropyridazine, which was confirmed by n.m.r. studies. The relative ease of nucleophilic displacement of a methylsulfonyl group versus a chloro group in equivalent positions on a pyridazine or a pyrimidine ring was compared. It was observed that the chloro rather than the methylsulfonyl group was preferentially replaced, as illustrated by substitution studies of 3-chloro-6-methylsulfonylpyridazine and 4-chloro-6-methylsulfonylpyrimidine.

Pyridazine derivatives, during the past decade, have become increasingly important in the field of organic, biological and medicinal chemistry. High yields of tetracycline, for instance, were obtained by the inhibition of fermentative chlorination with 3,6-disubstituted pyridazines (2). The "sulfa-derivative" of 3-amino-6-chloropyridazine has excellent antibacterial effects (3). Some 1-phenyl-6-pyridazones show analgesic and antipyretic activity (4). Dialkyl pyridazinyl phosphates and phosphothioates are active as insecticides (5). 3,6-Disubstituted 4-nitropyridazine 1-oxides exhibit carcinostatic and bacteriostatic action (6); and 3-sulfanilyl-6-alkylthiopyridazines inhibit the growth of the F. L. strain of human amnion cells (7).

Recently, 3-aziridinyl-6-chloropyridazine (Ia), described in two Japanese publications (8), has been reported to possess strong inhibitory activity against mouse Ehrlich (ascites) tumor (8a). The toxicity of this compound was also found to be quite low. Our studies of the aziridine derivatives (9), together with the controversial reports on the melting point for Ia (126-127° by Saijo and Inaba (8a), 268-269° dec. by Kumagai (8b)) led to the investigation of the synthesis of Ia and closely related compounds.

When a mixture of ethylenimine and 3,6-dichloropyridazine (Ib) was refluxed in benzene (8a), *iso*-propyl alcohol, or butyl alcohol (8b) according to the reported conditions, the expected product Ia was not isolated. The result of several runs was either the recovery of Ib or the formation of polymerized substances. When excess ethylenimine was refluxed with anhydrous potassium carbonate in dry benzene prior to the addition of Ib (10), a product was obtained and its melting point, 127-128°, as well as solubility characteristics, agreed with that reported by Saijo and Inaba (8a). However, elementary analyses and molecular weight determinations indicated that the product contained an additional molecule of ethylenimine (11). The structure of the product, therefore, must be II, III, IV or V.

Structure II was ruled out because the product gave a negative test for ionizable halide. Replacement of *both* chlorine atoms of Ib by ethylenimine could not have taken place under the present experimental conditions since only a *mono*-replaced product, 3-chloro-6-dimethylaminopyridazine (Ic), was obtained by heating a mixture of excess dimethylamine and Ib in a bomb at 120-130°. The possibility of the product having structure II or III was thus excluded.

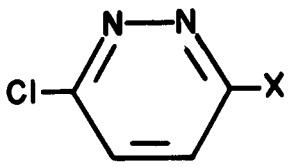
Our product possessed a strong N-H stretching band at 3.1 μ in the infrared. Its ultraviolet absorption spectrum resembled quite closely that of Ic. The molecular weight determination in both aqueous and nonaqueous solvents gave approximately the same value, suggesting that structure IV could not be the correct one. A compound of this type would dissociate in polar solvents.

The structure for our product was finally confirmed as 3-[β-(1-aziridinyl)ethylamino]-6-chloropyridazine (V) by means of nuclear magnetic resonance studies. The n.m.r. spectrum of our product, taken at 25° in $CDCl_3$ (internal standard: tetramethylsilane), furnished the information shown in Fig. 1.

The ring hydrogens show an AB group at δ (chemical shift) = 6.72 and 7.11 ppm, with a coupling constant, J = 9 cps. A broad N-H absorption at 6.2 ppm is observed. Two methylene absorptions were observed, methylene (C_1) quartet (peak heights: 1:3:3:1) at 3.62 ppm, J = 5.5 cps, and methylene (C_2) triplet (peak heights: 1:2:1) at 2.50 ppm, J = 5.5 cps. The aziridine CH_2 multiplets at 1.21 ppm (calculated 7.37 - 6.28 = 1.09 ppm) and 1.76 ppm (calculated 7.37 - 5.60 = 1.77 ppm), are at approximately the same positions reported by Bottini and Roberts (12) in their N-substituted aziridine studies. These multiplets indicated the presence of the "umbrella" aziridine nitrogen when the latter was attached to an aliphatic moiety (13).

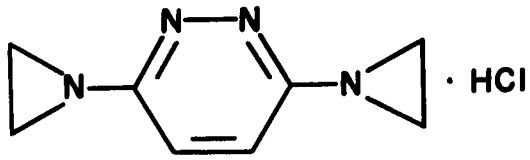
It is therefore concluded that the reaction product of ethylenimine and 3,6-dichloropyridazine (Ib) was V rather than the reported 3-aziridinyl-6-chloropyridazine (Ia) (8a). The formation of the ethylenimine dimer, β-(1-aziridinyl)ethylamine (VI), from ethylenimine under various conditions has been extensively described in the literature (14, 15, 16).

Since the methylsulfonyl group of 4,6-dichloro-2-methylsulfonylpyrimidine was preferentially replaced by ethylenimine (9a), the reaction of 3-chloro-6-methylsulfonylpyridazine (Id) with ethylenimine should yield the desired compound Ia. However, this did not prove to be the case and the resulting product was found to be 3-aziridinyl-6-(methylsulfonyl)pyridazine (VIIa) (13). Reactions between Id and other aliphatic

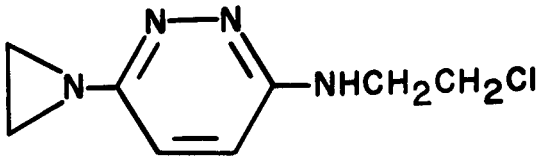


I

a. x=-N△
b. x= Cl
c. x= $N(CH_3)_2$
d. x= CH_3SO_2
e. x= CH_3S



II



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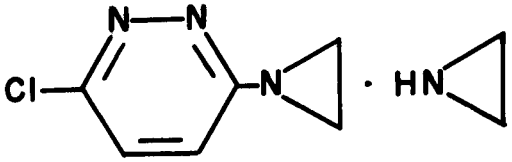
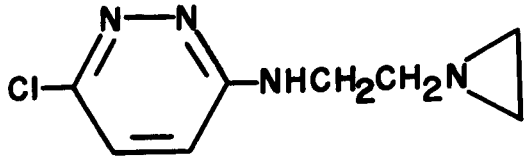
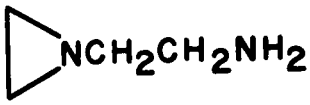


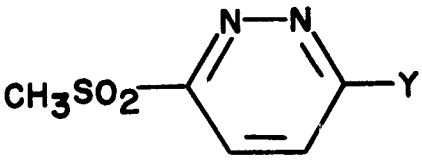
IV



V

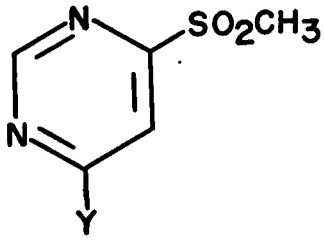


VI



VII

a. Y=-N△
b. Y= $N(CH_3)_2$
c. Y= $NH(CH_2)_3CH_3$
d. Y= NHC_6H_5
e. Y= NHC_6H_{11}



VIII

a. Y= Cl
b. Y= OH
c. Y=-N△
d. Y= $N(CH_3)_2$
e. Y= p-NHC_6H_4Br
f. Y=-N◯O

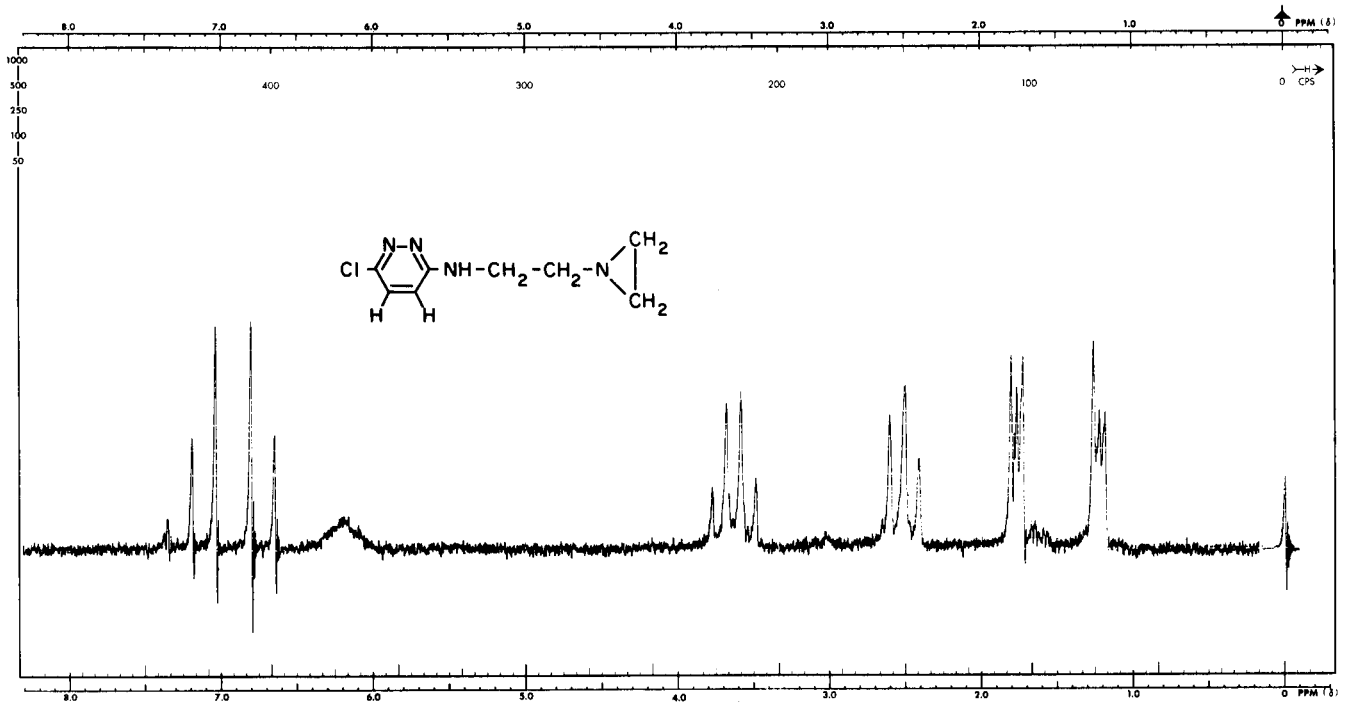


Fig. 1 - Nuclear magnetic resonance spectrum of 3-[β-(1-aziridinyl)-ethylamino]-6-chloropyridazine at 60 Mc.

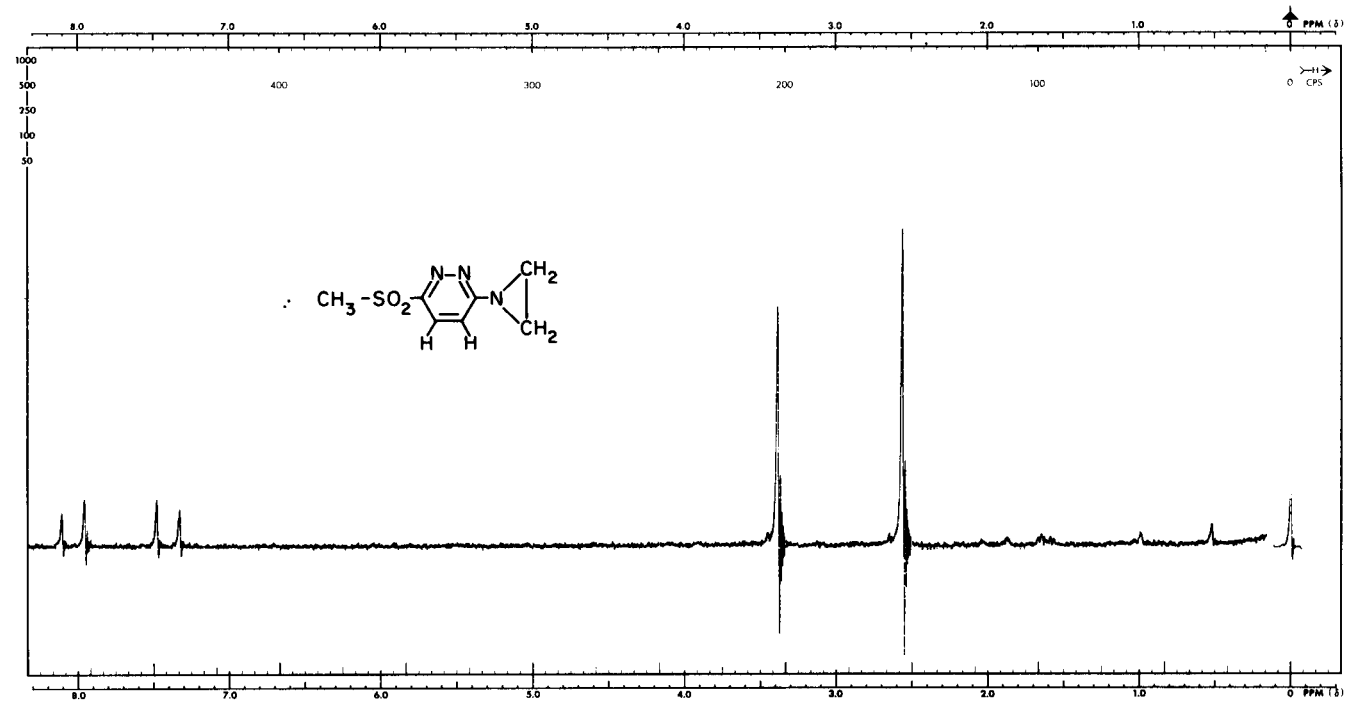


Fig. 2 - Nuclear magnetic resonance spectrum of 3-aziridinyl-6-methylsulfonylpyridazine at 60 Mc.

and aromatic primary and secondary amines gave exclusively 3-methylsulfonyl-6-(substituted amino)-pyridazines (VIIb-e), which indicated that the chloro group rather than the methylsulfonyl group was preferentially displaced.

The contradictory sequence of replacement of the methylsulfonyl versus the chloro group in 4,6-dichloro-2-methylsulfonylpyrimidine and in Id led to the investigation on the relative ease of replacement of these two groups in equivalent positions on a pyrimidine ring. Consequently, 4-chloro-6-methylsulfonylpyrimidine (VIIIa) was prepared. Results of the substitution study (VIIIb-f) have shown that the chloro group, again, was selectively replaced by nucleophilic agents.

EXPERIMENTAL (17)

3-[β-(1-Aziridinyl)ethylamino]-6-chloropyridazine (V).

A mixture of 35 g. of ethylenimine and 30 g. of finely powdered anhydrous potassium carbonate in 10 ml. of benzene was refluxed with vigorous stirring for 4 hr. To the refluxing mixture was added dropwise a solution of 15 g. of 3,6-dichloropyridazine in 30 ml. of benzene. After the addition the reaction mixture was again refluxed with vigorous stirring for 7 hr. (No polymerized material was observed at the end of the reaction.) Insoluble solid was filtered and washed with hot benzene. The combined washings and filtrate were evaporated *in vacuo* and the crude product, m.p. 125-127° (10-13 g.), was recrystallized very quickly from hot benzene in the presence of anhydrous potassium carbonate, m.p. 127-128°. The product was very soluble in ethanol, chloroform, and acetone, moderately soluble in ethyl acetate, water and hot benzene; and sparingly soluble in petroleum ether. It failed to yield an ionizable halide test in aqueous silver nitrate, but gave a positive halogen test after sodium fusion; λ max (*p*H 1) 240 mμ (ε 8,000), 308 mμ (ε 2,000); λ max (*p*H 11) 250 mμ (ε 13,000), 320 mμ (ε 1,800); λ max (Nujol) (μ) 3.1 (m), 3.25 (w), 3.5 (s), 6.25 (s), 6.72 (m), 6.9 (s), 7.35 (s), 7.75 (m), 8.0 (m), 8.7 (s), 9.1 (w), 9.25 (w), 9.6 (m), 9.95 (m), 11.85 (s), 12.2 (m), 12.4 (w), 12.8 (w), 13.0 (m), 13.9 (m).

Anal. Calcd. for $C_8H_{11}ClN_4$: C, 48.6; H, 5.79; N, 27.9; Cl, 17.9; Mol. wt. 198.5. Found: C, 48.4, 48.8, 48.5; H, 5.86, 5.91, 5.85; N, 28.2, 27.9; Cl, 18.2; Mol. wt. 195 ±5.

3-Chloro-6-methylthiopyridazine (Ie).

To a stirred solution of 12.3 g. of potassium hydroxide, 25 g. of methanthiol in 200 ml. of anhydrous methanol cooled to 0° was slowly added 29.8 g. of Ib dissolved in 200 ml. of anhydrous methanol. The resulting solution was stirred for 30 min. at room temperature and warmed on the steam bath for 1 hr. It was then cooled, filtered, and the filtrate evaporated to dryness *in vacuo*. Recrystallization of the crude product from heptane gave 27.9 g. (87% yield) of Ie, m.p. 103-104°; λ max (*p*H 1 and 11) 257 mμ (ε 12,800). This direct preparative method was found to be more practical than those reported previously (18a,b).

Anal. Calcd. for $C_5H_5ClN_2S$: C, 37.4; H, 3.12; N, 17.4. Found: C, 37.6; H, 3.46; N, 17.5.

3-Chloro-6-methylsulfonylpyridazine (Id).

Chlorine gas was slowly bubbled into a solution of 25 g. of Ie in 1,200 ml. of methanol and 5 ml. of water cooled to <-5°. A white precipitate gradually formed. After 20 min. the reaction mixture was cooled to <-20°. The crude product, m.p. 117-120°, was filtered and recrystallized from ethyl acetate and heptane to give 26 g. (87% yield) of Id, m.p. 118-120° (lit. (18) m.p. 114°); λ max (ethanol) 255 mμ (ε 1,400).

Anal. Calcd. for $C_5H_5ClN_2SO_2$: C, 31.3; H, 2.61; N, 14.6. Found: C, 31.2; H, 2.82; N, 14.8.

3-Aziridinyl-6-methylsulfonylpyridazine (VIIa).

Under strict anhydrous conditions, a mixture of 5 g. of 3-chloro-6-methylsulfonylpyridazine (Id), 6 g. of ethylenimine, 3 g. of triethylamine and 150 ml. of benzene was stirred at room temperature for 15 hr. The reaction mixture was then heated for 30 min. at 50°, and filtered. The filtrate was evaporated in the hood by passing a stream of air over the surface of the filtrate in an evaporating dish. The crude product was recrystallized from benzene and ether to give 3 g. (60% yield) of VIIa as white crystals, m.p. 147-148° dec. λ max (*p*H 1) 250 mμ (ε 12,500), 306 mμ (ε 1,600); λ max (*p*H 11) 249 mμ (ε 12,000). The product gave a positive test for sulfur and a negative test for chlorine.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.2; H, 4.52; N, 21.1. Found: C, 42.4; H, 4.76; N, 21.1.

3-Chloro-6-dimethylaminopyridazine (Ic).

A mixture of 15 g. of Ib and 200 ml. of aqueous 25% dimethylamine was heated in a bomb at 120-130° for 5 hr. and cooled. The solid product was filtered and recrystallized from heptane to give 10 g. (64% yield) of Ic, m.p. 100-101°; λ max (*p*H 1) 245 mμ (ε 6,000); λ max (*p*H 11) 257 mμ (ε 9,000).

Anal. Calcd. for $C_6H_8ClN_3$: C, 45.7; H, 5.09; N, 26.7. Found: C, 45.8; H, 5.30; N, 26.6.

3-Dimethylamino-6-methylsulfonylpyridazine (VIIb).

To a suspension of 5 g. of Id in 100 ml. of methanol was added 20 g. of 25% dimethylamine. An exothermic reaction occurred and all solids went into solution. The reaction mixture was then stirred at room temperature for 30 min. and cooled. The precipitated product was filtered and dried to give 4.5 g. (86% yield) of VIIb, m.p. 113-116°. Recrystallization from benzene raised the melting point to 116-118.5°; λ max (*p*H 1) 257 mμ (ε 16,700); λ max (*p*H 11) 275 mμ (ε 19,100).

Anal. Calcd. for $C_7H_{11}N_3O_2S$: C, 41.8; H, 5.47; N, 20.9. Found: C, 42.1; H, 5.50; N, 20.5.

3-Butylamino-6-methylsulfonylpyridazine (VIIc).

A solution of 4 g. of butylamine, 10 g. of Id, 5.5 g. of triethylamine in 500 ml. of benzene was refluxed for 20 hr. The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed with ether and recrystallized from benzene to give 11 g. (92% yield) of VIIc, m.p. 89-93°. Recrystallization from benzene raised the melting point to 117-118°; λ max (*p*H 1) 250 mμ (ε 13,800); λ max (*p*H 11) 266 mμ (ε 18,350).

Anal. Calcd. for $C_8H_{15}N_3O_2S \cdot 1/2\ H_2O$: C, 45.4; H, 6.73; N, 17.7. Found: C, 45.4; H, 6.54; N, 17.7.

3-Anilino-6-methylsulfonylpyridazine (VIId).

A solution of 5 g. of Id, 7 g. of aniline and 75 ml. of absolute ethanol was refluxed for 18 hr. On cooling, 5 g. (77% yield) of analytically pure VIId was obtained, m.p. 168-170°; λ max (*p*H 1) 272 mμ (ε 10,700); λ max (*p*H 11) 288 mμ (ε 15,000); λ max (ethanol) 294 mμ (ε 20,000).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.0; H, 4.43; N, 16.9. Found: C, 52.8; H, 4.72; N, 16.9.

3-Cyclohexylamino-6-methylsulfonylpyridazine (VIIe).

A mixture of 5 g. of Id, 10 g. of cyclohexylamine and 75 ml. of absolute ethanol was refluxed for 19 hr. The mixture was evaporated to dryness *in vacuo* and the residue treated with 300 ml. of water. The solid product was collected by filtration to give 6 g. (90% yield) of VIIe, m.p. 157-159°. Recrystallization from a mixture of water and methanol raised the melting point to 160-162°; λ max (*p*H 1) 252 mμ (ε 16,500); λ max (*p*H 11) 268 mμ (ε 22,850); λ max (ethanol) 266 mμ (ε 21,100).

Anal. Calcd. for $C_{11}H_{17}N_3O_2S$: C, 51.9; H, 6.67; N, 16.5. Found: C, 51.9; H, 6.49; N, 16.2.

4-Chloro-6-methylthiopyrimidine.

The procedure described by Marchal *et al.* (19) was found to be unsatisfactory in our laboratory. Consequently, a more direct synthetic approach to this compound, described as follows, was used.

To a stirred solution of 5.7 g. of analytical grade potassium hydroxide, 20 g. of methanthiol and 50 ml. of anhydrous methanol cooled to -10° was slowly added 14.9 g. of 4,6-dichloropyrimidine (20) dissolved in 100 ml. of anhydrous methanol. After the initial exothermic reaction had subdued, the reaction mixture was stirred for 30 min. at room temperature and followed by gentle warming on the steam bath for 1 hr. The insoluble inorganic salt was filtered and the filtrate evaporated to dryness. A quantitative yield of 4-chloro-6-methylthiopyrimidine was obtained, the melting point of the crude product was 46-50°. Recrystallization from hexane (84% recovery) raised the melting point to 52-54° (lit. (19) m.p. 50-51°); λ max (ethanol) 269 mμ (ε 9,900).

Anal. Calcd. for $C_5H_5ClN_2S$: C, 37.4; H, 3.12; N, 17.4. Found: C, 37.6; H, 3.42; N, 17.4.

4-Chloro-6-methylsulfonylpyrimidine (VIIIa).

Chlorine gas was slowly bubbled into a stirred solution of 23 g. of 4-chloro-6-methylthiopyrimidine, 50 ml. of concentrated hydrochloric acid, 500 ml. of water and 1 l. of methanol at 10°. A white precipitate was noted after 10 min. Addition of chlorine gas was discontinued after a total of 15 min. and the reaction mixture stirred for an additional 30 min. The white solid product was then filtered and washed with a small amount of cold water to give 20 g. (72% yield) of analytically pure VIIIa, m.p. 125-126°. The product gave positive tests for both halogen and sulfur; λ max (ethanol) 255 mμ (ε 4,200).

Anal. Calcd. for $C_5H_5ClN_2O_2S$: C, 31.2; H, 2.60; N, 14.5. Found: C, 30.9; H, 2.85; N, 14.4.

4-Hydroxy-6-methylsulfonylpyrimidine (VIIIb).

A stream of chlorine gas was passed through a solution of 300 ml. of methanol, 10 g. of 4-hydroxy-6-methylthiopyrimidine and 5 ml. of water. After 5 min. a sudden rise in temperature was noted. This was accompanied by the precipitation of a white solid. After an additional 10 min. the solid was filtered, and washed with methanol. Recrystallization of the product from ethyl acetate gave 10 g. (83% yield) of white solid, m.p. 223-224° (sublim.). The product gave positive sulfur and negative halogen tests; λ max (*p*H 1) 247 mμ (ε 4,000); λ max (*p*H 11) 230 mμ (sh) (ε 3,800), 263 mμ (ε 1,000).

Anal. Calcd. for $C_5H_6N_2O_3S \cdot H_2O$: C, 31.2; H, 4.17; N, 14.6. Found: C, 31.0; H, 3.99; N, 14.1.

4-Aziridinyl-6-methylsulfonylpyrimidine (VIIIc).

A mixture of 10 g. of VIIIa, 3 g. of ethylenimine, 5 ml. of triethylamine in 300 ml. of ethyl acetate was stirred at room temperature for 3 hr. The solid was filtered and the filtrate evaporated *in vacuo* to give an oil. A small amount of petroleum ether (b.p. 35-60°) was added to the oil, which caused the latter to solidify on standing. The solid, m.p. 106-108° (7.7 g., 75% yield), was recrystallized from a mixture of ethanol and hexane to give 4 g. (39% yield) of VIIIc, m.p. 112-113°; λ max (*p*H 1) 246 mμ (ε 13,600), 295 mμ (ε 4,000); λ max (*p*H 11) 241 mμ (ε 8,600), 277 mμ (ε 4,800); λ max (ethanol) 242 mμ (ε 9,600), 284 mμ (ε 3,900).

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.2; H, 4.52; N, 21.1. Found: C, 42.0; H, 4.88; N, 20.3.

4-Dimethylamino-6-methylsulfonylpyrimidine (VIIId).

Gaseous dimethylamine was bubbled into a stirred suspension of 10 g. of

VIIIa, 5 ml. of trimethylamine, 10 ml. of 25% dimethylamine and 100 ml. of ethanol. A slight temperature rise was noted at the beginning and all the solids dissolved. The passage of dimethylamine was continued for 1 hr. while the temperature of the reaction mixture was kept at 70°. The reaction mixture was then cooled and the precipitated product filtered to give 8.5 g. (72% yield) of VIIId, m.p. 138-141°. Recrystallization from absolute ethanol raised the melting point to 142.5-143.5°. The product gave positive sulfur and negative halogen tests; λ max (*p*H 1) 254 mμ (ε 13,400), 308 mμ (ε 4,000); λ max (*p*H 11) 254 mμ (ε 16,600), 312 mμ (ε 3,400).

Anal. Calcd. for $C_7H_{11}N_3O_2S$: C, 41.8; H, 5.47; N, 20.9. Found: C, 41.7; H, 5.54; N, 20.8.

4 (*p* Bromoanilino)-6-methylsulfonylpyrimidine (VIIIe).

A mixture of 14.5 g. of VIIIa, 25.8 g. of *p*-bromoaniline and 250 ml. of ethanol was refluxed for 6 hr. On cooling, 19 g. (77% yield) of analytically pure VIIIe was isolated, m.p. 218-219°; λ max (*p*H 1) 274 mμ (ε 14,750), λ max (*p*H 11) 276 mμ (ε 16,400).

Anal. Calcd. for $C_{11}H_{10}BrN_3O_2S$: C, 40.2; H, 3.06; N, 12.8. Found: C, 40.3; H, 3.29; N, 12.7.

4-Morpholino-6-methylsulfonylpyrimidine (VIIIf).

A mixture of 10 g. of VIIIa, 10 g. of morpholine and 250 ml. of absolute ethanol was refluxed for 3 hr. The hot reaction mixture was filtered from a small amount of solid impurities. On cooling, 12 g. (95% yield) of analytically pure VIIIf was collected from the filtrate; λ max (*p*H 1) 257 mμ (ε 18,500), 304 mμ (ε 6,050); λ max (*p*H 11) 256 mμ (ε 20,150), 310 mμ (ε 5,000).

Anal. Calcd. for $C_8H_{13}N_3O_2S$: C, 44.4; H, 5.35; N, 17.3. Found: C, 44.4; H, 5.37; N, 17.5.

Acknowledgment.

The authors wish to express their appreciation to Dr. Howard W. Bond for his interest in this problem, to Drs. Roland K. Robins and James J. Downs for the n.m.r. interpretations, and to Dr. S. Saijo for his information and sincere cooperation. They are also indebted to Mr. Hal P. Van Fossen, Mrs. Margaret L. Rounds, and Mr. John R. Gravatt for their analytical and instrumental measurements.

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(10) We thank Dr. S. Saijo of Simitomo Chemical Company, Osaka, Japan, for the information of this "pre-drying" procedure, which was used for the preparation of compounds described in their patent. *Cf.* ref. 8a.

(11) The elementary analysis for hydrogen was not reported in the Japanese patent, *cf.* ref. 8a.

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(13) For comparison, the n.m.r. spectrum of 3-aziridinyl-6-methylsulfonylpyridazine (VIIa) has also been examined (Fig. 2). This compound has an aziridinyl group attached directly to an aromatic system. The AB group was observed at 7.33 and 7.98 ppm. Sharp singlets were present at 3.36 ppm (CH_3 hydrogens) and 2.57 ppm (aziridinyl hydrogens). The result is consistent with the proposed totally planar aziridine nitrogen when the latter is attached to an aromatic system.

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Received October 2, 1963

Kansas City 10, Missouri