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[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

Pyrimidines. IV. Aziridinylpyrimidines[1]

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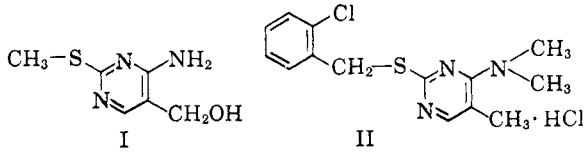
Syntheses of the aziridinylpyrimidine analogs of methioprim, DG-428 and DG-935 were accomplished. The activating effect of a 5-bromo group on the nucleophilic substitution of chloropyrimidines and methylsulfonylpyrimidines by ethylenimine was investigated. A new bromination method was reported.

The structures of 2-(1′-aziridinyl)-4,6-dichloropyrimidine and 4-(1′-aziridinyl)-2,6-dichloropyrimidine were definitely established by unambiguous syntheses and their chemical behavior was studied.

A number of alkylating agents of the ethylenimine type have been found to possess tumor inhibitory and cytotoxic activity,[2] especially in the treatment of the chronic leukemias, ovarian cancer, carcinoma of the breast, and the Hodgkin's disease.[2] Several of these compounds are being used clinically.[3] However, these compounds are, in general, quite toxic. It seems probable that a higher degree of selectivity might be attained by attaching the aziridinyl moiety to a "carrier" which could be transported *in vivo* to a particular site of action.[4]

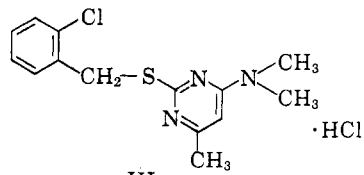
Early investigators[5] utilized the extremely reactive chloro-1,3,5-triazines to prepare numerous aziridinyl derivatives of considerable antitumor activity.[6] This would suggest that the pyrimidine ring, which is of more biological importance than the 1,3,5-triazine ring, might be advantageously utilized to design compounds with a more favorable therapeutic index. The pioneering study by Hendry and co-workers[7] has already indicated that in all cases where a comparison was possible, the pyrimidine derivatives proved to be more active than their triazine analogs. This apparent success strongly suggests that the specificity of action and, therefore, the antitumor activity might be further enhanced by utilizing, as carriers, pyrimidine derivatives more closely related to some known antimetabolites.

In an effort to enhance the known antimetabolic activity of methioprim (I),[8] DG-428 (II)[9] and DG-



I

II



III

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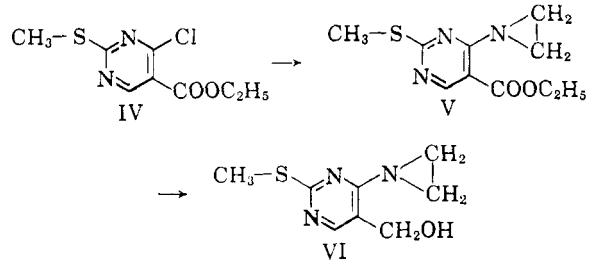
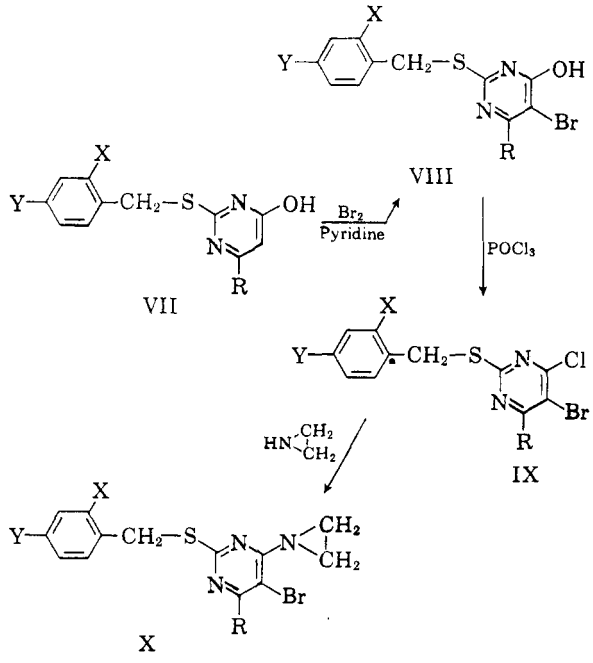
935 (III),[9] the ethylenimine moiety has been substituted for the amino and alkylamino groups of these compounds in the hope that these compounds might act as irreversible enzyme inhibitors.[10] 4-(1′-Aziridinyl)-5-hydroxymethyl-2-methylthiopyrimidine (VI) was prepared in a 47%



yield from the lithium aluminum hydride reduction of 4-(1′-aziridinyl)-5-carbethoxy-2-methylthiopyrimidine (V). V was in turn prepared from the corresponding 4-chloropyrimidine, IV,[11] with ethylenimine.

The rather mild conditions which must be employed with ethylenimine to effect the replacement of an active chloro group on the pyrimidine ring without causing polymerization greatly limits the selection of chloropyrimidines that can be used. In order to prepare aziridinylpyrimidines resembling structures II and III, the corresponding 4-chloropyrimidines must contain an electron withdrawing group at position 5. Although the presence of a nitro group at that position of the pyrimidine ring activates the system and favors nucleophilic replacement, the size and configuration of the nitro group is such that there is little chance for a nitropyrimidine to exhibit specific antimetabolic action. It is well known that the 5-bromouracil reversibly antagonizes thymine in DNA synthesis[12] apparently since a bromine atom approximates the size of a methyl group. This conception led logically to the investigation of the possibility of exploiting this "biologically acceptable" bromine atom to activate the ring.

Ordinary bromination procedures using bromine in acetic acid could not be employed for the bromination of 2-(substituted benzylthio)pyrimidines. Probably due to oxidative degradation of the benzylthio group, only unextractable substances were found at the end of the bromination. A new procedure has been devised in this laboratory using pyridine as the bromination medium and the yields were very satisfactory. For example, 5-bromo-2-(2′,4′-dichlorobenzylthio)-4-hydroxypyrimidine (VIII. X,Y = Cl, R = H) was obtained in 60%



yield by this method. Several 5-bromo compounds patterned after DG-428 (II) and DG-935 (III) were prepared *via* the chlorinated pyrimidines IX, but only the 4-(1′-aziridinyl)-5-bromopyrimidines containing 2-(*p*-chlorobenzylthio)- (X. R = H, CH_3; X = H, Y = Cl) and 2-(2′,4′-dichlorobenzylthio)- group (X. R = H; X, Y = Cl) could be purified successfully. The more closely related *o*-chlorobenzylthio- isomers, which are low melting, could not be isolated under the conventional mild conditions necessary for the purification of the thermally unstable aziridinyl compounds.

Several aziridinylpyrimidines were prepared through the replacement of a methylsulfonyl group rather than a chloro group since the former has been found to be more susceptible[13] to nucleophilic attack. An interesting example is the formation of 2-(1′-aziridinyl)-4,6-dichloropyrimidine (XIV) from 4,6-dichloro-2-methylsulfonylpyrimidine (XI)[13] even in the presence of an excess of ethylenimine. The structure of XIV was definitely established by elementary analyses and the fact that it gave a negative test for sulfur.

The presence of the 2-aziridinyl group in XIV greatly increased the electron density of the system, which protected the chlorine atoms at positions 4 and 6 against further nucleophilic displacement by an ethylenimino group. It is of interest to compare compound XIV with 2,4-di(1′-aziridinyl)-6-chloropyrimidine (XVI) which was prepared by Hendry and Homer[7b] from 2,4,6-trichloropyrimi-

(9) (a) K. Westphal and R. Bierling, *Naturwissenschaften*, **46**, 230 (1959); (b) *La Prensa Médica Argentina*, **46**, 2005 (1959); (c) G. Domagk, *Wien. med. Wochschr.*, No. 7, 131 (1960).

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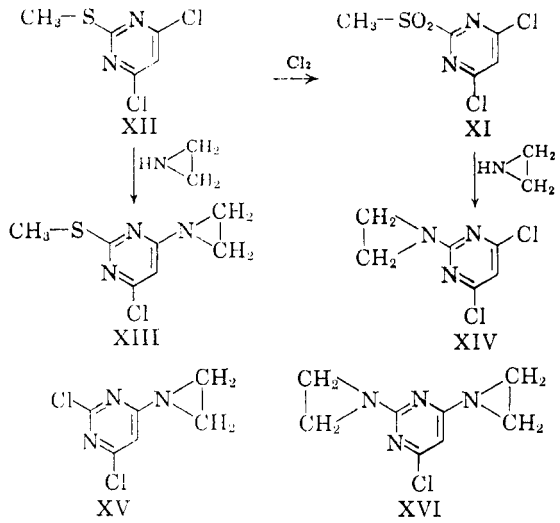


dine and excess ethylenimine. It is deduced that in the reaction of ethylenimine with 2,4,6-trichloropyrimidine, the chloro group at position 4 was replaced first (to form XV) followed by the replacement of the chloro group at position 2 to yield XVI, since the other order of replacement would have resulted in structure XIV, which would have prevented further replacement by ethylenimine.

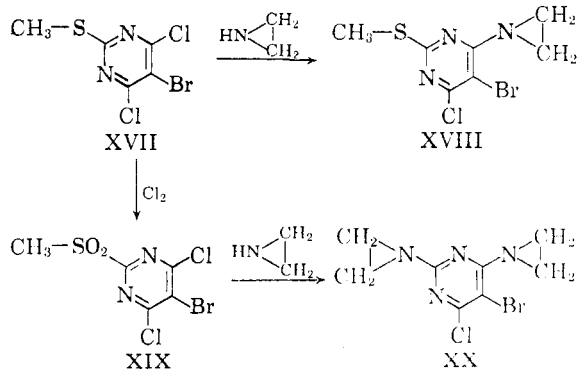
Hendry and Homer,[7b] in their study of the reaction of 2,4,6-trichloropyrimidine with one molecular proportion of ethylenimine, have reported the isolation of two products, which they tentatively assigned the structures of 2-(1′-aziridinyl)-4,6-dichloropyrimidine (XIV) for the less soluble fraction (m.p. 105°) and 4-(1′-aziridinyl)-2,6-dichloropyrimidine (XV) for the more soluble fraction (m.p. 111°) [the ratio of these two fractions is 5:1, respectively]. They have also reported that 2,4-di(1′-aziridinyl)-6-chloropyrimidine (XVI, m. p. 94–95°) was obtained in good yield from 2,4,6-trichloropyrimidine and excess ethylenimine. These findings are in direct conflict with our hypothesis that XVI can only be formed through XV but *not* through XIV.

Since the structure assignments made by Hendry and Homer[7b] are not supported by physical measurements other than melting point, it was necessary to reinvestigate the reaction of 2,4,6-trichloropyrimidine with one molecular proportion of ethylenimine. Only one product (fraction A′, m.p. 110–111°, see Experimental) was obtained. Fraction A′ was then reacted with excess ethylenimine to give a compound which was identified as 2,4-di(1′-aziridinyl)-6-chloropyrimidine (XVI, m.p. 93–95°) by comparison of its properties with those of a sample prepared directly from 2,4,6-trichloropyrimidine and excess triethylenimine.

From the facts that (1) both XIV and fraction A′, by elementary analysis, are shown to possess only one aziridinyl group and two chloro groups; (2) compound XVI can be prepared from fraction A′ but not from XIV; and (3) by comparison of ultraviolet absorption spectra, melting and mixed melting points, and R_f values of XIV and fraction A′, it is clearly demonstrated that these two compounds are distinctly different. Therefore, it is concluded that fraction A′ is the isomer of XIV, — *i.e.*, 4-(1′-aziridinyl)-2,6-dichloropyrimidine (XV).

A careful comparison of the experimental data submitted by Hendry and Homer[7b] with the data obtained in this laboratory indicates that the fraction, m.p. 111°, isolated by these workers was actually 4-(1′-aziridinyl)-2,6-dichloropyrimidine (XV) and suggests that the fraction, m.p. 105°, possibly was impure XV.

Only one chloro group of the compound 4,6-dichloro-2-methylthiopyrimidine (XII) was replaced under the rather mild condition by ethylenimine, hence 4-(1′-aziridinyl)-6-chloro-2-methylthiopyrimidine (XIII) was obtained. The presence of a bromine atom at position 5 still did not activate the pyrimidine system sufficiently to effect nucleophilic replacement by more than one ethylenimino group, thus a similar substitution product (XVIII) resulted from 5-bromo-4,6-dichloro-2-methylthiopyrimidine (XVII). Consequently 4-(1′-aziridinyl)-5-bromo-2-methylthiopyrimidine and 4-(1′-aziridinyl)-5-bromo-6-methyl-2-methylthiopyrimidine were obtained from 5-bromo-4-chloro-2-methylthiopyrimidine and 5-bromo-4-chloro-6-methyl-2-methylthiopyrimidine, respectively. On the other hand, a combined force of both the methylsulfonyl group and 5-bromo group did succeed in the replacement of *both* the methylsulfonyl group and one chlorine atom in 5-bromo-4,6-dichloro-2-methylsulfonyl pyrimidine (XIX) to give XX.



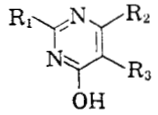
Methyl 6-chloro-2-methylthiopyrimidine-4-carboxylate and ethylenimine in benzene gave methyl 6-(1′-aziridinyl)-2-methylthio-4-pyrimidinecarboxylate. Probably due to the nonpolar nature of solvent used in this reaction, the expected rapid conversion of the ester group to an amide,[14] was not observed.

The ultraviolet absorption of aziridinylpyrimidines in ethanol is recorded in Table III. The

(14) G. Doyle Daves, Fred Baiocchi, R. K. Robins, and C. C. Cheng, "Pyrimidines. II. Orotic Acid Analogs," *J. Org. Chem.*, in press.

TABLE I

HYDROXYPYRIMIDINES

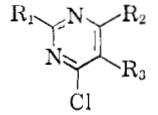


R_1	R_2	R_3	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3—S—[a]	OH	Br	>360	25.3	2.1	11.8	25.0	2.4	12.1
CH_3—S—[b]	CH_3	Br	144 (d)	30.1	2.9	11.9	30.1	3.0	11.9
CH_3—S—	OH	C_6H_5	299–301	56.4	4.2	12.0	56.0	4.0	11.7
o-Cl—C_6H_4—CH_2—S—	H	Br	182–184	39.8	2.7	8.4	40.0	2.9	8.3
o-Cl—C_6H_4—CH_2—S—	CH_3	Br	159–160	41.7	2.6	8.1	41.5	2.6	8.0
p-Cl—C_6H_4—CH_2—S—	H	Br	203–206	39.8	2.7	8.4	40.1	3.0	8.6
p-Cl—C_6H_4—CH_2—S—	CH_3	Br	169–171	41.7	2.6	8.1	41.7	2.9	8.3
2,4-$Cl_2C_6H_3$—CH_2—S—	H	Br	224–226	36.1	1.9	7.6	36.0	1.8	7.7

[a] Prepared from 2-thiobarbituric acid.[17] [b] Prepared from 2-mercapto-6-methyl-4-pyrimidinol.[18]

TABLE II

CHLOROPYRIMIDINES



R_1	R_2	R_3	Recrystallized Solvents	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3—S—	CH_3	Br	*n*-Heptane	69–70	28.5	2.6	11.0	28.7	2.7	11.1
CH_3—S—	Cl	Br	*n*-Heptane	83–85	21.9	1.1	10.2	21.7	1.3	10.4
CH_3—S—	Cl	C_6H_5	*n*-Heptane	108–110	48.7	3.0	10.3	48.5	3.2	10.6
CH_3—SO_2—	CH_3	Br	*n*-Heptane–ethyl acetate	140–142	25.2	2.1	9.8	25.1	2.1	9.8
CH_3—SO_2—	Cl	Br	*n*-Heptane–ethyl acetate	169–171	19.6	1.0	9.1	19.9	1.3	9.5
o-Cl—C_6H_4—CH_2—S—	H	Br	*n*-Heptane	55–56	37.5	2.9	8.0	37.3	2.6	8.2
o-Cl—C_6H_4—CH_2—S—	CH_3	Br	*n*-Heptane	80–82	39.5	2.5	7.7	39.4	2.4	7.7
p-Cl—C_6H_4—CH_2—S—	H	Br	*n*-Heptane	83–85	37.5	2.9	8.0	37.1	2.8	8.1
p-Cl—C_6H_4—CH_2—S—	CH_3	Br	*n*-Heptane	93–94	39.5	2.5	7.7	39.6	2.6	7.7
2,4-$Cl_2C_6H_3$—CH_2—S—	H	Br	*n*-Heptane	81–83	34.3	1.6	7.3	34.3	1.7	7.0

analogs of methioprim, DG-428 and DG-935 possess three characteristic absorption maxima in the vicinity of 230 mμ, 260 mμ, and 295 mμ.

EXPERIMENTAL[15]

2(o-Chlorobenzylthio)-4-pyrimidinol (VII. X = Cl, Y, R = H). To 800 ml. of 1*N* sodium hydroxide was added 150 ml. of *p*-dioxane followed by 64 g. (0.5 mole) of 2-thiouracil.[16] To this solution, was added 81 g. (0.5 mole) of *o*-chlorobenzyl chloride. The mixture was heated at 75–80° for 3 hr. with stirring. The resulting solution was then treated with charcoal, filtered, and acidified with acetic acid. The precipitate was filtered, washed with water and ligroin, and dried to give 116 g. (92%) of white solid, m.p. 216–219°. Recrystallization from ethyl acetate gave 2-(*o*-chlorobenzylthio)-4-pyrimidinol as white needles, m.p. 218–220°.

Anal. Calcd. for $C_{11}H_9ClN_2OS$: C, 52.4; H, 3.5; N, 11.1. Found: C, 52.4; H, 3.3; N, 11.0.

Other 2-(substituted-benzylthio)-4-hydroxypyrimidines were prepared by essentially the same procedure.

4,6-Dihydroxy-5-phenyl-2-pyrimidinethiol. To a mixture of 136 g. (2.5 moles) of sodium methoxide, 114 g. (1.5 moles) of thiourea, and 1500 ml. of methanol was added, with stirring, 233 g. (1 mole) of diethyl phenylmalonate. The mixture was carefully refluxed and stirred for 4 hr. The reaction mixture was then poured into 1 l. of hot water. The resulting pale green solution was treated with charcoal, boiled, filtered, and acidified with hydrochloric acid. The white precipitate was filtered and washed with water and acetone. The product was then recrystallized from a mixture of dimethylformamide and water to give 160 g. (73%) of white crystals, m.p. 261–263°.

Anal. Calcd. for $C_{10}H_8N_2O_2S_2$: C, 54.5; H, 3.6; N, 12.7. Found: C, 54.3; H, 3.4; N, 12.6.

Bromination of 2-methylthiopyrimidinols. Fifty grams of the 2-methylthiopyrimidine (the methylation of the mercapto group was described in Ref. 13) to be brominated was dissolved in 200 ml. of glacial acetic acid at 90°. To the solution was added, dropwise with stirring, an equivalent amount of bromine. After the reaction was complete, the heat was dis-

(15) All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2.

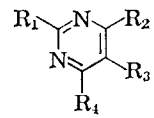
(16) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908).

(17) H. Michael, *J. prakt. Chem.*, [2], **35**, 456 (1887).

(18) M. Polonovski and H. Schmidt, *Bull. soc. chim. France*, [55], **17**, 616 (1950).

TABLE III

AZIRIDINYLPYRIMIDINES



Prepared from	R_1	R_2	R_3	R_4	Recrystallization Solvents	M.P.	U.V. Absorption (Ethanol) λ_{max}	ϵ	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	CH_3S—	A	—$COOC_2H_5$	H	Petroleum ether (b.p. 60–70°)	85–86	248 274 290 (s)	14,800 15,300 12,000	50.0	6.0	17.5	49.8	5.8	17.1
b	CH_3S—	A	—CH_2OH	H	Benzene–petroleum ether	156–157	235 250 (s) 289	23,600 14,000 7,900	48.7	5.6	21.3	48.7	5.5	21.5
c	*p*-Cl—C_6H_4—CH_2S—	A	Br	H	Methanol–petroleum ether	98–99	227 262 301	20,800 20,500 5,400	43.7	3.1	11.6	43.5	3.1	11.7
d	*p*-Cl—C_6H_4—CH_2S—	A	Br	CH_3	Benzene–petroleum ether	95–97	227 261 293 (s)	21,800 18,900 4,600	45.4	3.5	11.4	45.2	3.8	11.1
e	2,4-$Cl_2C_6H_3CH_2S$—	A	Br	H	Methanol–petroleum ether	87–89	232 261 301	22,700 19,600 5,500	39.8	2.6	10.7	39.7	2.5	10.6
f	CH_3—S—	A	H	Cl	Methanol–petroleum ether	88–90	237 253 (s) 289	18,200 15,200 5,300	41.6	3.9	20.8	41.5	3.8	20.6
g	CH_3—S—	MA	H	Cl	Petroleum ether	82–84	239 255 (s) 288	23,500 16,500 6,400	44.8	4.8	19.6	45.0	5.1	19.4
h	CH_3—S—	A	Br	H	Benzene–petroleum ether	93–94	237 261 302	14,300 17,000 4,400	34.1	3.2	17.1	34.0	3.5	16.8
i	CH_3—S—	A	Br	CH_3	Methanol–petroleum ether	75–77	235 260 295	15,300 18,500 5,200	36.9	3.8	16.1	36.9	4.0	15.9
j	CH_3—S—	A	Br	Cl	Methanol–petroleum ether	115–116	241 265 300	16,000 17,100 5,300	29.9	2.5	14.9	29.7	2.7	15.0
k	CH_3—S—	A	—C_6H_5	Cl	Methanol–petroleum ether	108–110	241 252 290 (s)	16,300 16,900 6,000	56.3	4.3	15.2	56.0	4.4	15.0
l	A	Cl	H	Cl	Methanol–petroleum ether	120–121	241 281	14,400 3,600	37.9	2.7	22.1	38.0	3.0	22.1
m	A	A	Br	Cl	Benzene–petroleum ether	135–136	227 246 (s) 292	22,400 14,600 6,900	34.8	2.9	20.3	34.6	3.1	20.2

TABLE III (*Continued*)

Prepared from	R_1	R_2	R_3	R_4	Recrystallization Solvents	M.P.	UV. Absorption (Ethanol) λ_{max}	ϵ	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
n	CH_3—	A	H	$-COOCH_3$	Acetone–petroleum ether	93–99	233 (s)	14,000	47.5	4.9	18.7	47.2	5.1	18.4
							251	15,700						
							321	3,900						
o	Cl	A	H	$-COOCH_3$	Methanol–petroleum ether	143–147	236 (s)	10,000	44.9	3.8	19.6	45.0	3.8	19.5
							296	5,200						
p	Cl	A	CH_3	H	Petroleum ether	77–79	234	8,000	49.4	4.7	24.7	49.2	4.8	24.5
							273	7,100						

[a] Ethyl 4-chloro-2-methyl-5-pyrimidinecarboxylate.[11] [b] See Experimental. [c] 5-Bromo-4-chloro-2-(*p*-chlorobenzylthio)pyrimidine, see Table II. [d] 5-Bromo-4-chloro-6-methyl-2-(*p*-chlorobenzylthio)pyrimidine, see Table II. [e] 5-Bromo-4-chloro-2-(2′,4′-dichlorobenzylthio)pyrimidine, see Table II. [f] 4,6-Dichloro-2-(methylthio)pyrimidine.[13] [g] Same as (*f*), with 2-methylaziridine. [h] 5-Bromo-4-chloro-2-(methylthio)pyrimidine.[20] [i] 5-Bromo-4-chloro-6-methyl-2-(methylthio)pyrimidine, see Table II. [j] 5-Bromo-4,6-dichloro-2-(methylthio)-pyrimidine, see Table II. [k] 4,6-Dichloro-5-phenyl-2-(methylthio)pyrimidine, see Table II. [l] 4,6-Dichloro-2-(methylsulfonyl)pyrimidine.[13] [m] 5-Bromo-4,6-dichloro-2-(methylsulfonyl)-pyrimidine, see Table II. [n] Methyl 6-chloro-2-methylthio-4-pyrimidinecarboxylate.[15] [o] Methyl 2,6-dichloro-4-pyrimidinecarboxylate.[15] [p] 2,4-Dichloro-5-methylpyrimidine.[21]

continued and the reaction mixture was stirred for 1 hr. During that time the brominated product separated from the warm reaction mixture. The product was filtered, washed with acetic acid and ether. It was then reprecipitated from dilute sodium hydroxide with acetic acid, and finally purified by recrystallization from water.

Bromination of 2-(substituted benzylthio)-4-pyrimidinols. Fifty-five grams of the pyrimidine was dissolved in 200 ml. of pyridine. The solution was warmed to 50°, and an equivalent amount of bromine was added dropwise with stirring. The rate of the addition was such that it maintained the temperature of the reaction mixture at 50–60°. Usually the brominated product started to crystallize from the warm mixture when half of the required bromine had been added. After the addition was complete, the mixture was stirred for 30 min. and then diluted with 500 ml. of water. A voluminous precipitate was obtained. This was filtered and washed with water. The crude material was dissolved in 1 l. of 1*N* hot sodium hydroxide. The resulting solution was chilled and the sodium salt of the brominated pyrimidine was collected. The sodium salt was then redissolved in 1 l. of boiling water, decolorized with charcoal, filtered and acidified with acetic acid. The resulting product was then recrystallized from water.

Chlorination of pyrimidinols. To 500 ml. of phosphorus oxychloride was added 80 g. of the corresponding pyrimidinol. The mixture was refluxed for 30 min. Excess phosphorus oxychloride was distilled from the clear solution under reduced pressure and the residue was poured onto crushed ice, with stirring. The crude chloropyrimidine was filtered, washed with water, and purified through ether extraction. It was then recrystallized from the appropriate solvent. The yields of all the purified chlorinated products were at 70–76%.

2-Methylsulfonylpyrimidines. To 200 ml. of absolute methanol was added 50 g. of the corresponding 2-methylthiopyrimidine. The suspension was cooled to 10°. A stream of dry chlorine gas was bubbled through the stirring mixture. A clear solution was formed after about 1 hr.; soon a precipitate reappeared. After another hour the resulting mixture was evaporated to dryness under a stream of cold air. The residue was recrystallized from a mixture of ethyl acetate and *n*-heptane to give the corresponding 2-methylsulfonylpyrimidine.

Preparation of aziridinylpyrimidines (see Table III). The aziridinylpyrimidines were prepared by the action of ethylenimine on chloropyrimidines or methylsulfonylpyrimidines in a low boiling, inert solvent. The methods used were modifications of the replacement of the chloro groups of 1,3,5-triazines with ethylenimine[19,5g] and of the method of Hendry and Homer.[7b] Examples are given as follows:

4-(1′-Aziridinyl)-5-carbethoxy-2-methylthiopyrimidine. To 200 ml. of benzene was added 32.4 g. (0.33 mole) of triethylamine and 14.2 g. (0.32 mole) of ethylenimine. The solution was warmed, with stirring, to 40°. A solution of 35.8 g. (0.15 mole) of 4-chloro-5-carbethoxy-2-methylthiopyrimidine[11] was added to the stirred solution at such a rate that the temperature was maintained at the range of 40–45°. After the completion of the addition, the reaction mixture was stirred for 45 min. The precipitated triethylamine hydrochloride was filtered and washed with benzene. The combined washings and filtrate were evaporated to dryness under a stream of cold air. The crude residue was recrystallized from petroleum ether (b.p. 60–70°) and methanol (care must be taken to avoid overheating of the crude solid product before a complete solution is obtained; a combined heater–magnetic

(19) (a) H. Bestian, *Ann.*, **566**, 210 (1950); (b) V. P. Wystrach, D. W. Kaiser, and F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5915 (1955); (c) H. Schroeder and C. Grundmann, *J. Am. Chem. Soc.*, **78**, 2447 (1956).

(20) T. B. Johnson and A. W. Joyce, *J. Am. Chem. Soc.*, **38**, 1557 (1916).

(21) O. Gerngross, *Ber.*, **38**, 3411 (1905).

stirrer is always found to be useful during the process of recrystallization) to give 24 g. of white crystals, m.p. 85–86°.

2-(1'-Aziridinyl)-4,6-dichloropyrimidine. To a solution of 64.7 g. of triethylamine and 28.2 g. of ethylenimine in 400 ml. of benzene was added, with stirring, 68 g. of 4,6-dichloro-2-methylsulfonylpyrimidine.[18] The temperature was kept below 45° throughout the reaction. Stirring was continued for 1 hr. after the addition. The polymerized substance was filtered and the filtrate was evaporated under a stream of cold air. The crude product was recrystallized from a mixture of petroleum ether and methanol to give 32 g. of white crystals, m.p. 120–121°. The product gave one spot in several paper chromatographic systems and gave a negative test for sulfur.

Attempted preparation of 2,4-di(1'-aziridinyl)-6-chloropyrimidine (XVI), from 2-(1'-aziridinyl)-4,6-dichloropyrimidine (XIV) with excess ethylenimine in benzene was unsuccessful. Only the starting material was isolated from the reaction mixture.

4-(1'-Aziridinyl)-5-hydroxymethyl-2-methylthiopyrimidine. To a 5-l. three-necked flask equipped with dropping funnel, stirrer, and a reflux condenser, was added 1 l. of anhydrous diethyl ether followed by 27.4 g. (0.72 mole) of finely powdered lithium aluminum hydride under an atmosphere of nitrogen. The mixture was stirred and heated to reflux. The heat was discontinued and a solution of 56.0 g. (0.24 mole) of 4-(1'-aziridinyl)-5-carbethoxy-2-methylthiopyrimidine in 1 l. of anhydrous diethyl ether was carefully added through the dropping funnel at such a rate that a gentle reflux was retained by the exothermic reaction. After the reaction was complete, the mixture was refluxed for 4 hr. The greenish suspension which formed at first was gradually turned white and by the end of the reaction, the reaction mixture had changed to a clear solution. Into the solution was dropped 1 l. of cold water with caution. This was followed by the addition of 1 l. of 2*N* sodium hydroxide. The resulting mixture was stirred for 30 min. The ether layer was separated and dried over anhydrous sodium sulfate. It was then filtered and the filtrate distilled under reduced pressure to give the product as white crystals. Recrystallization from benzene–petroleum ether (b.p. 60–70°) gave 22.0 g. (46%) of white needles, m.p. 156–157°.

Reaction between 2,4,6-trichloropyrimidine and one molecular proportion of ethylenimine. To a stirred solution of 30 g. (0.163 mole) of 2,4,6-trichloropyrimidine in 200 ml. of benzene was added a solution of 17.34 g. (0.17 mole) of triethylamine and 7.0 g. (0.163 mole) of ethylenimine in 200 ml. of benzene. The rate of addition was adjusted at such a rate that the temperature was kept between 30–35°. After the addition was complete, the mixture was stirred for 30 min. The precipitated triethylamine hydrochloride was filtered and washed with benzene. The combined filtrate was taken to dryness under a stream of cold air. Recrystallization of the crude solid from petroleum ether (b.p. 60–70°) yielded 20 g. of white crystals (fraction A), m.p. 90–110°. From the mother liquor, by evaporating to dryness, was isolated 4 g. of white crystals (fraction B), m.p. 90–95°. Recrystallization of fraction A from petroleum ether gave large, white rhombic crystals that melted at 110–111° (fraction A'). Further recrystallization did not raise the melting point of the product.

A mixed melting point of fraction A' and 2-(1'-aziridinyl)-4,6-dichloropyrimidine (m.p. 120–121°) gave a melting range between 93–96°. The melted liquid exploded suddenly at 97°. This phenomenon of explosion did not occur when these two compounds were melted separately.

Paper chromatography of the fraction A, fraction A', fraction B and 2-(1'-aziridinyl)-4,6-dichloropyrimidine in different solvent systems has indicated that neither fraction A, A', nor B contained 2-(1'-aziridinyl)-4,6-dichloropyrimidine, and fractions A and B were actually impure fraction A'. For instance, the R_f values of 2-(1'-aziridinyl)-4,6-dichloropyrimidine = 0.82, of fraction A = 0.68 (with slight tailing), of fraction A' = 0.68 and of fraction B = 0.68 (with tailing) in 4% sodium citrate at 24° (descending).

The elementary analyses of fraction A' indicated that only one aziridinyl group was present.

Anal. Calcd. for $C_6H_5Cl_2N_3$: C, 37.9; H, 2.6; N, 22.1. Found: C, 38.2; H, 2.7; N, 22.0.

Reaction of fraction A' and excess ethylenimine. To a solution of 18.0 g. (0.18 mole) of triethylamine and 7.3 g. (0.17 mole) of ethylenimine in 150 ml. of benzene was carefully added, with stirring, a solution of 16.0 g. (0.084 mole) of fraction A' in 150 ml. of benzene. The rate of addition was adjusted so the reaction temperature was kept in the range of 25–35°. After the addition was complete, stirring was continued for 30 min. The precipitated triethylamine chloride was filtered and washed with benzene. The combined filtrate was evaporated to dryness under a stream of cold air. The residue was recrystallized from petroleum ether (b.p. 60–70°) to give 10.0 g. of white crystals, m.p. 93–95°, R_f = 0.75 in 4% sodium citrate at 24° (descending). This compound was found to be identical with 2,4-di(1'-aziridinyl)-6-chloropyrimidine (m.p. 94–95°) prepared directly from 2,4,6-trichloropyrimidine.[7b]

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