temperature over 5% palladium on charcoal. The catalyst was filtered and the solvent removed *in vacuo*. The desired anhydride was obtained in colorless blocks in nearly quantitative yield, m.p. 99–101°. Recrystallization from benzene or ethyl acetate raised the m.p. to 105–106°. The unrecrystallized material is suitable for subsequent steps without further purification. The Δ^4 adduct cannot be recrystallized with heating as it decouples.

Endo-cis-3-methyl-3,6-endo-oxyhexahydrophthalic anhydride. Acetylene-1,2-diethyl carboxylate, 85 g. (0.50 mol.) and 2-methyl furan, 41.1 g. (0.50 mol.) were heated together at 100° for 20 hr. without solvent essentially as described[12,13,14] for furan and homologs. At the end of this period, all volatile products were removed by heating *in vacuo* at 70–80°. The adduct, a reddish brown oil, shown to be a $\Delta^{1,4}$ *endo*-oxycyclohexadiene[12] in the case of furan and acetylene-1,2-diethyl carboxylate, was hydrogenated in acetone with 5% palladium-charcoal to yield the Δ^1-adduct which was saponified with 20% methanolic potassium hydroxide to the free acid. This was obtained by evaporation to dryness on the water bath and extraction of the residue with two 200-ml. portions of ether. The ether was stripped and the resultant Δ^1-acid hydrogenated in methanol with 5% palladium-charcoal to yield the saturated acid. This was converted to the *endo-cis* anhydride by treatment with acetic anhydride containing 10% acetyl chloride and melted at 77–80° after distillation of excess reactants. Recrystallization from benzene, ethyl acetate, or acetone-ligroin raised the melting point to 87°.

Imides. The dimethylaminoethylimides of both anhydrides were prepared as previously described[6] by direct reaction of molar equivalents of the anhydrides and dimethylaminoethylamine without solvent. The imides were isolated as colorless oils boiling in the range 120–130°/0.2 mm. Imide hydrochlorides were prepared in isopropyl alcohol with alcoholic-hydrochloric acid. The boiling points of the imides and the melting points of their hydrochlorides were essentially identical (see Table II).

Isoindoles. The *exo-cis* and *endo-cis* isoindoles from the above imides were prepared[5] by reduction of 25.2 g. (0.10 mol.) quantities of the imides in anhydrous ether with lithium aluminum hydride and isolated by vacuum distillation. They were converted into dihydrochlorides and dimethiodides. Again the boiling points of the isoindoles, 100–105°/0.2 mm., and the melting points of the dimethonium salts were identical. The melting points of the dihydrochloride salts, however, differed considerably (see Table II).

FALLS CHURCH, VA.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXII.[2] Reactions of Orthoesters with 4,5-Diaminopyrimidines

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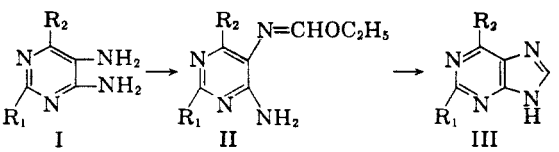
The usefulness of the reactions of triethyl orthoformate, triethyl orthoacetate, and triethyl orthopropionate with 4,5-diaminopyrimidines for the preparation of purines is discussed.

The preparation of chloropurines by the reaction of chloro-4,5-diaminopyrimidines with triethyl orthoformate–acetic anhydride[3] and with diethoxymethyl acetate (prepared from triethyl orthoformate and acetic anhydride)[4] has previously been reported from these laboratories.

In contrast to the behavior of 4,5-diamino-2-(or -6-)chloropyrimidine and 4,5-diamino-2,6-dichloropyrimidine, the reaction of 4,5-diaminopyrimidine with triethyl orthoformate–acetic anhydride gave 4,5-diacetamidopyrimidine[5] as the principal product and only a small amount of the expected purine. The reaction of 4,5-diaminopyrimidine and acetic anhydride alone also produced 4,5-diacetamidopyrimidine,[5] whereas 4,5-diamino-2-chloropyrimidine and acetic anhydride alone gave only the monoacetylated product, 5-acetamido-4-amino-2-chloropyrimidine. Apparently a chlorine atom in the 2 or the 6 position (or both) of the pyrimidine ring determines the course of the orthoester–acetic anhydride reaction.

Since hypoxanthine is readily formed from 4,5-diamino-6-pyrimidinol by merely refluxing the pyrimidine with formic acid, it seemed that treatment of the pyrimidine or one of its salts with triethyl orthoformate alone might also produce hypoxanthine. This surmise proved to be true, since the pyrimidine, its sulfate, and its hydrochloride gave hypoxanthine in good yield on refluxing with triethyl orthoformate, although the reaction mixture was heterogeneous in each case. The free pyrimidine



I II III

$CH_3COOC(OC_2H_5)=CHC(CH_3)(OC_2H_5)_2$

IV

$CH_3COOC(R)(OC_2H_5)_2$

V

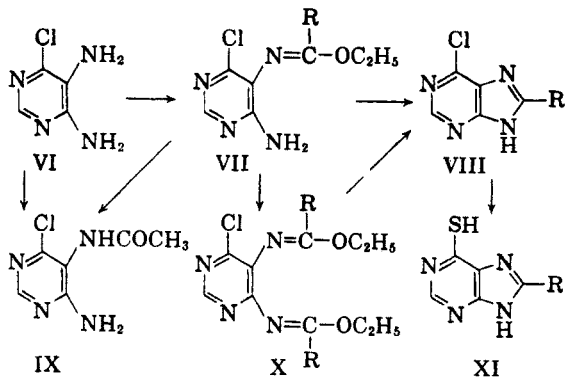
(1) Affiliated with the Sloan-Kettering Institute for Cancer Research. This work was supported by the Cancer Chemotherapy National Service Center (Contract No. SA-43-ph-1740) and by the C. F. Kettering Foundation.

(2) Part XXI. T. P. Johnston, C. L. Kussner, and L. B. Holum, *J. Org. Chem.*, **25**, 399 (1960).

(3) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

(4) (a) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **79**, 5238 (1957); (b) J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **80**, 404 (1958).

(5) D. J. Brown, *J. Appl. Chem.*, **7**, 109 (1957).



and diethoxymethyl acetate gave a homogeneous solution which yielded hypoxanthine on heating.

These results led us to reinvestigate the action of triethyl orthoformate alone on the chloro-4,5-diaminopyrimidines. The data now indicate that reaction takes place without acetic anhydride and that, in the case of the 2- and the 6-chloro-4,5-diaminopyrimidines, it is an intermediate such as II(R_1=Cl, R_2=H; R_1=H, R_2=Cl) which is formed; whereas 4,5-diamino-2,6-dichloropyrimidine is converted to 2,6-dichloropurine (III. R_1=R_2=Cl). In all cases the reaction is slow; however, the addition of formic acid or mixed alkane sulfonic acid to the reaction mixture increased the rate of all three reactions and also caused the 2- and the 6-chloro-4,5-diaminopyrimidines to be converted to the corresponding purines. A comparison of the results with diethoxymethyl acetate and ethyl orthoformate is shown in Table I.

TABLE I

Purine	% Yield: Diethoxymethyl Acetate	% Yield: Ethyl Orthoformate
6-Chloro-	75, 52[a]	53[b]
2-Chloro-	79[a]	64[b], 74[c]
2,6-Dichloro	89[d]	42, 78[c]
Hypoxanthine	48	75

[a] Using two equivalents of diethoxymethyl acetate in triethyl orthoformate. [b] Catalyst: mixed alkane sulfonic acid. [c] Catalyst: formic acid. [d] Ref. 4b.

Refluxing 4,5-diaminopyrimidine (I. R_1=R_2=H) with triethyl orthoformate alone gave 4-amino-5-(ethoxymethyleneamino)pyrimidine (II, R_1=R_2=H). Heating I(R_1=R_2=H) or II(R_1=R_2=H) in diethoxymethyl acetate converted them to purine; fusion at 180° also converted II (R_1=R_2=H) to purine.

Other experiments have shown that the usefulness of the orthoester ring closure for the preparation of purines is limited by lack of solubility of many 4,5-diaminopyrimidines in the medium and by the cost of the reagents. Its advantages are confined to the preparation of the chloropurines which cannot be prepared by other ring closure procedures because of concomitant hydrolysis of the chlorine atoms.

In an effort to extend the orthoester cyclization to the preparation of 8-alkylpurines, the reaction of triethyl orthoacetate and of triethyl orthopropionate with 4,5-diamino-6-chloropyrimidine was studied. Taylor[6] has reported the preparation of 2,8-dimethylhypoxanthine and, more recently, Prasad, Noell, and Robins[7] the preparation of 6,8-dimethylpurine by the use of triethyl orthoacetate and acetic anhydride. Since Post and Erickson[8] found that the reaction of triethyl orthoacetate and acetic anhydride gave IV instead of the methyl analog of diethoxymethyl acetate (V, R=CH_3), no attempts were made to prepare this compound or the ethyl analog (V, R=C_2H_5). Instead, the original orthoester-acetic anhydride cyclization procedure[3] was followed. 6-Chloro-8-methylpurine[9] and 6-chloro-8-ethylpurine were obtained from these reactions, but the yields were low. These low yields can probably be attributed to the predominance of side reactions. Our experimental evidence indicates that one of the side reactions is the acetylation of the pyrimidine (VI → IX) or the reaction of acetic anhydride with the initial product from the pyrimidine and the orthoester (VII → IX). In any case, it is doubtful whether acetic anhydride plays the same role in the reactions of triethyl orthoacetate and triethyl orthopropionate that it does in the reactions of triethyl orthoformate.[3,8]

In view of the success experienced in the acid-catalyzed reactions of triethyl orthoformate and the chloro-4,5-diaminopyrimidines mentioned above, this procedure was attempted with triethyl orthopropionate. The results were unexpected in that, instead of 6-chloro-8-ethylpurine (VIII, R=C_2H_5), a mixture of 4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine (VII, R=C_2H_5) and 6-chloro-4,5-bis(1-ethoxypropylideneamino)pyrimidine (X, R=C_2H_5) was obtained.

Other experiments showed that 4,5-diamino-6-chloropyrimidine heated with triethyl orthopro-

(6) E. C. Taylor, in G. E. W. Wolstenholme and C. M. O'Connor, eds., "The Chemistry and Biology of Purines" (A Ciba Foundation Symposium), J. and A. Churchill, Ltd., London, 1957, p. 20.

NOTE ADDED IN PROOF: Dr. Taylor has informed the authors of two papers in press describing this work in detail: E. C. Taylor and C. C. Cheng, *J. Org. Chem.*, **25**, 148 (1960) and E. C. Taylor, E. Richter, and J. E. Loeffler, *J. Org. Chem.*, in press.

(7) R. N. Prasad, C. W. Noell, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 193 (1959).

(8) H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

(9) Recently prepared by Koppel and Robins by another method.[10]

(10) H. C. Koppel and R. K. Robins, *J. Org. Chem.*, **23**, 1457 (1958).

pionate alone at 95–100° for two hours produced VII(R = C_2H_5) in good yield, and some 6-chloro-8-ethylpurine. Further heating of VII(R = C_2H_5) in triethyl orthopropionate at reflux temperature converted it to X(R = C_2H_5) (at 100° this conversion is slow). Heating VII(R = C_2H_5) in triethyl orthopropionate at 100° for one hour after the addition of a drop of formic acid also produced X(R = C_2H_5). Heating VII(R = C_2H_5) in triethyl orthopropionate for three hours after the addition of an equivolume of acetic anhydride produced a new compound whose ultraviolet absorption spectrum indicated that it was 5-acetamido-4-amino-6-chloropyrimidine (IX).

As expected, dry fusion of both VII(R = C_2H_5) and X(R = C_2H_5) produced 6-chloro-8-ethylpurine. Although better results were obtained with VII than with X, the yield from the former compound was only 36%. Attempts were made to improve the yield of the purine by the use of solvents. Heating the pyrimidine in *N,N*-dimethylformamide gave none of the desired purine; however, the use of dimethyl sulfoxide resulted in a 32% yield of the purine—about the same as by the dry fusion method. In later, large-scale runs the use of dimethyl sulfoxide was superior to the dry fusion.

The reaction of 4,5-diamino-6-chloropyrimidine and triethyl orthoacetate was very similar to the reaction of this pyrimidine with triethyl orthopropionate in that both the mono-(VII, R = CH_3) and disubstituted (X, R = CH_3) pyrimidines were formed; however, less of the disubstituted product was found in this case.

The identity of this latter compound (X, R = CH_3) was inferred from its ultraviolet and infrared absorption spectra; it was not isolated and purified. The 4-amino-6-chloro-5-(1-ethoxyethylideneamino)pyrimidine was converted to 6-chloro-8-methylpurine by dry fusion as in the case of 6-chloro-8-ethylpurine, but the yield was even lower (13%).

The 6-chloropurines were converted to the corresponding 6-purinethiols (XI, R = CH_3[10] and C_2H_5) in the usual manner,[4,11] since this work is a part of a study to determine the effect of substitution on the anticancer activity of 6-chloropurine and 6-purinethiol.

EXPERIMENTAL

The ultraviolet absorption spectra were determined in aqueous solution with a Beckman DK-2 spectrophotometer, but the optical densities at the maxima were determined with a Beckman DU. The infrared spectra were determined in pressed potassium bromide discs with a Perkin-Elmer model 21 spectrophotometer. Melting points were determined on a Kofler Heizbank and are corrected.

Purine. A solution of 4,5-diaminopyrimidine (500 mg.) in diethoxymethyl acetate (5 ml.) was heated at 120° for 1 hr. and then evaporated to dryness *in vacuo*. Volatile impurities were removed by dissolving the residue in methanol and evaporating the solution *in vacuo*. The brown solid obtained was dried *in vacuo* over phosphorus pentoxide: yield, 540 mg.; m.p., 190–194°. This material, a mixture of purine and 9(7)-acetylpurine, was recrystallized from a 3:1 mixture of ethyl acetate and toluene (200 ml.) using Norit treatment. The yield of recrystallized purine was 445 mg. (82%); m.p., 212–214° (lit.[12] 212–213°).

A small amount of material obtained from the mother liquor from the recrystallization was identified as 9(7)-acetylpurine by a comparison of its infrared spectrum with that of an authentic sample (see below).

9(7)-Acetylpurine. A suspension of purine (500 mg.) in acetic anhydride (3 ml.) was heated on a hot plate for several minutes. The solution was chilled, and the solid that deposited was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 175 mg.; m.p., 167–168° with sublimation.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 261 (6.9); *p*H 7: 263 (7.9); *p*H 13: 271 (7.7); C_2H_5OH: 264 (7.3). $\bar{\nu}$ in $cm.^{-1}$: 3050, 3000, 2940, and 2910 (CH); 1730 (C=O of active acetyl); 1595, 1570 and 1495 (C=C, C=N); 1400, 1330, 1300, 1275, 960, 800 and 715 (strong unassigned bands).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.56. Found: C, 51.80; H, 3.86; N, 34.41.

Dilution of the acetic anhydride filtrate with 1:1 ether-Skellysolve C (b.p. 85°–105°) (100 ml.) gave an additional 135 mg. of 9(7)acetylpurine; m.p., 166–167°. Total yield, 310 mg. (46%).

5-Acetamido-4-amino-2-chloropyrimidine. A suspension of 4,5-diamino-2-chloropyrimidine (700 mg.) in acetic anhydride (15 ml.) slowly became homogeneous when warmed at 40°, and then a white flocculent precipitate deposited. After standing overnight the solution was filtered and the solid that was collected was washed with absolute ethanol and dried *in vacuo* over phosphorus pentoxide: yield, 740 mg. (82%); m.p., 209–211°.

Recrystallization of the crude material (260 mg.) from propanol (8 ml.) gave a white solid: yield, 145 mg.; m.p., 214–215°.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$); *p*H 1: 240–270 (broad); *p*H 7: 235.5 (8.86), 280.5 (5.48); *p*H 13: 251.5 (broad) (7.14), 283.5 (6.75).

Anal. Calcd. for $C_6H_7ClN_4O$: C, 38.60; H, 3.78; N, 30.00. Found: C, 38.69; H, 4.12; N, 29.89.

4-Amino-5-(ethoxymethyleneamino)pyrimidine (II, $R_1 = R_2 = H$). A suspension of 4,5-diaminopyrimidine (500 mg.) in triethyl orthoformate (25 ml.) was heated on a hot plate for 5 min., the solution cooled, and the crystals that deposited collected by filtration, washed with Skellysolve C (25 ml.) and dried *in vacuo* over phosphorus pentoxide: yield, 360 mg.; m.p., 130°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 7: 252 (8.20), 284 (6.30); *p*H 13: 258 (8.4), 283 (6.6). $\bar{\nu}$ in cm^{-1}: 3380 and 3320 (NH); 2960 and 2920 (CH); 1640 (exocyclic C=N); 1630 (NH); 1585 and 1500 (C=C, C=N); 930 and 910 (ring CH).

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.60, H, 6.03; N, 33.70. Found: C, 50.81; H, 6.14; N, 33.92.

An additional 140 mg. of impure product was obtained from the triethyl orthoformate filtrate. The total yield was 500 mg. (66%).

Reaction of 4,5-diamino-6-chloropyrimidine with triethyl orthopropionate (A). A mixture of 4,5-diamino-6-chloropyrimidine (5.0 g.) and triethyl orthopropionate (100 ml.) containing a small amount of 98% formic acid (about 0.5 ml.) was heated with stirring at 100° for 15 min. The light yellow solution was heated at 100° for an additional 2 hr., and evaporated under diminished pressure to a semi-solid.

(11) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6037 (1954).

(12) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

The light brown solid, *4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine*, (VII, R = C_2H_5), was collected by filtration, washed with Skellysolve C (15 ml.), and dried *in vacuo* over phosphorus pentoxide: yield, 2.73 g. (34.5%); m.p., 128° (solidifies and remelts 135°). The ultraviolet spectrum indicates that this material decomposes to 4,5-diamino-6-chloropyrimidine in 0.1*N* hydrochloric acid.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 269 (6.4), 306 (8.1); *p*H 7: 250 (7.2), 284 (6.9); *p*H 13: 250 (7.25), 284 (6.95). $\bar{\nu}$ in cm.$^{-1}$: 3400, 3330, and 3210 (NH); 2990, 2950 and 2920 (aliphatic CH); 1660 (exocyclic C=N); 1630 (NH); 1560 and 1540 (C=C, C=N); 1470 and 1375 (aliphatic CH).

Anal. Calcd. for $C_9H_{13}ClN_4O$: C, 47.20; H, 5.68; N, 24.50. Found: C, 47.22; H, 5.65; N, 24.18.

The combined filtrate and wash were evaporated to dryness *in vacuo*, giving a brownish liquid, *6-chloro-4,5-bis(1-ethoxypropylideneamino)pyrimidine* (X, R = C_2H_5); yield, 6.86 g. (63.5%). The ultraviolet spectrum indicates that this material decomposes to 4,5-diamino-6-chloropyrimidine in 0.1*N* hydrochloric acid.

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 265 (6.9), 307 (6.2); *p*H 7: 250 (6.45), (8.7); *p*H 13: 250 (6.45), 287 (8.7). $\bar{\nu}$ in cm.$^{-1}$: 2990, 2960 and 2920 (aliphatic CH); 1670 (broad) (exocyclic C=N); 1540 and 1520 (C=C, C=N); 1470 and 1370 (aliphatic CH).

Distillation of this material (6.86 g.) *in vacuo* (0.1–0.05 mm.) gave a light brown liquid (5.8 g.). The ultraviolet and infrared spectra were practically identical with those given above.

Anal. Calcd. for $C_{14}H_{21}ClN_4O_2$: C, 53.70; H, 6.72; N, 17 90. Found: C, 53.71: H, 6.41; N, 17.50.

(*B*). A mixture of 4,5-diamino-6-chloropyrimidine (0.51 g.) and triethyl orthopropionate (25 ml.) was heated with stirring at 95–100° for 2 hr. A small amount of unchanged 4,5-diamino-6-chloropyrimidine was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The solid residue was triturated with Skellysolve C (5 ml.), and then collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 0.60 g. (75%); m.p., 128° (solidifies and remelts at 134–135°). The ultraviolet spectrum of this material was identical with that of *4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine* (VII, R = C_2H_5).

Impure *6-chloro-8-ethylpurine* (*0.24 g.*) was obtained by evaporation of the Skellysolve filtrate described above.

6-Chloro-8-ethylpurine (VIII, R = C_2H_5) (A). A melt of 4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine (1.00 g.) was heated in a beaker at 155–160° for 45 min. The resulting gum was extracted with three 100-ml. portions of hot benzene, and the combined extracts evaporated to dryness *in vacuo:* yield, 0.250 g.; m.p., 167° dec.

An additional amount of solid was obtained by extracting an aqueous solution of the residue from the benzene extraction with ether (100 ml.). Sublimation of the combined solids at 135° (0.1 mm.) gave 290 mg. (36%) of 6-chloro-8-ethylpurine; m.p., 170–172° dec. (when heated from 150°).

Spectral Data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 232 (3.86), 238 (3.93), 265 (11.2); *p*H 7: 270 (11.0); *p*H 13: 277 (11.8.) $\bar{\nu}$ in cm.$^{-1}$: 3060 (heterocyclic CH); 2995 and 2940 (aliphatic CH); 2800–2400 (acidic H); 1610, 1585 and 1520 (C=C, C=N); 1450 (aliphatic CH); 1380 (C—CH_3); 1235 and 1220 (unassigned).

Anal. Calcd. for $C_7H_7ClN_4$: C, 46.00; H, 3.84; N, 30.70. Found: C, 46.04; H, 3.88; N, 30.60.

(*B*). A solution of 280 mg. of 4-amino-6-chloro-5-(1-ethoxypropylideneamino)pyrimidine in dimethyl sulfoxide (2 ml.) was heated at 140° for 1 hr. The solution was then diluted with water (10 ml.) and extracted with three 20-ml. portions of ether. After being dried, the combined ether extracts were evaporated to dryness *in vacuo* and the residue sublimed at 140° (0.5–0.3 mm.) to give 70 mg. of 6-chloro-8-ethylpurine: m.p., 168° dec. (rapid heating from 150°). The ultraviolet and infrared spectra of this solid were practically identical with those given in (*A*) above.

4-Amino-6-chloro-5-(1-ethoxyethylideneamino)pyrimidine (VII, R = CH_3). A mixture of 4,5-diamino-6-chloropyrimidine (1.00 g.) and triethyl or thioacetate (60 ml.) was heated with stirring at 100–105° for 15 min., giving a yellow solution. The solution was evaporated to dryness *in vacuo*, the residue triturated with Skellysolve C, and the light brown solid collected by filtration and dried *in vacuo* at 80°: yield, 1.17 g. (79.5%); m.p., 144°. The ultraviolet spectrum indicates that this material decomposes to 4,5-diamino-6-chloropyrimidine in 0.1*N* hydrochloric acid.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 269 (6.6), 306 (8.7); *p*H 7: 249 (7.3), 283 (7.0); *p*H 13: 249 (7.3), 283 (7.0). $\bar{\nu}$ in cm.$^{-1}$: 3320 and 3150 (NH); 2970, 2920 and 2845 (aliphatic CH); 1660 (C=N); 1640 (NH); 1560 and 1550 (C=C, C=N); 1450 and 1380 (C—CH_3).

Anal. Calcd. for $C_5H_{11}ClN_4O$: C, 44.70; H, 5.12; N, 26.10. Found: C, 44.79; H, 5.08; N, 26.04.

The Skellysolve C filtrate was evaporated to dryness to give a small amount of brownish liquid. The ultraviolet and infrared spectra indicated that this material was impure *6-chloro-4,5-bis(1-ethoxyethylideneamino)pyrimidine*, since the spectra were very similar to those of 6-chloro-4,5-bis(1-ethoxypropylideneamino)pyrimidine.

6-Chloro-8-methylpurine[9] (VIII, R = CH_3) (A). A melt of 4-amino-6-chloro-5-(1-ethoxyethylideneamino)pyrimidine (1.10 g.) was heated in a sublimation tube at 150–155° for 1.5 hr. The resulting residue was then subjected to sublimation at the same temperature under reduced pressure. After a small amount of impure starting material was collected, the residue was sublimed at 180–185° to give a white solid; yield, 190 mg. This material decomposed at *ca.* 200°.

This sample was further purified by dissolving it in warm 2*N* sodium hydroxide (2 ml.) and extracting the cooled, neutralized solution with three 20-ml. portions of chloroform. Evaporation *in vacuo* of the combined extracts gave a white solid: yield, 110 mg. (13%); m.p., 225–227° dec. (rapid heating from 200°; lit,[10] 212–213°).

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 264 (11.0); *p*H 7: 269 (10.6); *p*H 13: 277 (10.6). $\bar{\nu}$ in cm.$^{-1}$; 2940 and 2870 (aliphatic CH); 1610, 1570, and 1520 (C=C, C=N); 1440 and 1380 (C—CH_3); 1340, 1220, and 1000 (unassigned).

Anal. Calcd. for $C_6H_5ClN_4$: C, 42.70; H, 2.97; N, 33.25. Found: C, 42.50; H, 3.12; N, 33.47.

(*B*). A mixture of 4,5-diamino-6-chloropyrimidine (2.00 g.) and triethyl orthoacetate (100 ml.) was heated with stirring at 95–100° for 20 min., and the resulting solution evaporated to dryness *in vacuo*. The residue was heated at 155° for 1.5 hr., and the resulting gum was treated with boiling water. After removal of the insoluble residue, the aqueous filtrate was evaporated to dryness, giving a solid residue which was sublimed at 180° *in vacuo*. This material (0.78 g.) on recrystallization from benzene gave impure 6-chloro-8-methylpurine; yield, 0.50 g.; m.p., 213–215° dec. (taken fast from 200°). This material was used, without further purification, for the preparation of 8-methyl-6-purinethiol.[10]

8-Ethyl-6-purinethiol (XI, R = C_2H_5). A solution of crude 6-chloro-8-ethylpurine (760 mg.) in propanol (10 ml.) containing thiourea (350 mg.) was refluxed for 4 hr., evaporated to dryness, and the residue dissolved in hot water (30 ml.). Concentration of the aqueous solution in a stream of nitrogen deposited hydrated 8-ethyl-6-purinethiol: yield, 370 mg. (48%); m.p., >260°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1: 227 (11.6); 327 (18.8); *p*H 7: 232 (10.9); 324 (19.4); *p*H 13· 234 (15.4); 309 (19.5). $\bar{\nu}$ in cm.$^{-1}$: 3000–2300 (aliphatic CH); 2800–2400 (acidic H); 1615, 1580, 1540, and 1500 (C=C, C=N); 1470 and 1375 (C—CH_3); 1340 and 1190 (unassigned).

Anal. Calcd. for $C_7H_8N_4S \cdot {}^1/_3H_2O$: C, 45.16; H, 4.66; N, 30.15. Found: C, 45.17; H, 4.73; N, 29.79.

The above material did not lose its water of crystallization after being dried *in vacuo* over phosphorus pentoxide. Anhydrous 8-ethyl-6-purinethiol was obtained by dissolving the hydrated material in hot methyl isobutyl ketone, and evaporating the solution to dryness *in vacuo*.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.66; H, 4.48; N, 31.10; Found: C, 46.37; H, 4.45; N, 30.60.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXI. Nitrosated Sulfonamides Related to Myleran

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A number of *N,N'*-polymethylenebis[*N*-nitrosomethanesulfonamide]'s and *N,N'*-dimethyl-*N,N'*-dinitrosoalkanedisulfonamides, structurally related to the anticancer agent Myleran and isomeric Myleran, respectively, have been prepared by the nitrosation of the corresponding bissulfonamides. In contrast, the nitrosation of simple *N*-substituted methanesulfonamides gave unstable products.

Current interest in the anticancer activity exhibited by 1-methyl-3-nitro-1-nitrosoguanidine[2,3] and particularly by 1-methyl-1-nitrosourea[3] against Leukemia L1210 in mice has focused attention on other *N*-nitroso compounds, such as *N*-nitrososulfonamides,[4] that have the common property of undergoing basic decomposition to give diazomethane. In the search for possible new anticancer agents containing a methyl-*N*-nitrosoamino group, a logical approach would appear to be the replacement of the functional group of known anticancer agents by a nitrosated function of the type described above. On the basis of structural similarity to the tetramethylene ester of methanesulfonic acid (Myleran), the synthesis and screening of certain bifunctional aliphatic nitrososulfonamides (Table I) were undertaken. Myleran belongs to a class of alkylating agents first reported as effective agents in the chemotherapy of neoplastic diseases by Haddow and Timmis[5] in 1953.

The following types of isomeric bisnitrososulfonamides have been prepared by the nitrosation of the corresponding bis-sulfonamides (see Table I): (1) *N,N'*-dimethyl-*N,N'*-dinitrosoalkanedisulfonamides (IIIa, b, c) and (2) *N,N'*-polymethylenebis-[*N*-nitrosomethanesulfonamide]'s (IVa,b,c). These nitrosations were performed by treating formic acid solutions of the bis-sulfonamides Ia, b, c and IIa, b, c with aqueous sodium nitrite solution. Pure samples of the bisnitrososulfonamides of each class are relatively stable solids when kept cool and dry; some have been stored for several months without appreciable decomposition. One mode of decomposition was observed when a sample of *N,N'*-tetramethylenebis[*N*-nitrosomethanesulfonamide] (VIb) was stored for six months at room temperature with no special precaution to keep it anhydrous: denitrosation to the corresponding bis-sulfonamide IIb occurred (*cf.* the thermal denitrosations of *N*-nitrosomethanesulfonanilide and *N*-nitroso-*p*-toluenesulfonanilide described by de Boer[6]). The liquid nitrosates derived from *N*-methyl[7]-, *N*-benzyl- and *N*-(*p*-chlorobenzyl)methanesulfonamides (VIa, b) are too unstable to permit isolation of pure products. The bisnitrososulfonamides IIIb and IVb were subjected to thermal decomposition in chlorobenzene by a procedure similar to that employed by de Boer in his study of the decomposition of *N*-methyl-[6] and other *N*-alkyl-*p*-toluenesulfonamides.[8] Compound IIIb evolved nitrogen smoothly at 90°, and relatively pure dimethyl 1,4-butanedisulfonate crystallized from the cooled reaction mixture, whereas IVb evolved nitrogen slowly at 85°, but the reaction product separated as an acidic brown oil, indicating that the tetramethylene ester of methanesulfonic acid apparently formed underwent excessive decomposition (m.p.[9] of pure Myleran, 116°).

The intermediate alkanedisulfonyl chlorides used to prepare the *N,N'*-dimethylalkanedisulfonamides Ia, b, c were also converted by treatment with sodium methoxide into the corresponding dimethyl

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