A suspension of 9.5 g. of the above hydrochloride in 50 ml. of water was adjusted to *p*H 7 with concentrated ammonia water. The resulting solution was diluted with 150 ml. of absolute ethanol. When the walls of the flask were scratched, the product began to crystallize; yield 4.75 g. (60%), m.p. 238–255° dec. No attempt was made to obtain a second crop. Several recrystallizations of a sample from 50% ethanol gave white crystals, m.p. 242–257° dec.[31]; λ_{max}^{KBr} 2.99 μ (NH_2), 3.40, 6.66 (NH_3^+), 7.10 (COO^-).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.71; N, 15.5. Found: C, 60.4; H, 6.77; N, 15.5.

Both the hydrochloride and the free base traveled on paper as a single spot (R_f 0.34) in solvent C.[26]

3-(*m*-Diazoniumphenyl)-DL-alanine Difluoborate (XXII).—A solution of 0.35 g. (2 mmoles) of XXI in 3 ml. of 48% fluoboric acid was cooled to 4° in an ice-bath, causing separation of a salt. The mixture was treated dropwise with stirring with a solution of 0.16 g. (2 mmoles) of sodium nitrite in 0.3 ml. of water. The solution was treated with 6 ml. of ice-cold 1:1 absolute ethanol–ether. The product which separated was collected on a filter and washed with 40 ml. of cold absolute ethanol in portions, then 40 ml. of cold ether in portions. The white solid, m.p. 99° dec., gradually turned pink on standing at room temperature; yield 0.45 g. (81%). For analysis a sample was quickly dissolved in the minimum of ice-water, then diluted with ice-cold 1:1 absolute alcohol–ether until turbid. The sample was collected on a filter and dried for 30 minutes at 0° and 4 mm., then immediately analyzed. The analysis indicated contamination with some monofluoborate since the C:H:N ratio was in close agreement for a salt of 3-(*m*-diazoniumphenyl)-DL-alanine.

Anal. Calcd. for $C_9H_{11}B_2F_8N_3O_2$: C, 29.5; H, 3.02; N, 11.5. Found: C, 30.8; H, 3.29; N, 12.5.

After three weeks at 20°, the sample had only 9.63% nitrogen, thus showing its instability even in the solid state. When dissolved in water at 0°, it evolved nitrogen at a noticeable rate. The freshly prepared analytical sample showed COOH absorption at 3.84 and 5.80 μ, $-N{\equiv}N$ at 4.36 μ, NH_3^+ at 6.14 and 6.58 μ and broad BF_4^- absorption centering at 9.50 μ in the infrared.

Acknowledgments.—The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry. The authors are also indebted to Mr. O. P. Crews, Jr., and his staff for large-scale preparation of certain intermediates.

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droxide hydrolysis; *cf.* H. R. Henze, W. B. Whitney and M. A. Eppright, THIS JOURNAL, **62**, 565 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XVIII. Synthesis of Substituted 4,5-Trimethylenepyrimidines

BY LEONARD O. ROSS, LEON GOODMAN AND B. R. BAKER

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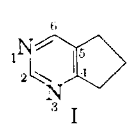
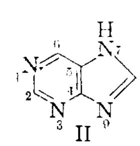
The condensations of 2-carbethoxycyclopentanone (III) with guanidine, thiourea and 2-methyl-2-thiopseudourea led to 2-amino-4-hydroxy- (IV), 4-hydroxy-2-mercapto- (XX) and 4-hydroxy-2-(methylthio)-5,6-trimethylenepyrimidine (XXIX), respectively. Compounds IV, XX and XXIX were converted to a variety of substituted 4,5-trimethylenepyrimidines, several of which are closely related structurally to biologically important purines.

Purines and pyrimidines are associated with a wide variety of biologically important systems and, accordingly, much work has been concerned with the synthesis of antimetabolites of these classes of compounds. The success of such compounds as 6-purinethiol[2] and 5-fluorouracil[3] as chemotherapeutic agents is justification for further investigations in these areas. The synthesis of 4,5-trimethylenepyrimidine (6,7-dihydro-5H-cyclopentapyrimidine) (I) and of a number of substitution products then leads to potential natural purine (II) antagonists as well as natural pyrimidine antagonists.



I



II

Condensation of 2-carbethoxycyclopentanone (III) with excess guanidine carbonate in ethanol gave 2-amino-4-hydroxy-5,6-trimethylenepyrimidine (IV), the analog of guanine, in about 50% yield. Attempts to prepare IV with guanidine hydrochloride by the procedure described by Hull, *et al.*,[4] gave yields of about 20% in contrast to the reported yield of 62.5%; a competing cleavage of III to methyl ethyl adipate seemed to be responsible for the poor yields of IV encountered. Compound IV has also been prepared (in unstated yield) by Braker, *et al.*,[5] by the fusion of III and guanidine carbonate.

The hydroxy compound IV was converted in high yield to the chloro compound V by careful treatment with phosphoryl chloride. Extended heating in the chlorination medium led to extensive decomposition and to low yields of V, a compound which has been reported previously.[4,5] Compound V was a versatile intermediate and it was converted to a variety of products (VI through XVIII).

Treatment of V with ethanolic ammonia at 150° gave a good yield of the diamino compound VI; the reaction was impractically slow at 110°. The 4-methylamino- VII 4-benzylamino- IX and 4-diethylamino-5,6-trimethylenepyrimidine X were similarly prepared. It is interesting that compounds VI and VII were directly isolable from

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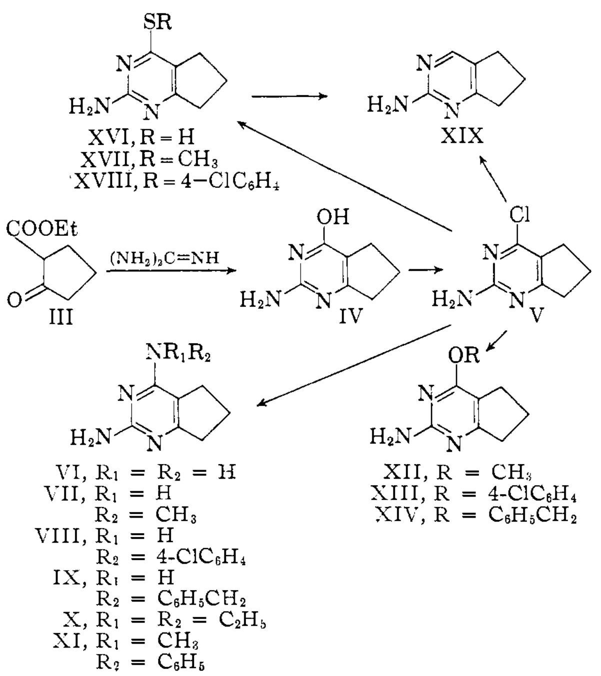
[1] This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* Helen F. Gram, Carol W. Mosher and B. R. Baker, THIS JOURNAL, **81**, 3103 (1959).

[2] G. B. Elion, E. Burgi and G. H. Hitchings, *ibid.*, **74**, 411 (1952).

[3] R. Duschinsky, E. Pleven and C. Heidelberger, *ibid.*, **79**, 4559 (1957).

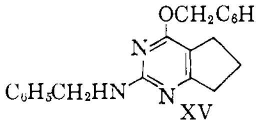
[4] R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman and A. R. Todd, *J. Chem. Soc.*, 361 (1946).

[5] W. Braker, E. J. Pribyl, J. T. Sheehan, E. R. Spitzmiller and W. A. Lott, THIS JOURNAL, **69**, 3072 (1947).



their reaction mixtures as their hydrochlorides in spite of the large excesses of ammonia and methylamine used in their formation from V, indicative of the strongly basic nature of the compounds. The 4-*p*-chloroanilino compound VIII and the 4-N-methylanilino compound XI were prepared in good yields by the reaction of V with an excess of the appropriate reagent in refluxing xylene.

The 4-methoxy derivative XII was prepared in excellent yield by treatment of V with excess sodium methoxide in refluxing xylene. Compound XII has been previously described by Braker, *et al.*[5] Reaction of V with sodium *p*-chlorophenoxide in refluxing diglyme yielded compound XIII. The 4-benzyloxy derivative XIV was prepared in reasonable yield by the reaction of V with a small excess of sodium benzyloxide in refluxing diglyme. The use of a large excess of sodium benzyloxide in the reaction with V gave 2-benzylamino-4-(benzyloxy)-5,6-trimethylenepyrimidine (XV). Compound XV was undoubtedly formed *via* 2-benzylideneamino-4-(benzyloxy)-5,6-trimethylenepyrimidine which, in turn, arose from the reaction of XIV with benzaldehyde formed from the sodium benzyloxide solution. The reaction is completely analogous to the benzylations described by Sprinzak.[6]

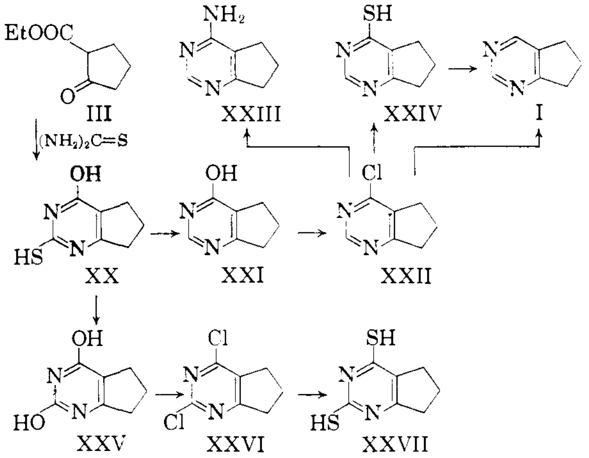


XV

Reaction of V with thiourea in refluxing ethanol gave a high yield of 2-amino-4-mercapto-5,6-trimethylenepyrimidine (XVI). The 4-(methylthio) derivative XVII could be prepared by the reaction of V with a methanolic solution of sodium methylmercaptide, but the product was difficult to purify. Compound XVII was better prepared by the alkylation of the 4-mercapto compound XVI with excess dimethyl sulfate in alkali. A high yield of the 4-(*p*-chlorophenylthio) derivative XVIII was realized from the reaction of V with sodium *p*-chlorophenoxide in refluxing 1-propanol.

Hydrogenation of V over a palladium catalyst in the presence of magnesium oxide led to a reasonable yield of 2-amino-5,6-trimethylenepyrimidine (XIX). Compound XIX could be prepared more conveniently and in better over-all yield by the desulfurization of the 4-mercapto compound XVI with Raney nickel.

Condensation of 2-carbethoxycyclopentanone (III) with excess thiourea and base in refluxing ethanol led to a fair yield of 4-hydroxy-2-mercapto-5,6-trimethylenepyrimidine (XX). Reductive desulfurization of XX with Raney nickel gave an excellent yield of the 4-hydroxy compound XXI, the analog of hypoxanthine. Chlorination of XXI with phosphoryl chloride led to a high yield of the 4-chloro compound XXII, which was converted to the 4-amino derivative XXIII and to the 4-mercapto compound XXIV by reactions similar to those used in the synthesis of VI and XVI from V. Compounds XXII, XXIII and XXIV are the analogs of 6-chloropurine, adenine and 6-purinethiol, respectively. Hydrogenolysis of XXII over a palladium catalyst yielded the parent pyrimidine I as a low melting, very hygroscopic and volatile solid. Compound I could also be prepared by desulfurization of XXIV. It was found that purification of I was best accomplished by converting crude I to its easily crystallizable picrate and decomposing the derivative with Dowex 2 (CO_3). The unsubstituted pyrimidine I separated from the aqueous solution when the solution was saturated with solid alkali.



Compound XX was hydrolyzed in good yield to 2,4-dihydroxy-5,6-trimethylenepyrimidine (XXV), the analog of xanthine, using aqueous chloroacetic acid. Compound XXV was also formed in reasonable yield when IV was treated with sodium nitrite in 5 *M* sulfuric acid. The dihydroxy compound XXV was chlorinated in high yield with phosphoryl chloride to the 2,4-dichloro derivative XXVI, which, in turn, was converted to the 2,4-dimercaptotrimethylenepyrimidine XXVII by reaction with thiourea.

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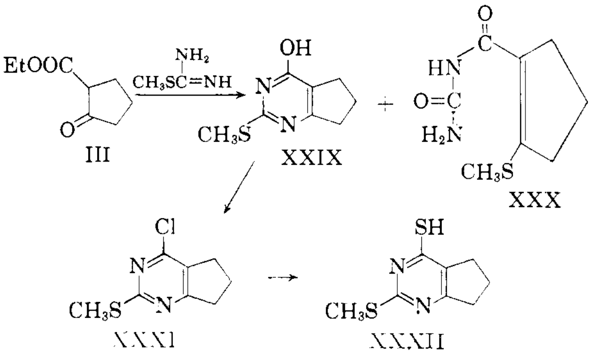
(6) Y. Sprinzak, THIS JOURNAL, **78**, 466 (1956).

A third group of substituted 4,5-trimethylenepyrimidines was derived from 2-carbethoxycyclopentanone (III) by way of its condensation with 2-methyl-2-thiopseudourea (XXVIII) to form 4-hydroxy-2-(methylthio)-5,6-trimethylenepyrimidine (XXIX). Compound XXIX was previously prepared by Curd, *et al.*,[7] in less than 8% yield.



By modifying the above authors' conditions the yield of XXIX was increased to 29% and in addition there was formed in the condensation 30% of a compound whose analysis, infrared and ultraviolet spectra suggest structure XXX. Efforts to identify the compound conclusively and to elucidate its mode of formation are in progress.

The pyrimidine XXIX was converted in high yield to the 4-chloro-2-(methylthio) derivative XXXI with phosphoryl chloride, and the chloro compound XXXI was in turn converted to the 4-mercapto compound XXXII with thiourea.

All of the pyrimidines described above were shown to be homogeneous by paper chromatography. The ultraviolet spectral data and the paper chromatographic data are collected in Table I. These compounds are currently undergoing investigation as potential anticancer agents.

Acknowledgments.—The authors are indebted to Dr. Peter Lim and his group for infrared interpretations and paper chromatography and to Mr. O. P. Crews, Jr., and his group for the large-scale preparation of intermediates.

Experimental[8]

2-Amino-4-hydroxy-5,6-trimethylenepyrimidine (IV).—A suspension of 3.42 g. (19.0 mmoles) of guanidine carbonate, 2.96 g. (19.0 mmoles) of 2-carbethoxycyclopentanone (III) and 15 ml. of absolute ethanol was heated under reflux for 18 hours. The ethanol was evaporated *in vacuo* and 20 ml. of water was added to the solid residue. The resulting solution was adjusted to *p*H 6.5–7.0 with glacial acetic acid, precipitating 1.7 g. (59%) of a solid which did not melt below 300°. The solid was dissolved in 85 ml. of 1 *M* sodium hydroxide, the solution treated with Norit and filtered, and the filtrate adjusted to *p*H 6.5–7.0 with glacial acetic acid, yielding 1.4 g. (48%) of purified IV, m.p. >300°; λ_{max}^{KBr} 2.90–3.03 (OH, NH), 5.90–6.20 (NH_2, pyrimidine ring), 6.70 μ (pyrimidine ring).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.5; H, 6.00; N, 27.8. Found: C, 55.5; H, 5.97; N, 27.8.

When 519 g. of 2-carbethoxycyclopentanone (III) was used in the above procedure the yield of IV was 217 g. (43%).

2-Amino-4-chloro-5,6-trimethylenepyrimidine (V).—A mixture of 4.0 g. (26.4 mmoles) of IV and 10 ml. of phosphoryl chloride was refluxed until the solid completely dissolved (15–20 minutes). The solution was immediately poured, with stirring, into 50 g. of ice and water. The resulting solution was extracted with 150 ml. of methylene chloride and the extracts were discarded. The aqueous solution was adjusted to *p*H 6.5–7.0 with cold concentrated ammonium hydroxide. The product, 2.5 g. (56%), m.p. 185–189°, precipitated and was recrystallized from 95% ethanol (1.0 g./40 ml.) to yield 1.9 g. (41%), m.p. 195–196° (lit. m.p. 197–198°,[4] 196–197°[5]). Its infrared spectrum possessed λ_{max}^{KBr} 2.92, 3.01 (NH), 6.17 (NH_2 and pyrimidine ring), 6.48, 6.76 μ (pyrimidine ring).

When 216 g. of IV was chlorinated as above, the yield was 145 g. (59%).

No yields or experimental details were recorded in the literature.[4,5]

2,4-Diamino-5,6-trimethylenepyrimidine (VI).—A mixture of 4.0 g. (23.2 mmoles) of V in 30 ml. of ethanolic ammonia (saturated at 0°) was heated in a stainless steel bomb at 150° for 14 hours. The resulting solution was evaporated *in vacuo* and to the residue was added 40 ml. of water. The solution was adjusted to *p*H 12 with 5% sodium hydroxide, precipitating the product, 2.6 g. (73%), m.p. 233–234°. From a previous run a product was isolated which, after recrystallization from water, had m.p. 230–232°; λ_{max}^{KBr} 2.90, 3.01, 3.20 (NH), 6.05–6.20, 6.30, 6.95 μ (NH_2 and pyrimidine ring).

Anal. Calcd. for $C_7H_{10}N_4$: C, 55.9; H, 6.70; N, 37.7. Found: C, 56.1; H, 6.73; N, 38.0.

When the ethanol solution was evaporated to dryness after the ammonolysis, the residue was a water-soluble, crystalline solid which did not melt up to 300°. It showed the same paper chromatographic behavior in solvent system A[8] as did VI, but its infrared spectrum differed significantly from that of VI in the 6.0–7.0 μ region. On treatment with 5% aqueous sodium hydroxide it was converted to the free base VI; therefore, the material is the hydrochloride salt of VI.

2-Amino-4-(methylamino)-5,6-trimethylenepyrimidine (**VII**).—A mixture of 1.0 g. (5.8 mmoles) of V, 2.2 ml. (29 mmoles) of 40% aqueous methylamine and 10 ml. of ethanol was heated in a stainless steel bomb at 150° for 14 hours. The solution was evaporated *in vacuo* and 20 ml. of water was added to the residue. The *p*H was adjusted to 12 by addition of 5% sodium hydroxide, resulting in the precipitation of 0.8 g. (82%), m.p. 175–177°, of product. In the infrared it had λ_{max}^{KBr} 2.87, 3.02 and 3.16 (NH), 6.16, 6.30, 6.60 (NH and pyrimidine ring), 7.20 μ (CH_3).

Anal. Calcd. for $C_8H_{12}N_4$: C, 58.5; H, 7.24; N, 34.2. Found: C, 58.5; H, 7.31; N, 34.2.

When, in the above procedure, the aqueous solution formed by dissolving the evaporation residue was neutralized to *p*H 7 with glacial acetic acid, a product, 0.9 g. (74%), m.p. >300°, precipitated that was the hydrochloride of VII. This was dissolved in 10 ml. of boiling absolute ethanol and precipitated by the addition of 50 ml. of hot benzene, yielding 0.4 g. (30%), m.p. >300°. In the infrared it had λ_{max}^{KBr} 3.10, 3.18 (NH), 6.05, 6.32 (NH_2 and pyrimidine ring), 7.20 μ (CH_3).

Anal. Calcd. for $C_8H_{12}N_4 \cdot HCl$: C, 47.8; H, 6.53; N, 27.9. Found: C, 47.8; H, 6.72; N, 28.4.

2-Amino-4-(*p*-chloroanilino)-5,6-trimethylenepyrimidine (**VIII**).—A stirred mixture of 1.0 g. (5.8 mmoles) of V, 2.1 g. (17 mmoles) of *p*-chloroaniline and 20 ml. of xylene was refluxed for 3 hours. The xylene was evaporated *in vacuo* and the residue was extracted with 30 ml. of boiling ether to remove the excess *p*-chloroaniline. Hot water (40 ml.) was added to the ether-insoluble residue and the aqueous solution was adjusted to *p*H 8.9–9.0 with concentrated ammonium hydroxide, precipitating 1.1 g. (72%), m.p. 165–168°. The product was dissolved in 20 ml. of ethanol, the solution treated with Norit and filtered, and the filtrate treated with 50 ml. of hot water to yield 0.8 g. (52%), m.p. 187–189°; λ_{max}^{KBr} 2.97, 3.15, 6.17 (NH), 6.25, 6.31-6.41, 6.63, 6.72

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(7) F. H. S. Curd, D. N. Richardson and F. L. Rose, *J. Chem. Soc.*, 378 (1946).

(8) Boiling points and melting points are uncorrected; the latter were measured using the Fisher–Johns apparatus. Paper chromatograms were run by the descending technique on Whatman No. 1 paper and the spots were detected by visual examination under ultraviolet light. The position of the spots was measured relative to that of adenine, *i.e.*, $R_{Adenine} = 1.00$. The following solvent systems were used: A, 1-butanol–acetic acid–water (5:2:3); *cf.* D. M. Brown, A. Todd and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956); B, 5% aqueous disodium hydrogen phosphate (no organic phase); *cf.* C. E. Carter, THIS JOURNAL, **72**, 1835 (1950).

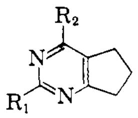

TABLE I

ULTRAVIOLET SPECTRA AND PAPER CHROMATOGRAPHIC DATA

	Compound		pH 1		pH 7		pH 13		
	R_1	R_2	λ_{max}	$\epsilon_{max} \times 10^{-3}$	λ_{max}	$\epsilon_{max} \times 10^{-3}$	λ_{max}	$\epsilon_{max} \times 10^{-3}$	R_{Ad}[a]
I	H	H	257	5.72	256	5.34	256	5.34	1.42
IV	NH_2	OH	230 267	9.30 8.20	229 287	9.20 8.30	232 277	8.20 7.20	1.34
V	NH_2	Cl	228 317	13.71 7.08	232 302	12.70 5.28	232 281	12.92 5.59	1.60
VI	NH_2	NH_2	277	7.11	280	6.71	286	6.91	1.03
VII	NH_2	CH_3NH	276	9.97	276	9.86	285	8.99	1.20
VIII	NH_2	$4\text{-}ClC_6H_4NH$	297	19.83	303	19.83	307	21.10	1.38
IX	NH_2	$C_6H_5CH_2NH$	277	11.71	280	11.25	287	10.48	1.37
X	NH_2	$(C_2H_5)_2N$	286	12.73	287	12.20	295	11.53	1.35
XI	NH_2	$C_6H_5(CH_3)N$	289	13.18	295	12.87	304	13.80	1.41
XII	NH_2	CH_3O	282	7.37	282	6.48	281	5.59	1.30
XIII	NH_2	$4\text{-}ClC_6H_4O$	291	9.71	225 287	19.40 8.05	226 287	18.88 8.00	1.53
XIV	NH_2	$C_5H_5CH_2O$	284	8.43	233 282	12.08 7.31	233 282	11.61 7.00	1.45
XVI	NH_2	SH	252 337	4.64 14.04	242 344	5.83 14.36	237 312	8.53 11.23	1.35
XVII	NH_2	CH_3S	236 271 315	10.05 11.60 12.89	234 308	14.91 10.04	234 308	14.91 10.04	1.30
XVIII	NH_2	$4\text{-}ClC_6H_4S$	260 310	8.20 15.29	312	9.39	312	10.68	1.50
XIX	NH_2	H	227 307	14.59 4.14	227 300	12.43 4.23	228 300	12.43 4.23	1.30
XX	SH	OH	280	18.17	280	15.72	263 310	12.51 7.80	1.11
XXI	H	OH	241	9.56	235 263	6.76 5.04	236 264	8.37 5.32	1.25
XXII	H	Cl	260	6.13	259	6.13	277	6.13	1.38
XXIII	H	NH_2	262	13.52	237 265	8.24 6.20	237 266	8.61 5.37	1.01
XXIV	H	SH	322	14.53	322	10.34	226 299	11.36 15.05	1.40
XXV	OH	OH	270	8.44	270	8.64	292	9.98	1.20
XXVII	SH	SH	294	23.19	284	18.65	272 323	23.78 7.82	1.27
XXIX	CH_3S	OH	254 284	10.00 9.11	250 284	9.32 8.14	254 280	10.00 7.43[b]	1.30
XXXII	CH_3S	SH	242	12.67	254 316	12.51 9.75	251 315	16.99 13.76	1.42
					λ_{max}[c]	$\epsilon_{max} \times 10^{-3}$			
XXVI	Cl	Cl			267	5.84			1.45
XXXI	CH_3S	Cl			256 298	19.40 3.38			1.45

[a] In solvent A.[8] [b] Shoulder. [c] Spectra measured in 95% ethanol.

(pyrimidine and benzene rings), 12.07 μ (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{13}H_{13}ClN_4$: C, 59.8; H, 5.02; Cl, 13.6. Found: C, 60.1; H, 5.17; Cl, 13.9.

In another run another crystal modification, m.p. 175–177°, was isolated. Its paper chromatographic behavior was identical with that of the above material, but its infrared spectrum was significantly different.

Anal. Found: C, 59.7; H, 5.19; Cl, 13.4.

2-Amino-4-benzylamino-5,6-trimethylenepyrimidine (IX).—A mixture of 1.0 g. (5.8 mmoles) of V, 2.48 g. (23.2 mmoles) of benzylamine and 15 ml. of absolute ethanol was heated in a stainless steel bomb at 150° for 14 hours. The solution was evaporated *in vacuo* and the residue was extracted with two 20-ml. portions of hot methylene chloride, filtering each time. The combined methylene chloride filtrates were evaporated *in vacuo* and 20 ml. of water was added to the residue. The solid product, 1.41 g. (100%), m.p. 93–97°, was recrystallized from 35 ml. of 50% aqueous alcohol, yielding 0.90 g. (64%), m.p. 137–145°; λ_{max}^{KBr} 2.93, 3.02 (NH), 6.16–6.37 (NH_2, phenyl and pyrimidine ring), 13.56, 14.35 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.9; H, 6.71; N, 23.0. Found: C, 69.6; H, 6.76; N, 23.3.

2-Amino-4-diethylamino-5,6-trimethylenepyrimidine (X).—A mixture of 1.0 g. (5.8 mmoles) of V, 2.81 g. (38 mmoles) of diethylamine and 10 ml. of absolute ethanol was heated in a stainless steel bomb at 150° for 14 hours. The mixture was evaporated *in vacuo* and 20 ml. of water was added to the residue, yielding 1.20 g. (99%), m.p. 139–144°. The product was recrystallized from 50 ml. of 5% aqueous ethanol to yield 0.90 g. (74%), m.p. 149–150°; λ_{max}^{KBr} 2.98, 3.13, 6.01 (NH), 6.32, 6.42 (pyrimidine ring), 7.24, 7.32 μ (CH_3).

Anal. Calcd. for $C_{11}H_{18}N_4$: C, 64.0; H, 8.79; N, 27.2. Found: C, 64.2; H, 8.86; N, 26.8.

2-Amino-4-(N-methylanilino)-5,6-trimethylenepyrimidine (XI).—A mixture of 1.0 g. (5.8 mmoles) of V, 2.53 g. (23.2 mmoles) of freshly distilled N-methylaniline and 15 ml. of xylene was refluxed under nitrogen for 3.5 hours. The mixture was evaporated *in vacuo* and to the residue was added 20 ml. of water. The mixture was adjusted to *p*H 1 with 6 *M* hydrochloric acid and was extracted with 10 ml. of methylene chloride. The aqueous layer was brought to *p*H 8 with concentrated ammonium hydroxide, yielding 1.40 g. (99%) of product, m.p. 180–190°. Recrystallization from 40 ml. of 40% aqueous ethanol yielded 1.0 g. (71%), m.p. 198–200°; λ_{max}^{KBr} 2.92, 3.02, 3.15, 6.13 (NH), 6.33–6.43, 6.65, 6.90 (pyrimidine and benzene rings), 7.19 (CH_3), 14.31 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.9; H, 6.66; N, 23.3. Found: C, 70.0; H, 6.67; N, 23.6.

2-Amino-4-methoxy-5,6-trimethylenepyrimidine (XII).—A solution of 1.06 g. (19.8 mmoles) of sodium methoxide in 5 ml. of absolute methanol was added to a solution of 1.0 g. (5.8 mmoles) of V in 10 ml. of xylene and the mixture was refluxed for 3 hours. Evaporation *in vacuo* left a solid residue which, after addition of 20 ml. of water, was brought to *p*H 7.5 with glacial acetic acid, yielding 0.95 g. (98%) of solid, m.p. 78–85°. The product was recrystallized from 5 ml. of water with the aid of Norit to give 0.60 g. (62%) of material, m.p. 120–121° (lit.[5] m.p. 119–120°); λ_{max}^{KBr} 3.00, 3.17, 6.09 (NH), 6.55, 6.61, 6.74–6.85 (pyrimidine ring), 6.90 (CH_3), 8.32 μ (C–O–C).

No details for the preparation of XII and no yield figures were recorded in reference 5.

2-Amino-4-(*p*-chlorophenoxy)-5,6-trimethylenepyrimidine (XIII).—A solution of sodium *p*-chlorophenoxide was prepared from 0.58 g. (11 mmoles) of sodium methoxide, 1.40 g. (10.9 mmoles) of *p*-chlorophenol and 5 ml. of absolute methanol; to this solution was added 1.0 g. (5.8 mmoles) of V and 15 ml. of the dimethyl ether of diethylene glycol (diglyme). The mixture was refluxed 4 hours, then was evaporated *in vacuo*. Water (20 ml.) was added to the residue and the solution was adjusted to *p*H 1 with 6 *M* hydrochloric acid. The acid solution was extracted with two 20-ml. portions of methylene chloride. Upon neutralization of the aqueous layer, 0.40 g. (27%) of product, m.p. 100–110°, precipitated; it was the 4-methoxy compound XII, as shown by infrared spectrum and paper chromatography.

The methylene chloride extracts were evaporated *in vacuo*, leaving a solid residue which was triturated with 20 ml. of 5% aqueous sodium hydroxide. The undissolved solid, 0.70 g. (46%), m.p. 160–165°, was recrystallized twice from 75% aqueous ethanol, yielding 0.50 g. (32%) of product, m.p. 185–187°; λ_{max}^{KBr} 2.98, 3.04, 3.15, 6.14 (NH), 6.45 (pyrimidine ring), 6.75 (benzene ring), 8.22 (C–O), 11.97 μ (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{13}H_{12}ClN_3O$: C, 59.6; H, 4.61; Cl, 13.5. Found: C, 59.3; H, 4.81; Cl, 13.5.

2-Amino-4-(benzyloxy)-5,6-trimethylenepyrimidine (XIV).—A mixture of 2.0 g. (19.2 mmoles) of benzyl alcohol and 0.25 g. (10.6 mmoles) of sodium hydride was heated on the steam-bath for 20 minutes. To this solution was added 1.0 g. (5.8 mmoles) of V and 15 ml. of diglyme and the resulting mixture was refluxed for 3 hours. The solution was poured over 20 g. of ice and the aqueous solution was neutralized with glacial acetic acid, precipitating 0.80 g. (56%) of solid, m.p. 98–103°. The product was recrystallized from 20 ml. of 50% aqueous alcohol with the aid of Norit, yielding 0.60 g. (42%) of solid, m.p. 118–119°; λ_{max}^{KBr} 3.00, 3.15, 6.10 (NH), 6.22–6.42, 6.82 (pyrimidine and benzene rings), 8.42, 9.53 (C–O), 13.22, 14.35 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.9; H, 6.26; N, 17.4. Found: C, 70.0; H, 6.38; N, 17.5.

2-Benzylamino-4-(benzyloxy)-5,6-trimethylenepyrimidine (XV).—The procedure was similar to that of XIV except that 4.16 g. (38.4 mmoles) of benzyl alcohol was used and 15 ml. of xylene was employed as solvent. After 3 hours at reflux, the mixture was evaporated *in vacuo* and 20 ml. of water was added to the residue. Upon adjustment of the *p*H to 5 with acetic acid, 1.4 g. (72%) of product, m.p. 120–122°, precipitated. It was recrystallized from 30 ml. of ethanol to yield 1.3 g. (67%) of solid, m.p. 137–139°; λ_{max}^{KBr} 2.92, 3.10 (NH), 6.20 (pyrimidine and benzene rings), 6.42 (NH, pyrimidine ring), 8.40, 9.35 (C–O), 13.22, 14.32 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.4; H, 6.40; N, 12.7. Found: C, 76.2; H, 6.50; N, 12.5.

2-Amino-4-mercapto-5,6-trimethylenepyrimidine (XVI).—A mixture of 1.0 g. (5.8 mmoles) of V, 0.86 g. (11.6 mmoles) of thiourea and 10 ml. of absolute ethanol was refluxed for 3 hours. The solution was evaporated *in vacuo* and 20 ml. of water was added to the residue. The aqueous solution was brought to *p*H 1 with 6 *M* hydrochloric acid, chilled and adjusted to *p*H 4 with cold concentrated ammonium hydroxide, precipitating a solid, 0.82 g. (84%), m.p. 250–258° dec. The product was dissolved in 20 ml. of 1% aqueous sodium hydroxide, the solution treated with Norit and filtered, and the filtrate neutralized with glacial acetic acid, yielding 0.60 g. (61%) of product, m.p. 270–273° dec.; λ_{max}^{KBr} 2.91, 3.02, 6.05, 6.15 (NH), 6.25–6.42 (pyrimidine ring), 7.99 μ (C=S).

Anal. Calcd. for $C_7H_9N_3S$: C, 50.3; H, 5.40; S, 19.2. Found: C, 50.4; H, 5.55; S, 19.6.

2-Amino-4-(methylthio)-5,6-trimethylenepyrimidine (XVII).—A solution of 2.24 g. (17.9 mmoles) of dimethyl sulfate in 10 ml. of absolute methanol was added dropwise and with good stirring to a solution of 1.0 g. (5.8 mmoles) of XVI in 60 ml. of water containing 0.22 g. (6.0 mmoles) of sodium hydroxide. After the addition, the solution was stirred for 10 minutes at room temperature and 1% aqueous sodium hydroxide was added to bring the *p*H to 8.5. A product, 0.95 g. (88%), precipitated, m.p. 133–135°, and was recrystallized by solution in 20 ml. of hot benzene, treatment with Norit, and addition of 50 ml. of hot Skellysolve B to the filtrate, to give 0.70 g. (65%) of product, m.p. 140–141°; λ_{max}^{KBr} 2.89, 3.06, 3.20, 6.20 (NH), 6.35–6.50 μ (pyrimidine ring).

Anal. Calcd. for $C_8H_{11}N_3S$: C, 53.0; H, 6.11; S, 17.7. Found: C, 53.1; H, 6.45; S, 17.4.

2-Amino-4-(*p*-chlorophenylthio)-5,6-trimethylenepyrimidine (XVIII).—A mixture of 0.34 g. (6.3 mmoles) of sodium methoxide, 0.91 g. (6.3 mmoles) of *p*-chlorobenzenethiol and 10 ml. of 1-propanol was heated on the steam-bath for 10 minutes. To the solution was added 1.0 g. (5.8 mmoles) of V and the resulting solution was refluxed for 3 hours. The solution was evaporated *in vacuo* and to the residue was added 10 ml. of water and 2 ml. of 1% aqueous sodium hydroxide. A solid, 1.4 g. (86%), m.p. 133–134°, was obtained and was recrystallized by solution in 8 ml. of hot benzene, treatment with Norit and addition of 25 ml. of hot Skellysolve B to the filtrate, to yield 1.1 g. (68%) of product, m.p. 135–137°; λ_{max}^{KBr} 2.96, 3.05, 3.16 (NH), 6.17, 6.37, 6.53 (NH_2, pyrimidine and benzene rings), 12.08, 12.22 μ (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{13}H_{12}ClN_3S$: C, 56.1; H, 4.35; Cl, 12.7. Found: C, 56.1; H, 4.48; Cl, 12.7.

2-Amino-4,5-trimethylenepyrimidine (XIX). (A) By Hydrogenolysis of V.—A stirred suspension of 0.50 g. (5.1 mmoles) of magnesium oxide, 0.1 g. of 5% palladium-on-charcoal, 1.0 g. (5.8 mmoles) of V and 10 ml. of absolute ethanol was hydrogenated at room temperature (*ca.* 24°) and atmospheric pressure until hydrogen absorption ceased. The amount of hydrogen used was 220 ml. (9.82 mmoles).

The solution was filtered and the filtrate evaporated *in vacuo*, leaving 0.50 g. (63%) of solid, m.p. 140–148°. The product was recrystallized from 7.5 ml. of water, with the aid of Norit, yielding 0.40 g. (51%) of solid, m.p. 160–162°; $\lambda_{\max}^{\text{KBr}}$ 3.03, 6.19 (NH), 6.06 (NH_2 and pyrimidine ring), 6.25, 6.42, 6.78 μ (pyrimidine ring).

Anal. Calcd. for $C_7H_9N_3$: C, 62.2; H, 6.71; N, 31.0. Found: C, 61.9; H, 6.98; N, 30.7.

The picrate of XIX was prepared by mixing aqueous solutions of XIX and of picric acid. The salt precipitated immediately, m.p. 190–205° dec., and was recrystallized from water, yielding the product, m.p. 240–247° dec.

Anal. Calcd. for $C_{13}H_{12}N_6O_7$: C, 43.0; H, 3.30; N, 23.0. Found: C, 43.1; H, 3.41; N, 22.3.

When the hydrogenation procedure was scaled up, much lower yields of XIX were obtained and there appeared to be large amounts of product in which the pyrimidine ring was partially hydrogenated.

(B) **By Desulfurization of XVI.**—A stirred suspension of 9.0 g. (54 mmoles) of the 4-mercapto compound XVI, 16 g. of Raney nickel catalyst[9] and 125 ml. of water was refluxed for 6 hours. The suspension was filtered and the aqueous filtrate was evaporated *in vacuo*. The solid residue was washed with 30 ml. of 1% sodium hydroxide and water, which left 4.0 g. (55%) of XIX, m.p. 160–162°, identical in all respects with the material prepared by hydrogenolysis of V.

4-Hydroxy-2-mercapto-5,6-trimethylenepyrimidine (XX).—To a refluxing suspension of 3.60 g. (47 mmoles) of thiourea, 1.48 g. (9.5 mmoles) of 2-carbethoxycyclopentanone (III) and 11 ml. of absolute ethanol was added dropwise a solution of 1.28 g. (23.7 mmoles) of sodium methoxide in 11 ml. of absolute ethanol. The addition required 1.5 hours and the solution was refluxed for 4 hours more. The mixture was evaporated *in vacuo* and ice water (20 ml.) was added to the residue. The cold solution was neutralized with glacial acetic acid, precipitating 0.75 g. (48%) of product. The solid was recrystallized from 35 ml. of water to yield 0.43 g. (26%) of a solid that partially decomposed near 270° but showed no signs of melting up to 300°. In the infrared it had $\lambda_{\max}^{\text{KBr}}$ 3.13–3.25 (NH), 5.99 (C=O), 6.44 (pyrimidine ring), 8.35–8.45 μ (C=S).

Anal. Calcd. for $C_7H_8N_2OS$: C, 49.9; H, 4.79; S, 19.0. Found: C, 50.0; H, 4.96; S, 18.7.

When 325 g. of III was employed in the above procedure the yield of XX was 135 g. (38%).

4-Hydroxy-5,6-trimethylenepyrimidine (XXI).—Compound XX (20 g.) was desulfurized with 80 g. of Raney nickel catalyst[9] in 400 ml. of water for 3 hours at reflux. After filtration, the aqueous solution was concentrated to 200 ml. *in vacuo* and the solution was treated with Norit and filtered. Evaporation of the filtrate to dryness left 12.0 g. (70%) of product, m.p. 248–249° dec.; $\lambda_{\max}^{\text{KBr}}$ 3.23 (NH); 3.50–3.75 (acidic NH or OH), 6.05 (C=O), 6.28, 6.45 μ (pyrimidine ring).

Anal. Calcd. for $C_7H_8N_2O$: C, 61.7; H, 5.91; N, 20.5. Found: C, 61.7; H, 6.08; N, 20.3.

4-Chloro-5,6-trimethylenepyrimidine (XXII).—A mixture of 2 ml. of phosphoryl chloride and 1.0 g. (7.4 mmoles) of XXI was heated at 100° for 3 to 4 minutes during which time a complete solution resulted. The solution was poured into 35 ml. of cold saturated sodium carbonate solution. On standing, a yellow solid formed and was extracted from the mixture with 30 ml. of methylene chloride. The extract was treated with Norit, filtered and the methylene chloride evaporated *in vacuo* to leave 1.0 g. (88%) of product, m.p. 39–40°; $\lambda_{\max}^{\text{KBr}}$ 6.32–6.37, 6.50, 7.02, 7.30 μ (pyrimidine ring), no NH absorption near 3.0 μ nor C=O absorption near 6.0 μ.

Anal. Calcd. for $C_7H_7ClN_2$: C, 54.3; H, 4.56; Cl, 22.9. Found: C, 54.1; H, 4.73; Cl, 22.7.

4-Amino-5,6-trimethylenepyrimidine (XXIII).—The 4-chloro compound XXII (3.0 g., 18.8 mmoles) was ammonolyzed by the same procedure used for the preparation of VI from V. After evaporation of the ammonolysis mixture and treatment of the residue with 50 ml. of ice-water, 2.0 g. (77%) of product, m.p. 235–238°, was isolated. This was recrystallized from 60 ml. of water to yield 1.9 g. (73%) of pure material, m.p. 238–239°; $\lambda_{\max}^{\text{KBr}}$ 3.02, 3.20, 6.02 (NH), 6.29, 6.41, 6.72 μ (NH_2 and pyrimidine ring).

Anal. Calcd. for $C_7H_9N_3$: C, 61.6; H, 6.71; N, 31.0. Found: C, 61.7; H, 6.50; N, 30.9.

4-Mercapto-5,6-trimethylenepyrimidine (XXIV).—A mixture of 1.0 g. (6.5 mmoles) of XXII, 1.47 g. (19.4 mmoles) of thiourea and 10 ml. of absolute ethanol was refluxed for 3 hours. The solution was evaporated *in vacuo* and 25 ml. of 5% sodium hydroxide was added to the residue. The alkaline solution was treated with Norit and filtered and the filtrate was brought to *p*H 5 with glacial acetic acid. The product, 0.6 g. (61%), m.p. 255–265° dec., precipitated. In the infrared it had $\lambda_{\max}^{\text{KBr}}$ 3.20 (NH), 6.27, 6.49 (pyrimidine ring), 7.92 μ (C=S).

Anal. Calcd. for $C_7H_8N_2S$: C, 55.2; H, 5.29; S, 21.0. Found: C, 54.9; H, 5.37; S, 20.8.

4,5-Trimethylenepyrimidine (I). (A) **By Hydrogenolysis of XXII.**—A mixture of 2.0 g. (12.9 mmoles) of XXII, 1.0 g. of 5% palladium-on-charcoal, 0.50 g. of magnesium oxide and 10 ml. of absolute ethanol was shaken with hydrogen at room temperature until hydrogen absorption ceased (2 hours, 300 ml. (14.4 mmoles) of hydrogen used). The mixture was filtered, the residue was washed with alcohol, and to the filtrate was added a solution of 4.0 g. (17.4 mmoles) of picric acid in 40 ml. of hot water. The resulting solution was chilled and yielded 3.70 g. (82.5%) of picrate, m.p. 130–134° dec. A small amount of the picrate was recrystallized from water (1 g./40 ml.) to yield the analytical sample, m.p. 133–135° dec.; $\lambda_{\max}^{\text{KBr}}$ 4.0–5.0 (broad N^+ absorptions), 6.15, 6.23 (pyrimidine and benzene rings), 6.40, 6.73 (pyrimidine ring), 6.56, 7.59 μ (NO_2).

Anal. Calcd. for $C_{13}H_{11}N_5O_7$: C, 44.6; H, 3.11; N, 20.0. Found: C, 44.6; H, 2.99; N, 20.1.

(B) **By Desulfurization of XXIV.**—A stirred suspension of 1.50 g. (9.9 mmoles) of XXIV, 3 g. of Raney nickel[9] and 20 ml. of water was heated under reflux for 3 hours. The mixture was filtered, the residue washed with water and the combined filtrate and washings were added to a hot solution of 4.0 g. (17 mmoles) of picric acid in 30 ml. of ethanol. On being chilled, the solution yielded 2.0 g. (58%) of product, m.p. 130–132°. Its infrared spectrum was identical with that of the picrate of I prepared from XXII.

A suspension of 6.0 g. (17 mmoles) of the picrate (prepared by method A, *cf.* above), 40 g. of Dowex 2 (CO_3) and 50 ml. of water was stirred at room temperature for 3 hours. The mixture was filtered and the solid residue was washed with 10 ml. of water. To the chilled (0°) combined filtrate and washings was added 40 g. of solid potassium hydroxide. The resulting solution was extracted with two 30-ml. portions of ether, the ether was dried over magnesium sulfate and the mixture was filtered. Most of the ether was distilled from the filtrate through a short Vigreux column using a bath temperature of 40–50° and the last traces of ether were removed by subjecting the residue to a pressure of 10 mm. for about 10 minutes. The pyrimidine I was recovered as a hygroscopic and volatile crystalline solid, 0.70 g. (34%). The melting range, 29–31°, was determined by observing the point of liquefaction when the solid, in a closed flask, was slowly heated with a water-bath. The hygroscopic nature of I was responsible for the poor agreement of the analytical results with theory for I (*cf.* below). The infrared spectrum taken on a liquid film showed 3.32 (aromatic C–H), 6.28 and 6.39 (C=N and C=C), 6.85 μ (CH and pyrimidine ring).

Anal. Calcd. for $C_7H_8N_2$: C, 69.9; H, 6.71; N, 23.3. Found: C, 68.2; H, 7.57; N, 22.7, 22.0, 21.6 (these determinations show the increased moisture absorption upon standing).

2,4-Dihydroxy-5,6-trimethylenepyrimidine (XXV). (A) **By Hydrolysis of XX.**—A solution of 2.0 g. (21 mmoles) of XX, 6.84 g. (72.7 mmoles) of chloroacetic acid and 40 ml. of water was refluxed for 6 hours. The solution was chilled and 1.80 g. (100%) of product, m.p. >300°, precipitated. The solid was dissolved in 40 ml. of 1% aqueous sodium hydroxide and reprecipitated with glacial acetic acid to yield 1.60 g. (89%) of product, m.p. >300°; $\lambda_{\max}^{\text{KBr}}$ 2.94 (OH), 3.17 (NH), 5.83–5.95 (C=O), 6.03, 6.97 μ (pyrimidine ring).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.2; H, 5.30; N, 18.4. Found: C, 55.4; H, 5.47; N, 18.0.

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(9) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

The method used was patterned after the procedure of Henze and Kahlenberg.[10]

(**B**) **By Diazotization of IV.**—A mixture of 100 ml. of water, 50 ml. of concentrated sulfuric acid and 5.0 g. (33.0 mmoles) of IV was chilled to 5–10°. To the cold solution was added dropwise with stirring a solution of 18.0 g. (0.26 mole) of sodium nitrite in 50 ml. of water. The solution was allowed to stand at room temperature for 48 hours during which time 2.80 g. (56%) of product, m.p. >300°, precipitated. It was identical with the product from the hydrolysis of XX as evidenced by paper chromatography and infrared spectrum.

2,4-Dichloro-5,6-trimethylenepyrimidine (XXVI).—A mixture of 15 g. (0.10 mole) of XXV and 75 ml. of phosphoryl chloride was refluxed for 30 minutes. The phosphoryl chloride was evaporated *in vacuo* and the sirupy residue was added to 400 ml. of cold, saturated aqueous sodium carbonate solution, causing the precipitation of solid. The solid was washed with 60 ml. of water and dried to give 13.6 g. (76%) of product, m.p. 69–70°; $\lambda_{\max}^{\text{KBr}}$ 6.37, 6.54, 7.52, 8.13, 11.45 μ (pyrimidine ring). Attempts to purify the product further by recrystallization were unsuccessful.

Anal. Calcd. for $C_7H_6Cl_2N_2$: C, 44.4; H, 3.16; Cl, 37.5. Found: C, 44.2; H, 3.31; Cl, 36.8.

2,4-Dimercapto-5,6-trimethylenepyrimidine (XXVII).—A mixture of 1.0 g. (5.3 mmoles) of XXVI, 1.20 g. (15.8 mmoles) of thiourea and 15 ml. of diglyme was refluxed for 1 hour. The solution was evaporated *in vacuo* and, to the solid residue, was added 30 ml. of 5% sodium hydroxide solution. The alkaline solution was treated with Norit and filtered and the filtrate was adjusted to *p*H 5 with glacial acetic acid, which precipitated 0.90 g. (93%) of solid, m.p. >300°. The product was dissolved in 30 ml. of 5% sodium hydroxide solution and neutralized with acetic acid to yield 0.70 g. (72%) of hygroscopic product, m.p. >300°; $\lambda_{\max}^{\text{KBr}}$ 3.25 (NH), 6.22, 6.43 (pyrimidine ring), 8.60 μ (C=S).

Anal. Calcd. for $C_7H_8N_2S_2$: C, 45.5; H, 4.37; S, 34.8. Found: C, 45.7; H, 4.65; S, 34.5.

4-Hydroxy-2-(methylthio)-5,6-trimethylenepyrimidine (XXIX).—To a stirred solution of 24.0 g. (0.43 mole) of potassium hydroxide, 60.0 g. (0.32 mole) of 2-methyl-2-thiopseudourea sulfate and 300 ml. of water was added dropwise 33.3 g. (0.21 mole) of 2-carbethoxycyclopentanone (III) over a period of 5 minutes. The resulting mixture was stirred 8 hours, a solution of 10 g. (0.14 mole) of potassium hydroxide in 200 ml. of water was added and the suspension was heated on the steam-bath for 30 minutes. The insoluble solid XXX (13.0 g., 30%) was collected and the filtrate was adjusted to *p*H 5 with glacial acetic acid, which precipitated 11.0 g. (29%) of XXIX, m.p. 274–276° dec. (lit.[7] m.p. 270–272°). In the infrared it had $\lambda_{\max}^{\text{KBr}}$ 2.93 (OH), 3.45–3.70 (acidic NH or OH), 6.10, 6.49, 6.79 μ (pyrimidine ring).

The literature[7] yield of XXIX was 8.5%. When the heating period in the above procedure was omitted, the yield of XXIX was much lower.

[2-(Methylthio)-1-cyclopentene-1-carbonyl]-urea (XXX).—The base-insoluble material isolated as a by-product in the preceding preparation of XXIX had m.p. 220–222° dec. It was recrystallized from methyl Cellosolve (1 g./30 ml.) to yield the analytical sample, m.p. 232–237° dec.; $\lambda_{\max}^{\text{KBr}}$ 2.93, 3.04, 3.13, 6.55 (NH), 5.93 (C=O), 6.12 μ (C=C). In the ultraviolet it had $\lambda_{\max}$ 308 mμ (ϵ 12,900) in 95% ethanol, and on paper chromatography in solvent system A[8] it showed a single spot with R_{Ad} 1.30.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 48.0; H, 6.04; N, 14.0; S, 16.0. Found: C, 48.1; H, 6.23; N, 14.4; S, 16.0.

4-Chloro-2-(methylthio)-5,6-trimethylenepyrimidine (XXXI).—A mixture of 0.90 g. (5.0 mmoles) of XXIX and 2 ml. of phosphoryl chloride was heated at 90° for 10 minutes, when complete solution resulted. The solution was poured onto 15 g. of ice and water, whereupon 1.0 g. (91%) of solid, m.p. 95–96°, precipitated. In a previous run a product was obtained which, after recrystallization from 75% aqueous ethanol, melted at 95–97°. In the infrared it had $\lambda_{\max}^{\text{KBr}}$ 6.36, 6.57, 7.46 μ (pyrimidine ring).

Anal. Calcd. for $C_8H_9ClN_2S$: C, 47.8; H, 4.52; Cl, 17.6. Found: C, 48.1; H, 4.79; Cl, 18.0.

4-Mercapto-2-(methylthio)-5,6-trimethylenepyrimidine (XXXII).—By use of the same procedure employed in the preparation of XXIV and XXVII, 2.5 g. (12 mmoles) of XXXI was converted to 2.0 g. (81%) of XXXII, m.p. 230–232° dec. The product was recrystallized from 50 ml. of methyl Cellosolve to yield 1.60 g. (65%) of product, m.p. 241–243° dec.; $\lambda_{\max}^{\text{KBr}}$ 3.23 (NH), 6.39, 6.48 (pyrimidine ring), 7.94 μ (C=S).

Anal. Calcd. for $C_8H_{10}N_2S_2$: C, 48.8; H, 5.08; S, 32.3. Found: C, 48.6; H, 5.14; S, 32.0.

MENLO PARK, CALIF.

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(10) H. R. Henze and E. N. Kahlenberg, THIS JOURNAL, **80**, 1664 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Characterization of the Products from Oxidation of Cholestenone with Osmium Tetroxide

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Repetition of Butenandt's[1] earlier osmium tetroxide oxidation of cholestenone has yielded two 4,5-dihydroxy-3-keto steroids (diolones), only the higher melting of which was found earlier. Each diolone has been monoacetylated, diacetylated, reduced to a triol, and dehydrated. From a comparison of the rates of the latter reaction, which yields the same diosphenol from each diolone, the configurations shown in II and III have been assigned to the lower and higher melting diolones, respectively. Confirmation of this assignment has been obtained through hydrogenolysis of the carbonyl groups from the two diolones to produce the two possible *cis*-4,5-dihydroxycholestanes. These diols have been distinguished by the epimerization of the 4-hydroxy group of one to give the previously known 4β,5-dihydroxycholestane, and by the hydrogenolysis of the 4-hydroxyl group of the other to give the previously unknown 5-hydroxycoprostane.

In 1938, Butenandt and Wolz found that cholestenone (I) reacts with one-tenth of an equivalent of osmium tetroxide in the presence of excess hydrogen peroxide to yield a compound $C_{27}H_{46}O_3$, m.p. 208°, which was shown as 4β,5-dihydroxycoprostan-3-one (II).[1] Repetition of the peroxide–tetroxide oxidation (equation 1) has now yielded two products, that of Butenandt and an isomeric compound, m.p. 112°. This paper reports some chemical characterization of these products and defines the stereochemistry of the pair. Our findings reveal that the higher melting compound obtained by Butenandt is in fact 4α,5-dihydroxycholestan-3-one (III, "α-diolone") and that the new isomer is 4β,5-dihydroxycoprostan-3-one (II, "β-diolone").[2]

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(1) A. Butenandt and H. Wolz, *Ber.*, **71**, 1483 (1938).

(2) First presentation of these findings: Abstr. 131st Meeting, Am. Chem. Soc., Miami, Fla., 1957, p. 34-O.