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The Synthesis of 5-Allyluracil and the Pyrimidine Claisen Rearrangement[1]

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Several 2-substituted 5-allyl-4-pyrimidones were synthesized from ethyl α-allylformylacetate and appropriate ureas and amidines. Some of these compounds were also prepared from the corresponding 2-substituted 4-alloxypyrimidines by a Claisen rearrangement.

The importance of thymidylate synthesis and utilization as critical chemotherapeutic targets in human neoplastic cells has been of great interest in cancer research. One of the ultimate effects of several analogs of naturally occurring pyrimidines has been shown to be interference with thymidylate biosynthesis.[3] In addition, 5-bromodeoxyuridine, 5-iododeoxyuridine, and 5-chlorodeoxyuridine, have been shown to be incorporated as thymidine substitutes into deoxyribonucleic acid, leading to increased sensitivity of mammalian cells to ultraviolet light and x-radiation.[4]

In the course of preparing other compounds which may interfere with pyrimidine metabolic pathways, we have synthesized a variety of 5-allyl-2-substituted 5-allyl-4-pyrimidones, including 5-allyluracil (VI). Some of these compounds were obtained both by the condensation of an appropriate ester with substituted ureas or amidines and also by the Claisen rearrangement of appropriately substituted 4-alloxypyrimidines.

For the syntheses, 1,1,1,3-tetrachloro-3-ethoxypropane (I), prepared by an adaptation of the method of Glickman,[5] was converted to ethyl β,β-diethoxypropionate (II)[6]; this was converted to ethyl α-allylformylacetate (IV) by the method of Croxall and Van Hook.[7]

The synthesis of 5-allyl-2-thiouracil (V) by condensing allyl α-allylformylacetate or ethyl α-allylformylacetate (VI) with thiourea has been described by Croxall and Fegley.[8] We have used this method of synthesis, with some changes, for the preparation of six new 5-allyl-2-substituted 5-allyl-4-pyrimidones.

Ester IV was condensed with *S*-methylthiourea, *S*-benzylthiourea, guanidine, acetamidine, and trifluoroacetamidine to give 2-methylthio-5-allyl-4-pyrimidone (VII), 2-benzylthio-5-allyl-4-pyrimidone (VIII), 2-amino-5-allyl-4-pyrimidone (IX), 2-methyl-5-allyl-4-pyrimidone (X), and 2-trifluoromethyl-5-allyl-4-pyrimidone (XI), respectively. These condensations were carried out both in anhydrous and aqueous media in 22–40% yield. Only VII could be prepared in substantially higher yields in aqueous ethanol. We obtained 5-allyluracil from V by treatment with chloroacetic acid.

The Claisen rearrangement of 4-alloxypyrimidines to 5-allyl-4-pyrimidones was investigated as a simple alternate to the route employing IV. Although this rearrangement could not result directly in the facile synthesis of the desired pyrimidones, V and VI, it was of interest for the synthesis of the other 2-substituted 5-allyl-4-pyrimidones, VII–XI. There are numerous examples of the thermal rearrangements of 2- and 4-pyrimidyl ethers to give substituted *N*-alkylpyrimidines,[9,10] but to our knowledge there have been no reports of the rearrangement of alkyl groups to a carbon atom, and in particular no reports of the Claisen rearrangement to give C-allylpyrimidines.[11]

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(2) Allied Chemical Corp. Fellow, 1960–1961.

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(7) W. J. Croxall and J. O. Van Hook, *J. Am. Chem. Soc.*, 72, 803 (1950).

(8) W. J. Croxall and M. F. Fegley, *J. Am. Chem. Soc.*, 72, 2888 (1950).

(9) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.* 52, 2001 (1930); G. E. Hilbert, *J. Am. Chem. Soc.*, 56, 190 (1934); H. J. Fisher and T. B. Johnson, *J. Am. Chem. Soc.*, 54, 727 (1932); E. Bergmann and H. Heimhold, *J. Chem. Soc.*, 955 (1935).

(10) The residues from the successful rearrangements were not examined thoroughly after removal of the 5-allylpyrimidines. However, a cursory examination of the residue resulting from the rearrangement of ether XIII revealed the same chemical and physical behavior as a mixture of the *N*-1- and *N*-3-allyl isomers synthesized from allyl bromide and 2-benzylthio-4-hydroxypyrimidine. This investigation was not carried through to the point where we could say *conclusively* that the residues contained these isomers.

(11) E. Bergmann and H. Heimhold, *J. Chem. Soc.*, 1365 (1935). These authors reported the thermal rearrangement of purine allylethers to give *N*-allyl substituted purines, but in that case there was no opportunity for the allyl groups to rearrange to an adjacent carbon atom.

To investigate the pyrimidine Claisen rearrangement the previously undescribed 2-substituted 4-alloxypyrimidines XII–XVI were prepared from the corresponding 4-chloropyrimidines. Phenolic allyl ethers are conveniently prepared by refluxing allyl bromide and a phenol in the presence of a base,[12] but heating a hydroxypyrimidine and an allyl halide in the presence of a base can lead to *N*-allyl substituted pyrimidines.[13] The ethers therefore were prepared from sodium alloxide and the 4-chloropyrimidines.

To effect the rearrangement the ethers were heated in *N*,*N*-diethylaniline (b.p. 216°) or *N*,*N*-diethyl-*m*-toluidine (b.p. 231°) from four to eight hours.

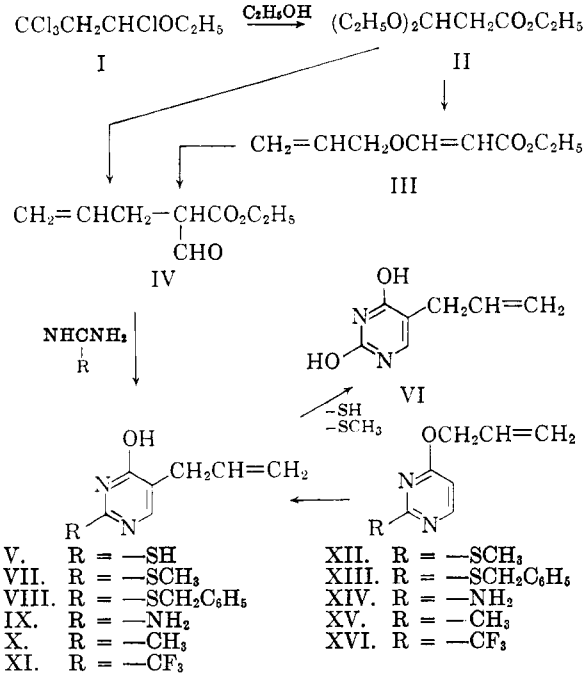
2-Methylthio-4-alloxypyrimidine (XII) and 2-benzylthio-4-alloxypyrimidine (XIII) rearranged smoothly to give 2-methylthio-5-allyl-4-pyrimidone (VII) and 2-benzylthio-5-allyl-4-pyrimidone (VIII), respectively, in 22–28% yield. The rearrangement appears to be a more suitable route to VII and VIII, and eventually VI, than the alternate route employing ester IV. When VII was refluxed with ethanol and concentrated hydrochloric acid, the methylthio group was removed easily to give 67% yield of relatively pure 5-allyluracil. Although the number of steps to the synthesis of 5-allyluracil by these two methods are comparable, the pyrimidine Claisen rearrangement was much more convenient.

The rearrangement of 2-amino-4-alloxypyrimidine (XIV) was erratic. After several runs under almost identical conditions, either the desired product IX, starting material XIV, or resinous substances were obtained besides the usual residues from the rearrangements. When *N*,*N*-diethylaniline was used as solvent, IX could almost always be isolated, but yields were so small and variable (about 2–14%) that the rearrangement promised little synthetic value. Apparently the conditions under which the ether XIV rearranges are also those that result in extensive resinification, decomposition, or formation of the isomeric *N*-allyl pyrimidines.

The 4-alloxypyrimidines XV and XVI, bearing a 2-methyl and a 2-trifluoromethyl group respectively, did not rearrange smoothly to the 5-allylpyrimidines. Although a trace of X was found in the reaction mixture from the thermal rearrangement of ether XV, the preparation of X and XI by this route was clearly not practical.

The rearrangement of 2-benzylthio-4-alloxypyrimidine (XIII) was studied in several solvents. Unlike the Claisen rearrangement of allylphenols this rearrangement would not proceed to a 5-allylpyrimidine in the absence of solvent or at temperatures much lower than 200°. When XIII was heated with *N*,*N*-dimethylaniline (b.p. 193°), dimethyl sulfoxide (b.p. 189°), *cis*-decalin (b.p. 193°), or no solvent (at 240°), very little or no rearrangement took place.

In the rearrangements described here the best yields were no more than 28%. It is probable that the rearrangement of the allyl group to one of the ring nitrogens located *ortho* and *para* to the alloxy



group is a competing reaction, and that these isomers comprise much of the residues remaining after isolation of the 5-allylpyrimidines.[10] In addition, the high temperatures required for the rearrangement seem to have an adverse effect on pyrimidines XIV, XV, and XVI, resulting in their decomposition or resinification.

Evidence that the products isolated from the pyrimidine Claisen rearrangements are 5-allylpyrimidines is the independent synthesis of VII, VIII, and IX by the route through ester IV. The compounds prepared by the two methods were identical in melting points. Mixed melting points gave no depression, and infrared and ultraviolet absorption spectra were identical. Ultraviolet spectrophotometric examination of 5-allyluracil over a range of *p*H values according to the method of Shugar and Fox[14] indicated the presence of two ionizable hydrogens, demonstrating that the alkyl substituent cannot be on either the 1- or 3-positions. Moreover, the ultraviolet curves of 5-allyluracil over a range of *p*H values closely resemble those of thymine with approximate pK_a values of 9.7 and above 13.[14]

Many of the new compounds described here have been assayed for biological activity. The results were negative for microbial growth inhibition (*Bacillus subtilis* ATCC-6051, *Escherichia coli* W and *Saccharomyces cerevisiae*, on minimal, chemically

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(13) O. Buckendorff, *Ann.*, **385**, 314 (1911).
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defined culture media).[15] Insignificant inhibition of transplanted subcutaneous Krebs 2 tumors in mice was found at maximum tolerated doses. These data will be presented elsewhere.

EXPERIMENTAL[16]

1,1,1,3-Tetrachloro-3-ethoxypropane (I). A process similar to the one used by Glickman[5] and by Nesmeyanov *et al.*[5] was followed to prepare this compound.

Dry vinyl ethyl ether (288 g., 4.00 moles) was added under the surface to 1085 g. (7.00 moles) of refluxing reagent grade carbon tetrachloride in the presence of 2.4 g. of catalyst, α,α-azodiisobutyronitrile.[5] The addition of the ether took 3 hr., and the reaction mixture was refluxed for an additional hr. Excess carbon tetrachloride was removed on a steam bath under reduced pressure. A preliminary cut was taken up to 66° (8 mm.). The residue was distilled to give 796 g. (88%) of 1,1,1,3-tetrachloro-3-ethoxypropane, b.p. 64° (7 mm.).

Ethyl β,β-diethoxypropionate (II).[6] A solution of 796 g. (3.52 moles) of I in 650 g. (14.1 moles) of absolute ethanol was refluxed on a steam bath for 5 hr. The excess ethanol was removed under reduced pressure. A preliminary cut was taken up to 66° (6 mm.). The residue was distilled at 68–70° (5–6 mm.) to give 455 g. (68%) of crude product. Ether (300 ml.) was added to the crude product, and the solution washed with three 150-ml. portions of distilled water in a separatory funnel. The product layer was separated and dried over anhydrous potassium carbonate. The ether was evaporated and the purified product distilled to give 341 g. (50%) of ethyl β,β-diethoxypropionate, b.p. 68° (8 mm.).

Ethyl β-alloxyacrylate (III) *and ethyl α-allylformylacetate* (IV). Ethyl β,β-diethoxypropionate (II) was converted to III and IV by the procedure of Croxall and Van Hook.[7] II was substituted for the ethyl β-ethoxyacrylate used by these authors with similar results.

5-Allyl-2-thiouracil (V). This compound was prepared from IV by the method of Croxall and Fegley.[8] On a 0.2-mole scale a 62% yield of product was obtained; $\lambda_{max(m\mu)}^{pH\ 1,7}$ 275 (ε 16,000); $\lambda_{max(m\mu)}^{pH\ 13}$ 260 (ε 12,400), 314 (ε 8300).

2-Methylthio-5-allyl-4-pyrimidone (VII). *Condensation in anhydrous media.* Sodium (2.30 g., 0.10 g.-atom) was dissolved in 150 ml. of absolute ethanol. 2-Methyl-2-thiopseudourea sulfate (7.00 g., 0.025 mole) and 7.80 g. (0.050 mole) of ethyl α-allylformylacetate were added and stirred at room temperature for 24 hr. After the ethanol was evaporated, the oil remaining was diluted with water and acidified with glacial acetic acid. The white precipitate which formed was collected and recrystallized from ethanol to give 2.2 g. (24%) of long needles, m.p. 152–154°. Further recrystallization gave the analytical sample, m.p. 155–157°; $\lambda_{max(m\mu)}^{pH\ 1}$ 233 (ε 9600), 287 (ε 8200); $\lambda_{max(m\mu)}^{pH\ 7}$ 234 (ε 10,000), 289 (ε 8700); $\lambda_{max(m\mu)}^{pH\ 13}$ 247 (ε 9400), 281 (ε 7600).

Anal. Calcd. for $C_8H_{10}N_2OS$: C, 52.75; H, 5.53; N, 15.38; S, 17.59. Found: C, 53.08; H, 5.51; N, 15.29; S, 17.73.

2-Methylthio-5-allyl-4-pyrimidone (VII). *Condensation in aqueous media.* 2-Methyl-2-thiopseudourea sulfate (7.00 g., 0.025 mole) was dissolved with stirring in 40 ml. (0.10 mole) of 2.5*N* sodium hydroxide. To this was added 7.80 g. (0.050 mole) of IV dissolved in 20 ml. of ethanol. Stirring at room temperature was continued for several hours, and the mixture allowed to stand overnight. Stirring was continued for another 2 hr.; then the solvents were removed at reduced pressure. The resulting oily mixture was dissolved in about 100 ml. of water and acidified with glacial acetic acid. The heavy white precipitate that formed was collected and washed with a little water. The crude crop weighed 5.8 g., (64%), m.p. 136–146°. After recrystallization from ethanol there was obtained 3.6 g. (40%) of product, m.p. 155–157°. Additional material was obtained by concentrating the filtrate.

2-Benzylthio-5-allyl-4-pyrimidone (VIII). Sodium (2.30 g., 0.10 g.-atom) was dissolved in 150 ml. of absolute ethanol. 2-Benzyl-2-thiopseudourea hydrochloride (10.14 g., 0.050 mole) and 7.80 g., (0.050 mole) of IV were added and stirred at room temperature for 24 hr. After the ethanol was evaporated, the residue was taken up in water and acidified with glacial acetic acid. The crude product was filtered and recrystallized from aqueous ethanol to give 4.2 g., (33%) of white crystals, m.p. 158–159°. The analytical sample was obtained from aqueous ethanol, m.p. 158–159°; $\lambda_{max(m\mu)}^{pH\ 1}$ 289 (ε 9200) $\lambda_{max(m\mu)}^{pH\ 7}$ 291 (ε 9600); $\lambda_{max(m\mu)}^{pH\ 13}$ 248 (ε 9900) 282 (ε 8800).

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.85. Found: C, 65.14; H, 5.51; N, 11.00.

This condensation was also carried out with comparable yields in aqueous ethanol according to the procedure for the preparation of VII.

2-Amino-5-allyl-4-pyrimidone (IX). Sodium (2.30 g., 0.10 g.-atom) was dissolved in 150 ml. of absolute ethanol. Guanidine nitrate (6.10 g., 0.050 mole) and 7.80 g., (0.050 mole) of IV were added and refluxed for 4 hr. The ethanol was evaporated, and the residue dissolved in the minimum amount of water, cooled, and acidified with glacial acetic acid, forming a white precipitate that was filtered to give 4.1 g. (52%) of crude product, m.p. 148–164°. The product was recrystallized from isopropyl alcohol to give 2.8 g., (37%) of yellowish white crystals, m.p. 202–206°. The analytical sample was obtained from isopropyl alcohol, m.p. 205–207°; $\lambda_{max(m\mu)}^{pH\ 1}$ 261 (ε 7600); $\lambda_{max(m\mu)}^{pH\ 7}$ 291 (ε 7000); $\lambda_{max(m\mu)}^{pH\ 13}$ 232 (ε 9300), 279 (ε 7000).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.86; H, 6.14; N, 27.55.

This compound is water soluble and can be recrystallized from water to yield a hydrate which is efflorescent at room temperature. The composition of the hydrate was not determined. The condensation was also carried out with comparable yields in aqueous ethanol according to the procedure for the preparation of VII.

2-Methyl-5-allyl-4-pyrimidone (X). Sodium (2.30 g., 0.10 g.-atom) was dissolved in 150 ml. of absolute ethanol. Acetamidine hydrochloride (4.73 g., 0.050 mole) and 7.80 g. (0.050 mole) of IV were added at room temperature and stirred and refluxed for 2 hr. The ethanol was evaporated, and the residue dissolved in about 50 ml. of water. A small amount of oily substance was removed by shaking with 20 ml. of ether in a separatory funnel. The aqueous layer was then acidified carefully with 6*M* hydrochloric acid. The pyrimidine was extracted from the solution with three 50-ml. portions of chloroform. The chloroform was evaporated, and the residue recrystallized from petroleum ether (b.p. 66–75°) using Norite. The product crystallized in slender needles to give 1.61 g. (22%) of product, m.p. 138–139°.

The analytical sample was obtained by further recrystallization from petroleum ether, m.p. 140–141°; $\lambda_{max(m\mu)}^{pH\ 1}$ 230 (ε 8300), 257 (ε 5200); $\lambda_{max(m\mu)}^{pH\ 7}$ 226 (ε 6800), 271 (ε 5700); $\lambda_{max(m\mu)}^{pH\ 13}$ 232 (ε 8900), 271 (ε 5600).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 64.27; H, 6.79; N, 18.96.

The condensation was also carried out in 50% aqueous ethanol according to the procedure for VII. After the solvents from the reaction mixture had been removed, the product was worked up according to the procedure for

(15) Robert Guthrie, Children's Hospital, Buffalo 22, N. Y., and J. R. Stanford, unpublished results.

(16) All melting points and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Ultraviolet absorption data were obtained on a Beckman DK-2 spectrophotometer. The maxima reported at *p*H 1 were obtained in 50% aqueous ethanol 0.1*N* in hydrochloric acid, at *p*H 13, in 50% aqueous ethanol 0.1*N* in sodium hydroxide, and at *p*H 7 in 50% aqueous ethanol alone.

anhydrous media. The yields for both procedures were similar.

2-Trifluoromethyl-5-allyl-4-pyrimidone (XI). Sodium (1.15 g., 0.050 g.-atom) was dissolved in 150 ml. of absolute ethanol. Trifluoroacetamidine[17] (5.61 g., 0.050 mole) and 7.80 g. (0.050 mole) of IV were added, and the solution refluxed for 4 hr. The ethanol was evaporated, and the residue dissolved in a minimum amount of water. Upon careful acidification with 6*M* hydrochloric acid a precipitate formed which was collected, washed, and dried. The crude product weighed 4.15 g., (41%), m.p. 125–141°. Recrystallization from about 500 ml. of petroleum ether (b.p. 66–75°) gave 2.55 g., (25%) of product, m.p. 152–154°. The analytical sample was obtained by further recrystallization from petroleum ether, m.p. 153–154°, $\lambda_{max(m\mu)}^{pH\ 1}$ 226 (ϵ 5900), 259 (ϵ 3800); $\lambda_{max(m\mu)}^{pH\ 7\ 6}$ 232 (ϵ 6300), 265 (ϵ 3600); $\lambda_{max(m\mu)}^{pH\ 13}$ 258 (ϵ 9800), 274 (ϵ 4500).

Anal. Calcd. for $C_5H_7N_2OF_3$: C, 47.06; H, 3.46; N, 13.72. Found: C, 47.10; H, 3.26; N, 13.77.

The condensation in aqueous ethanol was unsuccessful.

5-Allyluracil (VI) *from* V. 5-Allyl-2-thiouracil (V) (5.04 g. 0.030 mole) was boiled with 4.73 g. (0.050 mole) of monochloroacetic acid in 175 ml. of water. When the solids had dissolved, the solution was allowed to evaporate to dryness on the steam bath. The residue was recrystallized from ethanol twice to give 3.1 g. (68%) of white crystals, m.p. 280–281° dec.; $\lambda_{max(m\mu)}^{pH\ 2.20\ water}$ 263 (ϵ 8100); $\lambda_{max(m\mu)}^{pH\ 8.05\ water}$ 263 (ϵ 8100); $\lambda_{max(m\mu)}^{pH\ 13\ water}$ 289 (ϵ 6600).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.04; H, 5.26; N, 18.64.

5-Allyluracil (VI) *from* VII. A mixture of 2.00 g. of 2-methylthio-5-allyl-4-pyrimidone (VII), in 20 ml. of ethanol and 1.1 ml. of concd. hydrochloric acid was refluxed for 2 hr. The solids dissolved on heating, and after about 1 hr. a heavy precipitate appeared. After cooling to room temperature the precipitate was collected, washed with a small amount of 50% ethanol and air dried to fluffy tan plates weighing 1.12 g. (67%), m.p. 277–281° dec.

2-Substituted 4-hydroxypyrimidines. 2-Methylthio-4-hydroxypyrimidine,[18] 2-benzylthio-4-hydroxypyrimidine,[19] 2-amino-4-hydroxypyrimidine,[20] and 2-methyl-4-hydroxypyrimidine[21] were prepared according to procedures given in the literature. 2-Trifluoromethyl-4-hydroxypyrimidine was prepared according to the procedure of John A. Barone.[22]

2-Substituted 4-chloropyrimidines. The 2-substituted 4-hydroxypyrimidines were converted with phosphorus oxychloride to 2-methylthio-4-chloropyrimidine,[18] 2-benzylthio-4-chloropyrimidine,[23] 2-amino-4-chloropyrimidine,[24] and 2-methyl-4-chloropyrimidine,[21] according to procedures given in the literature. 2-Trifluoromethyl-4-chloropyrimidine was prepared according to the procedure of John A. Barone.[22]

2-Substituted 4-alloxypyrimidines. The procedure following for the preparation of XIII is typical also for the preparation of XII, XV, and XVI.

2-Benzylthio-4-alloxypyrimidine (XIII). Sodium (2.30 g., 0.10 g.-atom) was dissolved cautiously in 50 ml. of allyl alcohol and added to a solution of 23.7 g., (0.10 mole) of 2-benzylthio-4-chloropyrimidine dissolved in 50 ml. of allyl alcohol. After standing at room temperature for 1 hr., excess allyl alcohol was removed at reduced pressure. Water was added to the oily residue, the oil extracted with ether, and the ether washed with water and dried over magnesium sulfate. After removal of the ether the residual oil was distilled at reduced pressure, to give 22.4 g., (87%) of water-white product, b.p. 154° (0.8 mm.).

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.08; H, 5.46; N, 10.85. Found: C, 65.17; H, 5.53; N, 10.92.

2-Methylthio-4-alloxypyrimidine (XII) was obtained in 93% yield, b.p. 88° (0.5 mm.).

Anal. Calcd. for $C_8H_{10}N_2OS$: C, 52.75; H, 5.53; N, 15.38. Found: C, 53.09; H, 5.48; N, 15.50.

2-Methyl-4-alloxypyrimidine (XV) was obtained in 67% yield, b.p. 47° (0.5 mm.).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 64.21 H, 6.60: N, 18.51.

2-Trifluoromethyl-4-alloxypyrimidine (XVI) was obtained in 64% yield, b.p. 42° (0.4 mm.).

Anal. Calcd. for $C_8H_7N_2OF_3$: C, 47.06; H, 3.46; N, 13.72. Found: C, 46.90; H, 3.44; N, 13.84.

2-Amino-4-alloxypyrimidine (XIV). A solution of 1.07 g. of sodium in 30 ml. of allyl alcohol was added to a solution of 6.00 g. of 2-amino-4-chloropyrimidine in 150 ml. of hot allyl alcohol. After refluxing for 1 hr. the excess allyl alcohol was evaporated, and water was added to the residue. The product was extracted with ether; the ether extracts washed with water and dried over magnesium sulfate. Evaporation of the ether gave 6.23 g. (89%) of product, m.p. 78–83°. This was recrystallized from about 60 ml. of 1:3 benzene–petroleum ether (b.p. 66–75°) to give 5.50 g., (78%) of product, m.p. 85–87°. The analytical sample was recrystallized from petroleum ether, m.p. 85–87°.

Anal. Calcd. for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.78; H, 6.07; N, 27.72.

2-Methylthio-5-allyl-4-pyrimidone (VII) *by rearrangement.* A solution of 10.0 g. of XII in 30 ml. of *N,N*-diethyl-*m*-toluidine was refluxed for 6 hr. in an oil bath maintained at 255°. After cooling most of the solvent was vacuum distilled. The residue was allowed to cool and stand at room temperature for 2 hr. During this time VII crystallized. The crystals were mixed with a small amount of petroleum ether (b.p. 35–60°) to facilitate filtration and collected upon a small Büchner funnel. The product was washed with a minimum amount of diethyl ether (the product is somewhat soluble in this solvent) to remove traces of dark colored oils which may be isomers of VII. The crude brown product weighed 2.80 g. (28%), m.p. 147–153°.

The material obtained by further recrystallization was identical to VII prepared by the condensation of 2-methyl-2-thiopseudourea sulfate with ester IV.

This rearrangement also gave a 22% crude yield, m.p. 137–139°, when XII was refluxed in *N,N*-diethylaniline for 11 hr.

2-Benzylthio-5-allyl-4-pyrimidone (VIII) *by rearrangement.* A solution of 10.0 g., of XIII in 30 ml. of *N,N*-diethyl-*m*-toluidine was refluxed for 8 hr. in an oil bath maintained at 255°. After cooling most of the solvent was vacuum distilled. The residue was allowed to cool and remain at room temperature for 2 hr. During this time VIII crystallized. The crystals were mixed with diethyl ether and collected on a Büchner funnel, washed with more ether, and dried. The crude product weighed 2.40 g. (24%), m.p. 146–153°.

The material obtained by recrystallization from ethanol was identical to the VIII formed by the condensation of 2-benzyl-2-thiopseudourea hydrochloride with ester IV.

The rearrangement also took place in refluxing diethylaniline although usually in lower yield.

VIII was also obtained from the reaction mixture by successive extractions with 10% sodium hydroxide solution and subsequent acidification of the extracts. This method was not as satisfactory as the above procedure.

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2-Amino-5-allyl-4-pyrimidone (IX) *by rearrangement.* A mixture of 5.0 g. of XIV and 15 ml. of *N,N*-diethylaniline was heated in an oil bath. When XIV had melted, the mixture was swirled to insure complete solution. The solution was refluxed for 4 hr. at a bath temperature of 240°. On cooling a black oil separated. Most of the solvent was removed by vacuum distillation, and the tarry residue rinsed with a little ether, then extracted with five 50-ml. portions of boiling water. The aqueous extracts were concentrated to about 50 ml. and refrigerated. The product crystallized in slender needles as a hydrate. Additional material was obtained by concentrating the filtrate. The weight of efflorescent hydrate obtained varied from 0.12 g. to 0.80 g. An additional crystallization from isopropyl alcohol gave anhydrous IX.

2-Methyl-5-allyl-4-pyrimidone (X) *and 2-trifluoromethyl-5-allyl-4-pyrimidone* (XI) *by rearrangement.* Because the corresponding 4-alloxypyrimidines XV and XVI had boiling points lower than the temperature at which rearrangement occurred, they were heated with diethylaniline in a sealed tube at 240° for 8 hr. Examination of the reaction mixtures did not indicate the presence of any more than a trace of product along with tars and oils.

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Phosphorylated Pyrimidines[1]

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Several phosphorylated pyrimidines have been prepared from 5-hydroxymethyl- (I), 5-bromomethyl- (II), and 5-formyl-4-amino-2-methylthiopyrimidine (III). 5-Phosphonylmethylpyrimidines have been synthesized from II and trialkyl phosphites; 5-phosphonylhydroxymethylpyrimidines have been synthesized from III. Phosphorus oxychloride and thiophosphoryl chloride with I gave phosphorodichloridates and phosphorodichlorothioates, respectively. These latter compounds were converted to diamidates. Dialkyl chlorophosphates and thionochlorophosphates and I gave the corresponding tertiary phosphate esters.

Interest in 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I, methioprim) and related compounds has led to the synthesis of several related pyrimidines in this laboratory.[3] These compounds have been assayed in experimental rodent tumors and in microbiological systems. The results were encouraging to the extent that the synthesis of further related compounds seemed pertinent.

In clinical trial I was found to be inactive as a tumor inhibitor.[4] Experiments with rat liver homogenates have shown that in this system I was rapidly oxidized to the corresponding 5-formylpyrimidine and 5-hydroxymethylpyrimidine.[5] This suggested that those derivatives of I which are less susceptible to oxidation, might be better candidates for cancer chemotherapy. In a previous paper esters of I were reported.[3] The present paper deals with phosphonates, phosphates and phosphorodiamidates of I and related pyrimidines. As compounds of phosphorus that contain the ethyleneimine group such as triethylene phosphoramide and triethylene thiophosphoramide are of chemotherapeutic interest, it also seemed pertinent to incorporate this type of structure into methioprim.

The pyrimidine phosphonates were synthesized from 4-amino-5-formyl-2-methylthiopyrimidine (III)[6] and 4-amino-5-bromomethyl-2-methylthiopyrimidine hydrobromide (II).[6,7] Dialkyl and diaryl phosphites and III gave 5-(4-amino-2-methylthiopyrimidyl)hydroxymethylphosphonates (IV-VII). The ethyl ester (V) was formed in good yield and was used in further syntheses. Treatment of V with hydrochloric acid in ethanol gave diethyl 5-(4 - amino - 2 - hydroxypyrimidyl)hydroxymethylphosphonate hydrochloride (VIII). V and concentrated hydrochloric acid resulted in hydrolysis of the ester and the methylthio group to give 5-(4-amino - 2 - hydroxypyrimidyl)hydroxymethylphosphonic acid (IX).

When V was heated with alcoholic ammonia in a sealed tube, no reaction occurred. Oxidation of V in absolute ethanol by chlorine gave diethyl 5-(4 - amino - 2 - methylsulfonylpyrimidyl)hydroxymethylphosphonate (X). Treatment of X with alcoholic ammonia in a sealed tube gave diethyl 5 - (2,4 - diaminopyrimidyl)hydroxymethylphosphonate (XI).

5 - (4 - Amino - 2 - methylthiopyrimidyl)methylphosphonates (XII–XVI) were prepared from II and trialkyl phosphites by the Michaelis-Arbuzov reaction.

The reaction of phosphorus oxychloride with I gave 5 - (4 - amino - 2 - methylthiopyrimidyl)-methyl phosphorodichloridate (XVII). This served

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