Pyrimidines. X. (Antibiotics. II) Synthesis of Bacimethrin, 2-Methoxy Analog of Thiamine, and Related Alkoxypyrimidines[1]

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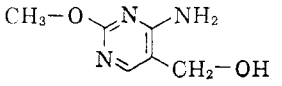
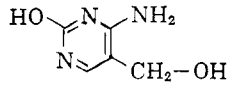
The proposed structure for the antibiotic bacimethrin has been confirmed synthetically as 4-amino-5-hydroxymethyl-2-methoxypyrimidine. The 2-methoxy analog of thiamine has been prepared from the synthetic bacimethrin. Several reactions indicating the effect of a substituent group in the "5" position of a pyrimidine ring on the ease of nucleophilic replacement of a 2-alkylsulfonyl group have been reported.

The structure of bacimethrin, a new antibiotic recently isolated from *Bacillus megatherium*, has been proposed as 4-amino-5-hydroxymethyl-2-methoxypyrimidine (I) from degradation studies.[2]

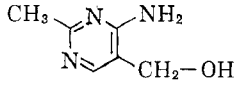


I

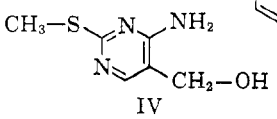
This compound has low toxicity in mice and is active against the growth of various yeasts and bacteria.[2] Since this antibiotic is structurally similar to the known biologically active HMC (5-hydroxymethylcytosine, II),[3] toxopyrimidine (4-amino-5-hydroxymethyl-2-methylpyrimidine, III),[4] and methioprim [2-methylthio-4-amino-5-(hydroxymethyl)pyrimidine, IV][4d,e,h] as well as Bayer DG-428 [2-(*o*-chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine, V][5], the investigation of the synthesis of this type of 2-alkoxypyrimidine was therefore undertaken. The biological interference of this type of compound with *in vivo* DNA synthesis, or with some other vital metabolic pathway, as suggested by Ulbricht and Price,[4d] might well give rise to certain carcinostatic activity.



II



III



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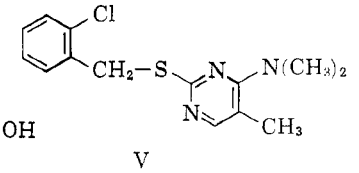
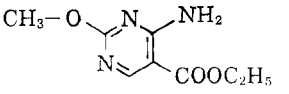
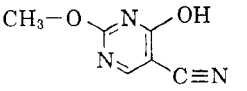


V

Condensation between O-methylisourea and ethyl ethoxymethylenecyanoacetate could yield theoretically two possible products, 4-amino-5-carbethoxy-2-methoxypyrimidine (VI) and/or 5-cyano-2-methoxy-4-pyrimidinol (VII) *via* two different ring closures:



VI



VII

In our laboratories it was found that when the above condensation was carried out in methanol, compounds VI (14%) and VII (50%) were isolated together with the transesterified[6] product of VI, 4-amino-5-carbomethoxy-2-methoxypyrimidine,[7] 17%. Since the desired compound VI was obtained in rather low yield (14%), the following synthetic route was employed.

4-Amino-5-carbethoxy-2-(ethylsulfonyl)pyrimidine[8] (VIII), when treated with sodium methoxide, gave 4-amino-4-carbethoxy-2-methoxypyrimidine (IX. R = CH_3).[9] Reduction of IX with lithium aluminum hydride in anhydrous ether or tetrahydrofuran gave a 67% yield of 4-amino-5-hydroxymethyl-2-methoxypyrimidine (X. R = CH_3). This compound was found to be identical with an authentic sample of bacimethrin.[10] The cor-

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) F. Tanaka, S. Takeuchi, N. Tanaka, H. Yonehara, H. Umezama, and Y. Sumiki, *J. Antibiotics* (Tokyo), *Ser. A.*, **14**, 161 (1961).

(3) (a) G. R. Wyatt and S. S. Cohen, *Nature*, **170**, 1072 (1952); (b) G. R. Wyatt and S. S. Cohen, *Biochem. J.*, **55**, 774 (1953); (c) A. Dornow and G. Petsch, *Ann.*, **588**, 45 (1954); (d) C. S. Miller, *J. Am. Chem. Soc.*, **77**, 752 (1955).

(4) (a) R. Abderhalden, *Arch. Ges. Physiol.*, **240**, 647 (1938); *ibid.*, **242**, 199 (1939); (b) A. Watanabe, *J. Pharm. Soc. Japan*, **59**, 133 (1939); (c) K. Makino, T. Kinoshita, T. Sasaki, and T. Shioi, *Nature*, **173**, 34 (1954); *ibid.*, **174**, 275, 1056 (1954); (d) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956); (e) R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exp. Biol. Med.*, **94**, 792 (1957); (f) M. Kawashima, *J. Pharm. Soc. Japan*, **77**, 758 (1957); (g) A. Schellenberger and K. Winter, *Z. Physiol. Chem.*, **322**, 173 (1960); (h) T. Okuda and C. C. Price, *J. Org. Chem.*, **23**, 1738 (1959), and references cited therein.

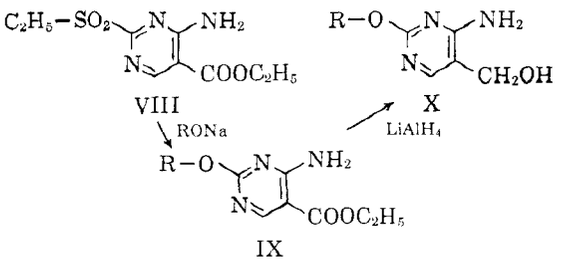
(5) K. Westphal and R. Bierling, *Naturwissenschaften*, **46**, 230 (1959).

(6) The transesterification reaction can be illustrated by another example: Refluxing a mixture of O-methylpseudourea and diethyl ethoxymethylenemalonate in methanolic sodium methoxide gave 5-carbomethoxy-2-methoxy-4-pyrimidinol rather than the expected ethyl ester.

(7) This methyl ester, owing to its insolubility in ethereal solvents, could not be readily reduced by lithium aluminum hydride to yield the desired compound I.

(8) J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **57**, 2254 (1935).

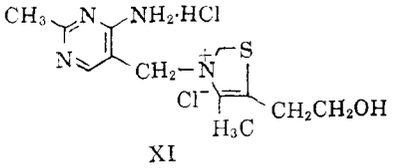
(9) The use of 2-methylsulfonyl homolog rather than IX gave, after the replacement reaction, a very poor yield of X.



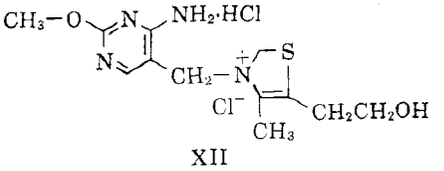
VIII X IX

responding ethoxy derivatives of IX and X have also been synthesized.

Since toxopyrimidine (III) has been shown to be both a biological precursor[11] and a hydrolysis product[4b] of Vitamin B_1 (thiamine, XI, shown as the chloride hydrochloride), the synthesis of

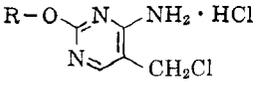


XI



XII

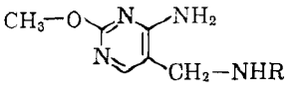
the corresponding 2-methoxy analog of thiamine (XII), which is metabolically quite closely related to bacimethrin, was also investigated. Chlorination of X (R = CH_3) with thionyl chloride gave the unstable 4-amino-5-chloromethyl-2-methoxypyrimidine hydrochloride (XIII. R = CH_3), which was used directly to react with 4-methyl-5-(β-hydroxy-



XIII

ethyl)thiazole[12] to give the desired 2-methoxy analog of thiamine (XII). Similarly the corresponding 2-ethoxy homolog was prepared from compound XIII (R = C_2H_5).

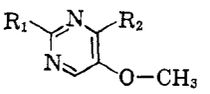
4-Amino-5-aminomethyl-2-methoxypyrimidine (XIV. R = H) could not be isolated from the reaction of XIII and ammonia under a variety of experimental conditions. Catalytic (Raney nickel) hydrogenation of 4-amino-5-cyano-2-methoxypy-



XIV

rimidine[13] in the presence of acetic anhydride with several pellets of sodium hydroxide[14] gave the acetylated derivative (XIV. R = CO—CH_3).

Because of the interesting biological properties of bacimethrin (I), the synthesis of the isomeric 4-amino-2,5-dimethoxypyrimidine (XV) was also investigated. Methyl α-formyl-α-methoxyacetate[15]



XV. R_1 = CH_3O, R_2 = NH_2
XVI. R_1 = CH_3S, R_2 = OH
XVII. R_1 = CH_3S, R_2 = NH_2
XVIII. R_1 = CH_3SO_2, R_2 = NH_2
XIX. R_1 = CH_3SO_2, R_2 = OH

was treated with S-methylisothiouronium iodide to give 5-methoxy-2-methylthio-4-pyrimidinol (XVI). Chlorination of XVI with phosphorus oxychloride followed by amination yielded 4-amino-5-methoxy-2-(methylthio)pyrimidine (XVII). Compound XVII was then treated with chlorine gas at low temperature to form the corresponding sulfone XVIII. The methylsulfonyl group (and in later experiments, ethylsulfonyl group) in compound XVIII could not be replaced by methoxide ion in boiling methanol. The replacement was finally achieved by heating the reaction mixture in a pressure bomb at high temperature for several hours. The methylsulfonyl group of 5-methoxy-2-methylsulfonyl-4-pyrimidinol (XIX), prepared from the chlorine oxidation of XVI, behaved similarly. The stability of these alkylsulfonyl groups in compounds XVIII and XIX can probably be explained by the strong electron donating effect exerted by the 5-methoxy group. On the other hand, when the 5-position is occupied by an ester, as in the case of 4-amino-5-carbethoxy-2-(ethylsulfonyl)pyrimidine (VIII), the ease of replacement of this alkylsulfonyl group can be readily demonstrated by treatment of VIII with ethylenimine at relatively low temperature to form 4-amino-2-(1′-aziridinyl)-5-carbethoxypyrimidine (XX).

(10) An authentic sample of bacimethrin was kindly provided by Dr. F. Tanaka and Dr. H. Yonehara of the Institute of Applied Microbiology, the University of Tokyo, Tokyo, Japan. A preliminary account of this work has already been published: H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **27**, 1492 (1962).

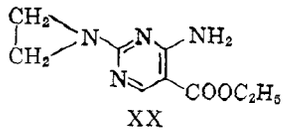
(11) P. Albersheim and J. Bonner, "Metabolic Pathways," Vol. 2, D.M. Greenberg, ed., Academic Press, Inc., New York, 1961, pp. 176–625, and references cited therein.

(21) R. R. Williams, U. S. Patent 2,134,015, October 25, 1939.

(13) (a) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Am. Chem. Soc.*, **82**, 5712 (1960). (b) Lithium aluminum hydride reduction of this compound in tetrahydrofuran, although theoretically possible [cf. W. G. Brown, *Org. Reactions*, 480 (1951), and references cited therein], also failed to yield the 5-aminomethyl derivative.

(14) This hydrogenation condition was recommended by Dr. Arthur F. Ferris of our Institute. See also F. E. Gould, G. S. Johnson, and A. F. Ferris, *J. Org. Chem.*, **25**, 1658 (1960).

(15) (a) L. Shreiner, *Ann.*, **197**, 8 (1879); (b) T. B. Johnson and H. Guest, *Am. Chem. J.*, **42**, 271 (1909); (c) T. B. Johnson and F. Heyl, *ibid.*, **38**, 237 (1907); (d) J. H. Chesterfield, J. F. W. McOmie, and M. S. Tute, *J. Chem. Soc.*, 4590 (1960).



XX

Experimental[16]

Reaction of O-Methylisouronium Sulfate with Ethyl Ethoxymethylenecyanoacetate.—To a stirred solution of 50 g. (0.29 mole) of O-methylisouronium sulfate in 250 ml. of anhydrous methanol was added a methanolic solution of sodium methoxide prepared by dissolving 17 g. (0.74 mole) of sodium in 250 ml. of anhydrous methanol. The mixture was boiled for 15 min., the precipitated sodium sulfate was filtered and washed with 75 ml. of anhydrous methanol, and the combined washing and filtrate were added to a stirred solution of 50 g. (0.30 mole) of ethyl ethoxymethylenecyanoacetate in 250 ml. of methanol. A precipitate had appeared after 12 hr. This was filtered and recrystallized from ethanol to give 8 g. (17% yield) of **4-amino-5-carbomethoxy-2-methoxypyrimidine**, m.p. 208–210°. $\lambda_{max}^{pH\ 1}$ 239 mμ (ε 11,900); 273 mμ (ε 6,000); $\lambda_{max}^{pH\ 11}$ 241 mμ (ε 11,200); 286 mμ (ε 8,100).

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.9; H, 4.9; N, 22.9. Found: C, 46.2; H, 4.9; N, 22.7.

The filtrate was refluxed for 20 hr. and evaporated to dryness under reduced pressure. The residue was dissolved in 300 ml. of water. The pH of the solution was adjusted to 1 with concentrated hydrochloric acid and a precipitate was formed. After 1 hr. stirring the solid was filtered and recrystallized from ethanol to yield 23 g. (50%) of **5-cyano-2-methoxy-4-pyrimidinol** (**VII**), m.p. 199–201°. It possessed the characteristic nitrile peak at 4.5 μ. $\lambda_{max}^{pH\ 1}$ 223 mμ (ε 8,300); 280 mμ (ε 8,000); $\lambda_{max}^{pH\ 11}$ 234 mμ (ε 9,100), 283 mμ (ε 9,400).

Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.6; H, 3.3; N, 27.8. Found: C, 47.7; H, 3.5; N, 27.8.

The resulting filtrate was neutralized and refrigerated for 5 days. A third solid product was collected by filtration and recrystallized from a mixture of methanol and water to give 10 g. (14%) of **4-amino-5-carbethoxy-2-methoxypyrimidine** (**VI**), m.p. 151–153°. $\lambda_{max}^{pH\ 1}$ 239 mμ (ε 12,200), 273 mμ (ε 6,500); $\lambda_{max}^{pH\ 12}$ 241 mμ (ε 11,400); 286 mμ (ε 8,300).

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.7; H, 5.6; N, 21.3. Found: C, 48.8; H, 5.8; N, 21.6.

A better method to prepare 4-amino-5-carbethoxy-2-methoxypyrimidine is described as follows: To a stirred suspension of 28 g. (0.105 mole) of powdered 4-amino-5-carbethoxy-2-(ethylsulfonyl)pyrimidine[8] in 200 ml. of anhydrous methanol cooled at 0° was added dropwise a solution of sodium methoxide prepared by dissolving 3.7 g. (0.16 g.-atom) of sodium in 50 ml. of methanol. The temperature during the addition was held below 10°. The mixture was allowed to stir for 1 hr. after the addition. The white solid was then filtered and washed with a small amount of cold benzene. Recrystallization from benzene yielded 16 g. (76% yield) of IX (R = CH_3) as long, white needles, m.p. 151–153°. There is no depression on mixed melting point determination. The ultraviolet and infrared absorption spectra of the two products prepared by different methods were found to be identical.

4-Amino-5-hydroxymethyl-2-methoxypyrimidine (**X. R = CH_3**).—One hundred grams (0.49 mole) of IX (R = CH_3) was reduced by 36.9 g. (1 mole) of lithium aluminum hydride in 2 l. of anhydrous tetrahydrofuran in the usual manner to give, after recrystallization from a mixture of ethanol and ether, 52 g. (69% yield) of white prisms, m.p. 174°. (This compound can also be prepared in 60% yield using anhydrous ether as solvent and introducing the carbethoxypyrimidine by continuous extraction in a Soxhlet apparatus.[17])

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.9; N, 27.1. Found: C, 46.5; H, 6.2; N, 27.1.

This compound exhibited the following ultraviolet absorption: $\lambda_{max}^{H_2O}$ 227 mμ (ε 7,600), 271 mμ (ε 7,300); $\lambda_{max}^{0.1N\ HCl}$ 229 mμ (ε 8,400), 261 mμ (ε 9,500); $\lambda_{max}^{0.1N\ NaOH}$ 231 mμ (ε 6,200), 271 mμ (ε 7,600). Its infrared absorption spectrum in Nujol possesses the following bands (in cm.$^{-1}$): 3390 (w), 3340 (w), 3220 (m), 2900 (s), 2830 (s), 1650 (s), 1610 (s), 1560 (s), 1460 (s), 1400 (m), 1360 (s), 1295 (s), 1215 (w), 1195 (m), 1125 (s), 1005 (s), 980 (m), 950 (w), 940 (s), 805 (s), 775 (s), and 735 (w). These data, when compared with the published physical constants for bacimethrin,[2] confirm in every respect, the previously assigned structure I for that antibiotic.

4-Amino-2-ethoxy-5-(hydroxymethyl)pyrimidine (**X. R = C_2H_5**) was similarly prepared from the corresponding 2-ethoxy derivative in tetrahydrofuran in 70% yield after recrystallization from ethyl acetate, m.p. 149–150°. $\lambda_{max}^{pH\ 1}$ 229 mμ (ε 8,500), 261 mμ (ε 9,300); $\lambda_{max}^{pH\ 11}$ 231 mμ (ε 6,800), 271 mμ (ε 7,600).

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.7; H, 6.5; N, 24.8. Found: C, 49.6; H, 6.6; N, 24.7.

General Preparation of 2-Alkoxy-4-amino-5-chloromethylpyrimidine Hydrochloride (XIII).—To a chilled and rapidly stirred solution of 300 ml. of thionyl chloride and 150 ml. of chloroform was added portionwise 30 g. of 2-alkoxy-4-amino-5-(hydroxymethyl)pyrimidine (X). A yellow precipitate formed immediately. After the addition, the mixture was refluxed for 45 min. and then evaporated *in vacuo* to dryness. The residue was triturated twice with 200 ml. of anhydrous acetone, filtered, and washed with anhydrous ether to give 40–50 g. of product sufficiently pure for the following synthesis. Both the methoxy (XIII. R = CH_3), and the ethoxy (XIII. R = C_2H_5) homologs decomposed slowly over 250°. Attempts to purify these compounds led only to decomposition.

3-(4′-Amino-2′-methoxy-5′-pyrimidylmethyl)-5-(β-hydroxyethyl)-4-methylthiazolium Chloride Hydrochloride (**XII**).—To a solution of 20 g. of crude 4-amino-5-chloromethyl-2-methoxypyrimidine hydrochloride (XIII. R = CH_3) in 200 ml. of anhydrous methanol warmed to 45° was added 14 g. of 5-(β-hydroxyethyl)-4-methylthiazole. The resulting solution was gently boiled on the steam bath for 15 min. To the hot reaction mixture was carefully added ethyl acetate until crystallization commenced. After refrigerating overnight the crystals were filtered and washed with isopropyl alcohol. Purification was effected by recrystallization of the crude product from a mixture of methanol and ether. Three and four-tenths grams of light yellow crystals was obtained which decomposed at 193–194°. $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 13,100); $\lambda_{max}^{H_2O}$ 267 mμ (ε 11,300); $\lambda_{max}^{methanol}$ 268 mμ (ε 9,900).

Anal. Calcd. for $C_{12}H_{17}ClN_4O_2S \cdot HCl$: C, 40.8; H, 5.1; N, 15.9; S, 9.1; Cl^-, 20.1. Found: C, 40.8; H, 5.4; N, 15.7; S, 9.0; Cl^-, 20.3.

3-(4′-Amino-2′-ethoxy-5′-pyrimidylmethyl)-5-(β-hydroxyethyl)-4-methylthiazolium Chloride Hydrochloride was similarly prepared from 30 g. of crude XIII (R = C_2H_5) to give 10 g. of light yellow crystals, decomposed at 193–195°. $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 13,200); $\lambda_{max}^{H_2O}$ 267 mμ (ε 10,300); $\lambda_{max}^{methanol}$ 268 mμ (ε 9,600).

Anal. Calcd. for $C_{13}H_{19}ClN_4O_2S \cdot HCl$: C, 42.5; H, 5.4; N, 15.2; S, 8.7; Cl^-, 19.3. Found: C, 42.1; H, 5.4; N, 15.0; S, 8.8; Cl^-, 19.6.

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

(17) (a) J. A. Barone, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, **24**, 198 (1959); (b) H. C. Koppel, R. H. Springer, and C. C. Cheng, *ibid.*, **26**, 1884 (1961). We thank Professor Tieckelmann of the University of Buffalo for his helpful information with regard to this type of reduction.

5-Acetamidomethyl-4-amino-2-methoxypyrimidine (XIV, R = $COCH_3$).—A mixture of 4.5 g. sodium hydroxide pellets,[14] 10 g. of Raney nickel, 15 g. (0.1 mole) of 4-amino-5-cyano-2-methoxypyrimidine,[13] and 150 ml. of acetic anhydride was hydrogenated in a Parr hydrogenator at 60° and 60 p.s.i. The theoretical amount of hydrogen was absorbed in 2.5 hr. The solid was filtered and washed with acetic anhydride. The combined filtrate and washings were taken to dryness *in vacuo*. The residue was dissolved in a mixture of 150 ml. of concentrated ammonium hydroxide and 200 ml. of water. After boiling for 15 min., the solution was treated with charcoal and filtered. The solid product deposited from the filtrate was collected and recrystallized from a mixture of ethanol and ethyl acetate to give 8.2 g. (42% yield) of white crystals which decomposed at 203–206°. $\lambda_{max}^{pH\ 1}$ 239 mμ (ε 15,100), 273 mμ (ε 9,400); $\lambda_{max}^{pH\ 11}$ 240 mμ (ε 14,700), 284 mμ (ε 9,800).

Anal. Calcd. for $C_8H_{12}N_4O_2$: C, 49.0; H, 6.1; N, 28.5. Found: C, 48.8; H, 6.4; N, 28.3.

5-Carbomethoxy-2-methoxy-4-pyrimidinol.—Fifty grams of O-methylisouronium sulfate in 250 ml. of anhydrous methanol was added to 250 ml. of methanolic sodium methoxide (prepared by dissolving 6.7 g. of sodium in methanol) and heated on the steam bath for 15 min. The precipitated sodium sulfate was filtered and washed with methanol. The combined filtrate and washings were added to 250 ml. of methanolic sodium methoxide (containing 6.7 g. of dissolved sodium) followed by cautious addition of 62.6 g. of diethyl ethoxymethylenemalonate. The resulting solution was refluxed and stirred overnight, during which time a precipitate had formed. The solid was filtered, dissolved in 250 ml. of warm water, and acidified with acetic acid. The crude product was filtered and recrystallized from a mixture of water and dimethylformamide to give 18 g. of white needles, m.p. 199–201°. $\lambda_{max}^{pH\ 1}$ 226 mμ (ε 8,300), 273 mμ (ε 6,400); $\lambda_{max}^{pH\ 11}$ 236 mμ (ε 7,700), 276 mμ (ε 9,200).

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.6; H, 4.6; N, 15.2. Found: C, 45.5; H, 4.4; N, 14.9.

5-Methoxy-2-methylthio-4-pyrimidinol (XVI).—To a mixture of 1200 ml. of anhydrous ether and 200 ml. of ethyl formate was added 57.5 g. of sodium wire. To the stirred mixture was added dropwise 260 g. of methyl α-methoxyacetate.[15] Stirring was continued for 4 hr. after the addition. The ether layer was decanted and to the residue was carefully added 1 l. of cold water. The resulting solution was stirred and 496 g. of S-methylisothiouronium iodide was added, followed by 66 g. of potassium hydroxide pellets. The mixture was stirred for 4 hr. at room temperature, heated on the steam bath for 1 hr., treated with charcoal, and filtered. The filtrate was then acidified with acetic acid. The resulting white precipitate was filtered, washed with water and acetone and dried. Recrystallization of the crude product from a mixture of water and dimethylformamide gave 178 g. (39% yield) of XVI as white, heavy needles, m.p. 192–194°. $\lambda_{max}^{pH\ 1}$ 230 mμ (ε 9,800), 278 mμ (ε 9,500); $\lambda_{max}^{pH\ 11}$ 252 mμ (ε 8,600), 283 mμ (ε 6,500).

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.8; H, 4.6; N, 16.2. Found: C, 41.9; H, 4.7; N, 16.1.

4-Chloro-5-methoxy-2-methylthiopyrimidine.—A mixture of 80 g. of XVI and 500 ml. of phosphorus oxychloride was refluxed for 1 hr. (solution took place rather rapidly upon heating). Excess phosphorus oxychloride was distilled *in vacuo* and the sirupy residue worked up with crushed ice and extracted with ether. The crude product was recrystallized from heptane to give 82 g. (86% yield) of white needles, m.p. 74–75°. $\lambda_{max}^{methanol}$ 255 mμ (ε 18,500), 316 mμ (ε 3,200).

Anal. Calcd. for $C_6H_7ClN_2OS$: C, 37.7; H, 3.6; N, 14.6. Found: C, 37.6; H, 3.7; N, 14.5.

4-Amino-5-methoxy-2-(methylthio)pyrimidine (XVII).—A mixture of 60 g. of the preceding compound and 400 ml. of 20% ethanolic ammonia was heated at 135° in a bomb for 6 hr. The reaction mixture was then evaporated to dryness *in vacuo*. Recrystallization of the residual solid from 500 ml. of benzene gave 30 g. (60% yield) of XVII as white needles, m.p. 130–132°, $\lambda_{max}^{pH\ 1}$ 244 mμ (ε 27,200); $\lambda_{shoulder}^{pH\ 1}$ 277 mμ (ε 8,900); $\lambda_{max}^{pH\ 11}$ 252 mμ (ε 10,900), 294 mμ (ε 6,500).

4-Amino-5-methoxy-2-methylsulfonylpyrimidine (XVIII).—To a solution of 28 g. of XVII, 45 ml. of concentrated hydrochloric acid, and 340 ml. of water cooled at 10° was introduced a stream of chlorine gas. After 30 min. crystallization began. The white solid was collected after 1 hr. by filtration and washed with water and acetone. Recrystallization from ethanol gave 26 g. (80% yield) of white needles, m.p. 168–169°. $\lambda_{max}^{pH\ 1}$ 264 mμ (ε 9,300), $\lambda_{shoulder}^{pH\ 1}$ 282 mμ (ε 7,700); $\lambda_{max}^{pH\ 11}$ 261 mμ (ε 9,500), 283 mμ (ε 7,100).

Anal. Calcd. for $C_6H_9N_3O_3S$: C, 35.4; H, 4.4; N, 20.7. Found: C, 35.3; H, 4.7; N, 21.0.

5-Methoxy-2-methylsulfonyl-4-pyrimidinol (XIX) was similarly prepared from XVI in 50% yield. Recrystallization from a mixture of 2-butanone and dimethylformamide gave white crystals, m.p. 232–233°. $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 8,100); $\lambda_{max}^{pH\ 11}$ 273 mμ (ε 7,600).

Anal. Calcd. for $C_6H_8N_2O_4$: C, 35.1; H, 3.9; N, 13.7. Found: C, 35.2; H, 4.2; N, 13.9.

4-Amino-2,5-dimethoxypyrimidine (XV).—To a solution of 3.45 g. (0.15-g.-atom) of sodium in 400 ml. of anhydrous methanol was added 20.3 g. (0.1 mole) of XVIII. The mixture was heated in a stainless steel bomb at 140° for 8 hr. The resulting mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to give 9.0 g. (60% yield) of white prisms, m.p. 174–176°. $\lambda_{max}^{pH\ 1}$ 231 mμ (ε 7,800), 276 mμ (ε 10,100); $\lambda_{max}^{pH\ 11}$ 230 mμ (ε 5,900), 284 mμ (ε 8,500).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.9; N, 27.1. Found: C, 46.1; H, 6.0; N, 26.8.

4-Amino-2-(1′-aziridinyl)-5-carbethoxypyrimidine (XX).—To a hot solution of 16 g. (0.06 mole) of 4-amino-5-carbethoxy-2-ethylsulfonylpyrimidine[8] in 300 ml. of ethyl acetate was added 100 ml. of acetone. To the solution cooled to 50° was added, with stirring, a solution of 6 g. (0.15 mole) of ethylenimine and 16.2 g. (0.16 mole) of triethylamine in 100 ml. of ethyl acetate at such a rate that the temperature was maintained at 40–50° during the addition. The mixture was then stirred for 1 hr. and the precipitated triethylamine hydrochloride was filtered and washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness under the hood with a stream of air. The residue was recrystallized twice from a mixture of petroleum ether (b.p. 60–80°) and ethanol to yield 6 g. of long white needles, m.p. 112–113°. The yield was 44%. $\lambda_{max}^{methanol}$ 249 mμ (ε 13,500), 296 mμ (ε 10,100).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.9; H, 5.8; N, 26.9. Found: C, 51.8; H, 6.0; N, 26.9.

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