times with 10-ml. portions of water, and the filtrate and washings were combined. Sodium hydroxide (20 g.) was added to the aqueous solution, and it was distilled slowly to yield a volatile amine (probably trimethylamine) and a colorless liquid with b.p. < 70°. The distillate was dried over potassium hydroxide and redistilled to yield 1.3 g. (84%) of a liquid with b.p. 64.5–65°, n_D^{25} 1.3278, which had an infrared spectrum identical with that of methanol.

B. An aqueous solution of 1-(2-hydroxy-3-butenyl)trimethylammonium hydroxide, prepared from 12.85 g. (0.05 mole) of 1-(2-hydroxy-3-butenyl)trimethylammonium iodide and 0.06 mole of freshly prepared silver oxide, was concentrated at 45° and 100 mm. The syrupy residue was heated in an oil bath at 135°. Vigorous frothing occurred, a volatile amine was evolved, and the distillate with b.p. 55–95° was collected. A polymerization reaction was noted to occur in a portion of the distillate that was collected over sodium hydroxide. Examination of the infrared spectrum of another portion of the distillate that had been dried over sodium sulfate indicated that it consisted of methanol and methyl vinyl ketone.

C. A concentrated aqueous soultion of 1-(2-hydroxy-3-butenyl)trimethylammonium hydroxide, prepared from 12.85 g. of 1-(2-hydroxy-3-butenyl)trimethylammonium iodide, was added to a solution prepared from 40 g. of sodium hydroxide and 30 ml. of water. The mixture became warm and a volatile amine was evolved. The mixture was stirred overnight at 40° during which time a small amount of polymeric substance separated. The mixture was then heated at 110°. More volatile amine was evolved, and more polymer formed, but no distillate was collected with b.p. <100°.

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DAVIS, CALIF.

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

The Structure of the Tricyclic Purine Derived from the Purin-6-yl Analog of Nitrogen Mustard[2]

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The structure of the ionic product obtained by several investigators from the attempted synthesis of the purin-6-yl analog I of nitrogen mustard has been clarified by an unambiguous synthesis of 9-ethyl-7,8-dihydro-9*H*-imidazo[2,1-*i*]purine (XI). Spectral and chromatographic comparisons of XI and the tricyclic purine derived from I show that ring closure occurred at N_1 of the starting purine.

Recent reports of attempts to synthesize the purin-6-yl analog of nitrogen mustard, N^6,N^6-bis(2-chloroethyl)adenine (I), express conflicting speculations concerning the structure of the apparently identical ionic products obtained.[3,4] Huber[3] proposed a dimeric structure, 1,4-bis(2-chloroethyl)-1,4-dipurin-6-ylpiperazinium dichloride (II), and attributed the low order of toxicity observed to the formation of such a structure, whereas Lyttle and Petering[4] proposed, without preference, one or the other of the quaternary ammonium structures III and IV involving the interaction of one of the 2-chloroethyl groups with either N_1 or N_7 of the purine ring. Di Paco and Tauro[5] presented their product as the covalent structure I without further elaboration.

The facile formation of 7,8-dihydrothiazolo-[2,3-*i*]purine[6] (V) from 6-(2-chloroethylthio)purine[6,7] suggests that a similar ring closure might also be involved with the nitrogen mustard analog I. The activity shown by 6-(2-chloroethylthio)-purine against Sarcoma 180 and Adenocarcinoma 755 in mice was not retained in the cyclized form V.[8] We repeated the synthesis of the water-soluble ionic product derived from I by methods similar to those described previously,[3-5] and by careful treatment of the salt thus formed with sodium hydroxide solution we isolated an an alytical'y and chromatographically pure free base ($C_9H_{10}ClN_5$) to which could be assigned either structure VI or structure VII. The ultraviolet absorption spectra of the base and of the salt in aqueous solutions at *p*H's 1, 7, and 13 are practically identical. The structures III and IV are examples of the several protonated forms that the salts of the free bases VI and VII might assume, depending on the relative basicities of the nitrogen atoms.

2-[(6-Amino-5-nitro-4-pyrimidinyl)ethylamino]-ethanol (VIII), the product of the reaction of 4-amino - 6 - chloro - 5 - nitropyrimidine[9] and 2-ethylaminoethanol, provided a starting point for

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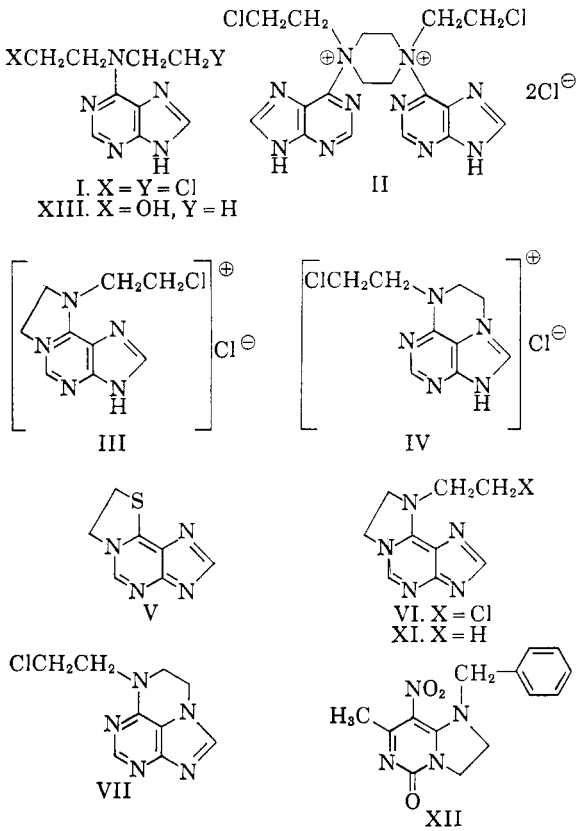
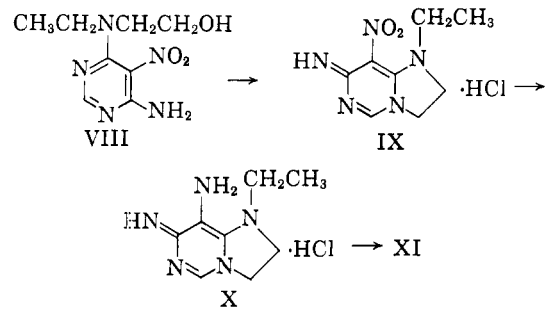


an unambiguous synthesis of the 7,8-dihydro-9*H*-imidazo[2,1-*i*]purine ring system via the sequence VIII→XI. Ambiguity was precluded by the closure of the dihydroimidazole ring to give IX before the nitro group was reduced, the ring closure being evidenced by the marked difference in the ultraviolet absorption spectra of VIII and IX and by the quantitative ionic chlorine content of IX. Although the recent literature furnishes many examples of the formation of 2,3-dihydroimidazo-[1,2-*c*]pyrimidines from 4-(2-chloroethylamino)pyrimidines having either a C-5 amino group or a potentially tautomeric C-2 substituent (an amino, hydroxyl, or mercapto group),[10-13] there appears to be only one previous example involving a 4-[alkyl-(2-chloroethyl)amino]pyrimidine—*viz.*, the formation of 1-benzyl-2,3-dihydro-7-methyl-8-nitroimidazo[1,2-*c*]pyrimidin-5(1*H*)-one (XII) presumably from 4-[benzyl(2-chloroethyl)amino]-6-methyl-5-nitropyrimidin-2(3*H*)-one.[14] The cited instance differs from the conversion VIII→IX in that the starting pyrimidine has a tautomeric group at C-2 rather than at C-6 as in VIII. The Raney nickel-catalyzed hydrogenation of 1-ethyl-1,2,3,7-tetrahydro - 7 - imino - 8 - nitroimidazo[1,2 - *c*]-pyrimidine hydrochloride (IX) proceeded smoothly, and the resulting 8-amino derivative X, characterized only by absorption spectra, underwent the expected ring closure with diethoxymethyl acetate[15] to give 9-ethyl-7,8-dihydro-9*H*-imidazo-[2,1-*i*]purine (XI). This ring closure appears to be the first example of the conversion of a pyrimidine to a purine ring system that has an unnatural fixed arrangement of double bonds.



Compound XI is identical in every respect with the free base derived from the product obtained when 2-[ethyl(purin-6-yl)amino]ethanol (XIII) was treated with thionyl chloride. Furthermore, the ultraviolet and infrared absorption spectra shown by VI and XI are practically identical. As further substantiation, evidence for the removal of the chlorine atom from the side chain of VI by hydrogenolysis catalyzed by palladium-on-charcoal to give the hydrochloride of XI was obtained by paper chromatography, although the reduction was slow and incomplete at room temperature. The unequivocal identity of VI confirms the inability of the purin-6-yl nitrogen mustard to exist in the covalent state and establishes that the tricyclic purine derived therefrom results from ring closure at N_1 rather than N_7.

EXPERIMENTAL[16]

2-[Ethyl(purin-6-yl)amino]ethanol (XIII). 2-Ethylaminoethanol (29 g., 0.32 mole) was added to a stirred suspension of 6-chloropurine[17] (5.00 g., 0.032 mole) in 100 ml. of propyl alcohol. The resulting solution was heated under reflux for 3 hr., then concentrated to about 3/4 volume and refrigerated overnight. The white solid (4.75 g.) that formed was recrystallized from water and dried over phosphorus pentoxide *in vacuo* at 60° for 6 hr.; yield 4.50 g. (67%); m.p. 202°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—280 (16.1), *p*H 7—

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276 (18.4), *p*H 13—281.5 (18.4); R_{Ad}[18]: A^{19} —1.78; B—1.27; C—1.61; D—1.54.

Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.17; H, 6.33; N, 33.81. Found: C, 51.98; H, 6.34; N, 33.40.

2,2'-(Purin-6-ylimino)diethanol. This compound was prepared from 6-chloropurine[17] and 2,2'-iminodiethanol by a procedure essentially the same as that described above for XIII. Recrystallization from water gave an 85% yield of the product as white crystals, which melted at 217–219°[20] (lit.[3] m.p. 216–218°) after being dried *in vacuo* over phosphorus pentoxide at 80° for 4 hr.

2-[(6-Amino-5-nitro-4-pyrimidinyl)ethylamino]ethanol (VIII). A solution of 4-amino-6-chloro-5-nitropyrimidine[9] (500 mg., 2.86 mmoles) in 15 ml. of methyl alcohol containing 2-ethylaminoethanol (510 mg., 5.72 mmoles) was heated under reflux for 2 hr. The resulting solution was concentrated and cooled; the yellow solid that precipitated was recrystallized from water and dried *in vacuo* over phosphorus pentoxide for 6 hr. at 60°; yield of VIII as tiny, bright yellow needles 410 mg. (65%); m.p. 122°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—254 (21.4), 297 (3.12), 360 (5.04); *p*H 7—254 (21.8), 296 (3.05), 360 (5.00); *p*H 13—295 (6.90), 370 (3.85); R_{Ad}[18]: A^{19}—1.65; B—1.27; C—1.57; D—1.89.

Anal. Calcd. for $C_8H_{13}N_5O_3$: C, 42.29; H, 5.77; N, 30.82. Found: C, 42.06; H, 5.91; N, 30.53.

1-Ethyl-1,2,3,7-tetrahydro-7-imino-8-nitroimidazo[1,2-c]-pyrimidine hydrochloride (IX). A solution of 2.6 ml. of thionyl chloride in 3 ml. of chloroform was added dropwise to a stirred suspension of 2-[(6-amino-5-nitro-4-pyrimidinyl)-ethylamino]ethanol (VIII) (500 mg., 2.20 mmoles) in 5 ml. of chloroform. The mixture, stirred at room temperature for 1 hr. was warmed for 1 hr., and finally heated under reflux for about 1.5 hr. The white solid in the cooled reaction mixture was separated by filtration, washed with chloroform, and recrystallized from ethyl alcohol; the yield of the hydrochloride as a light-yellow powder dried *in vacuo* over phosphorus pentoxide at 110° for 6 hr. was 480 mg. (89%); m.p. 248° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—225 (19.2), 256 (12.7), 335 (4.37); *p*H 7—225 (10.5), 331 (16.6); *p*H 13—240 (sh.), 300 (10.4); EtOH—225 (16.8), 257 (14.4), 317 (4.20); R_{Ad}[18]: A^{19}—0.43; B—1.07; C—1.27; D—2.56.

Anal. Calcd. for $C_8H_{11}N_5O_2 \cdot HCl$: C, 39.11; H, 4.93; N, 28.51; Cl (ionic), 14.4. Found: C, 39.23; H, 4.79; N, 28.31; Cl (ionic), 14.0. Neut. equiv.: Calcd.: 245.7. Found: 244.7 (apparent pK_a 6.58 ± 0.10).

9-(2-Chloroethyl)-7,8-dihydro-9H-imidazo[2,1-i]purine (VI). (a) *Hydrochloride.* 2,2'-(Purin-6-ylimino)diethanol (13.0 g., 0.058 mole) was added to 130 ml. of ice-cold thionyl chloride with stirring. The resulting suspension was stirred in the cold for 1 hr., then at room temperature for 1 hr., and finally heated near the boiling point of thionyl chloride for about 1.5 hr. Cooled to room temperature, the reaction mixture was filtered and the collected solid product recrystallized from ethyl alcohol to give small white platelets, which were dried *in vacuo* over phosphorus pentoxide at 100° for 4 hr.; yield 12.9 g. (85%); m.p.[20] 245–247° dec. (lit. m.p. values: 243–247° dec.,[3] 253–255° dec.,[4] 245° dec.[5]); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—214 (19.0), 267 (13.9); *p*H 7—230 (17.8), 278 (12.1); *p*H 13 —131 (20.0), 280 (12.3); MeOH—233 (23.9), 283 (12.0); R_{Ad}[18]: A^{19}—0.57; B—1.06; C—1.25; D—2.04.

Anal. Calcd. for $C_9H_{10}ClN_5 \cdot HCl$: C, 41.55; H, 4.26; N, 26.93. Found: C, 41.76; H, 4.35; N, 27.16. Neut. equiv.: Calcd.: 260.1. Found: 258.0 (apparent pK_a 6.64 ± 0.10).

(b) *Free base.* A solution of 2.00 g. (7.68 mmoles) of the hydrochloride from (a) in 10 ml. of cold water was carefully brought to *p*H 10 by the dropwise addition of 0.1*N* sodium hydroxide solution. The filtered solution was then evaporated to dryness under reduced pressure and the residue extracted with 50 ml. of boiling acetonitrile. The product crystallized from the refrigerated concentrated extract as white platelets, which were recrystallized from acetonitrile and dried *in vacuo* over phosphorus pentoxide at 60° for 4 hr.; yield 1.55 g. (90%); m.p. indefinite[21]; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—215 (18.9), 268 (15.0); *p*H 7—230 (17.7), 278 (11.9); *p*H 13—230 (22.0), 280 (12.5); R_{Ad}[18]: A^{19}—0.59; B—1.05; C—1.25; D—2.02.

Anal. Calcd. for $C_9H_{10}ClN_5$: C, 48.32; H, 4.51; N, 31.31. Found: C, 48.40; H, 4.49; N, 31.12.

9-Ethyl-7,8-dihydro-9H-imidazo[2,1-i]purine (XI). (a) *From 2-[ethyl(purin-6-yl)amino]ethanol* (XIII). The alcohol XIII (4.0 g., 0.019 mole) was added in small portions to 40 ml. of cold, stirred thionyl chloride. Allowed to warm to room temperature, the mixture became a clear solution, which, after 1 hr., was heated under reflux for 3 hr., a white solid being formed. The reaction mixture was cooled, and the solid was collected, washed with carbon tetrachloride, and recrystallized from water; yield of the hydrochloride of XI as white crystals 3.5 g. (80%); m.p. >260°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—268 (14.2); *p*H 7—272 (12.6); *p*H 13—229 (21.7), 277 (12.7); R_{Ad}[18]: A^{19}—0.38; B—0.99; C—1.15; D— 2.10.

Anal. Calcd. for $C_9H_{11}N_5 \cdot HCl$: C, 47.89; H, 5.36; N, 31.03. Found: C, 47.92; H, 5.38; N, 31.19. Neut. equiv.: Calcd.: 225.7. Found: 227.1 (apparent pK_a 7.01 ± 0.10).

The free base XI was obtained by the following procedure: A solution of the above described hydrochloride (3.0 g., 0.013 mole) in 90 ml. of water was made basic (*p*H 10) by the dropwise addition of 0.1 *N* sodium hydroxide. The resulting solution was evaporated to dryness under reduced pressure and the white residue extracted with boiling acetonitrile. When cooled, the concentrated extract deposited the dihydroimidazopurine as tiny hygroscopic white needles, which were dried *in vacuo* over phosphorus pentoxide at 110° for 12 hr.; yield 2.22 g. (90%); m.p. 225°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—268 (14.3); *p*H 7—274 (12.0); *p*H 13—229 (21.0), 278 (12.3); R_{Ad}[18]: A^{19}—0.44; B—1.00; C—1.16; D—2.10.

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.15; H, 5.86; N, 37.02. Found: C, 56.89; H, 5.94; N, 36.93.

(b) *From 1-ethyl-1,2,3,7-tetrahydro-7-imino-8-nitroimidazo-[1,2-c]pyrimidine hydrochloride* (IX). The dihydroimidazopyrimidine hydrochloride IX (500 mg., 2.10 mmoles), dissolved in 25–30 ml. of ethyl alcohol, was hydrogenated over 2.5 g. of Raney nickel[22] at room temperature (23°) and atmospheric pressure, hydrogen consumption (152 ml.) being near the calculated volume for the nitro group (157 ml.) in 35 min. The catalyst was removed by filtration and washed with ethyl alcohol (2 × 10 ml.). The combined filtrate and washings was treated with activated carbon and evaporated to dryness under reduced pressure, leaving a tan crystalline residue; λ_{max} in mμ: *p*H 1—237 (strong), 283 (weak); *p*H 7—236 (strong), 289 (weak); *p*H 13—237 (strong), 297 (weak). The residue was dissolved in 20 ml. of diethoxymethyl acetate[15] with stirring and occasional heating. The resulting solution was stirred at room temperature for 2 hr. and then evaporated to dryness under reduced pressure to give a thick syrup, which formed a tan crystalline residue when subjected to repeated evaporations with ethyl alcohol. A solution of the residue in 15 ml. of water was treated dropwise with 0.1*N* NaOH to *p*H 10. The alkaline solution,

(18) Paper chromatography was done by the descending technique on Whatman No. 1 paper; spots were viewed in ultraviolet light. R_{Ad} values were determined by locating spots relative to adenine arbitrarily assigned R_f of 1.00.

(19) Solvent systems: A, water-saturated butyl alcohol; B, 5:2:3 (by volume) butyl alcohol–acetic acid–water; C, 14:1:5 (by volume) isopropyl alcohol–concentrated ammonium hydroxide-water; D, acetate buffer (0.1*N* potassium acetate brought to *p*H 6.1 with 0.1*N* acetic acid).

(20) Determined in a capillary, and is uncorrected.

(21) This material melts, resolidifies, and melts again, both melting points being dependent on rate of heating.

(22) Raney Catalyst Co., Chattanooga 2, Tenn.

after treatment with charcoal, was evaporated to dryness *in vacuo*, and the white crystalline residue extracted with hot acetonitrile (25 ml.). The cooled extract deposited tiny white needles, which were recrystallized from acetonitrile and dried *in vacuo* over phosphorus pentoxide at 110° for 12 hr.; yield of 9-ethyl-7,8-dihydro-9*H*-imidazo[2,1-*i*]-purine (XI) 158 mg. (41%); m.p. 225°; mixed m.p. with XI from (a) undepressed; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—268 (13.9); *p*H 7—274 (11.8); *p*H 13—230 (20.2), 278 (12.0); R_{Ad}[18]: A[19]—0.53; B—0.99; C—1.12; D—2.08.

Hydrogenolysis of 9-(2-chloroethyl)-7,8-dihydro-9H-imidazo-[2,1-i]purine (VI). A solution of 1.0 g. of 9-(2-chloroethyl)-7,8-dihydro-9*H*-imidazo[2,1-*i*]purine (VI) in 35 ml. of ethyl alcohol was shaken under a hydrogen atmosphere (50 p.s.i.) in the presence of 200 mg. of 5% palladium-on-charcoal at room temperature for 72 hr. The filtered reaction mixture, when evaporated to dryness under diminished pressure, left a white solid residue, which moved as two spots on paper chromatograms developed by water-saturated butyl alcohol; R_{Ad}[18]: A[19]—0.41, 0.61. The slower moving component moved as the hydrochloride of the expected product XI; and the faster-moving component, as the starting free base VI. At room temperature the hydrogenolysis of the chlorine atom was slow and incomplete after 3 days; when the reaction temperature was increased to 50°, some undesired ring reduction presumably occurred as evidenced by additional spots on the paper chromatograms.

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BIRMINGHAM 5, ALA.

[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Pyrimidines. VI. *N*-Methyl-*as*-triazine Analogs of the Natural Pyrimidines[1]

KWANG YUEN ZEE-CHENG AND C. C. CHENG

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N-Methyl substituted *as*-triazine analogs of the naturally occurring pyrimidines, uracil, thymine, and cytosine, have been prepared by unambiguous synthesis. Their physical and chemical properties have been studied.

It has recently been reported that 6-azauracil (3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine) inhibits the growth of a number of microorganisms and certain experimental tumors.[2] However, this compound is highly toxic and less effective in the treatment of human cancer than its riboside, 6-azuaridine.[3,4] It was also found that 6-azathymidine is a more potent thymine antagonist than 6-azathymine (3,5-dioxo-6-methyl-2,3,4,5-tetrahydro-*as*-triazine) in DNA bisynthesis.[5] In certain clinical trials 5-fluoro-2′-deoxyuridine, 5-FUDR, has been reported to be superior to 5-fluorouracil.[6] These findings suggest that *as*-triazine analogs of the naturally occurring pyrimidines bearing substituents on the nitrogen which would normally bear the pentose moiety (in the *as*-triazine system, N-2) might possess interesting biological activity.

A methyl group was selected as the substituent group for this study since it is relatively easy to introduce. Simple *N*-alkyl substitution in other heterocyclic systems has resulted in favorable therapeutic indices when compared with the corresponding *N*-unsubstituted or *N*-aryl substituted compounds in certain test systems.[7] For the purpose of comparison, several 4-methyl- and 2,4-dimethyl-*as*-triazines have also been prepared.

The methylation of *as*-triazines to produce the

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(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.

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