(ϵ 16,500). By mixed fusion of VI and its picrate with nordehydro-α-matrinidine and its picrate, no melting point depression was observed, and there was good agreement between their infrared spectra.

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A New Synthesis of Purines

Sir:

Classical chemical purine syntheses, which involve the cyclization by pyrolysis of 4-amino-5-formamidopyrimidines[1] or modifications such as cyclization of 4,5-diaminopyrimidine sulfate salts by means of boiling formic acid or formamide,[2] have been shown to fail when applied to the conversion of chloropyrimidines to chloropurines.[2b,3,4] Rather, all chloropyrines described in the literature have been synthesized by chlorination of purinones,[3,5] a procedure which is often unsatisfactory.

Since chloropurines are important intermediates for the synthesis of natural and unnatural purine nucleosides[6] a new synthesis of purines was sought.

We have found that when 4,5-diaminopyrimidines are refluxed with mixtures of alkyl orthoformates and carboxylic acid anhydrides,[7,8,9] mixtures of purines and N-acylpurines are formed. Methyl, ethyl, and propyl orthoformates and acetic, propionic, and butyric anhydrides have been used successfully; evaporation of the excess reagents leaves a residual mixture of purine and N-acylpurine, the acyl group deriving from the anhydride. The acylpurine is hydrolyzed to the corresponding purine by action of dilute aqueous base (without heating and for limited time with chloropurines).

In this way 4,5-diaminopyrimidines bearing at the 2- and 6-positions amino, chloro, dimethylamino, hydrogen, hydroxyl, methyl, and methylthio substituents give the corresponding purines in good yield. This appears to be a general synthetic route to purines. It also allows for the ready isotopic labeling of purines by using esters of carbon-labeled orthoformate.

4,5-Diamino-6-dimethylamino-2-(methylthio)pyrimidine[10] (I), 0.500 g., 5 ml. of ethyl orthoformate, and 5 ml. of acetic anhydride, refluxed 2¼ hrs., the solution evaporated *in vacuo*, the residual 6-dimethylamino-2-(methylthio)purine[10] (II) and N-acetyl-6-dimethylamino-2-(methylthio)-purine heated 5 min., steam-bath, with 10 ml. of 1 *N* sodium hydroxide, and brought to *p*H 3.8 with acetic acid, yielded 0.428 g. (82%) of II, m.p. 278.5–281° (dec.), m.p. 285–286.5° (dec.) from sodium hydroxide followed by acetic acid. Calc'd for $C_8H_{11}N_5S$: C, 45.9; H, 5.30; N, 35.5; S, 15.3. (Found: C, 46.2; H, 5.55; N, 33.7; S, 15.4).

Similarly, I was cyclized to II by refluxing ethyl orthoformate-propionic anhydride (76% yield), ethyl orthoformate-butyric anhydride (23% yield), methyl orthoformate-acetic anhydride (80% yield), and propyl orthoformate-acetic anhydride (96% yield).

2,4,5-Triamino-6-pyrimidinol,[11] condensed with ethyl orthoformate and acetic anhydride, gave after hydrolysis 64% of guanine hemisulfate hydrate;[12] $\lambda_{max.}^{0.1\ N\ HCl}$ 248 mμ (ϵ 12,400); $\lambda_{max.}^{0.1\ N\ NaOH}$ 273 mμ (ϵ 9,760).

(1) cf. (a) Gabriel and Colman, *Ber.*, **34**, 1234 (1901). (b) Traube, *Ber.*, **37**, 4544 (1904). (c) Isay, *Ber.*, **39**, 250 (1906).

(2) (a) Bendich, Tinker, and Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948). (b) Robins, Dille, Willits, and Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

(3) Bendich, Russell, and Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(4) Robins, Dille, and Christensen, *J. Org. Chem.*, **19**, 930 (1954).

(5) *Cf.* (a) Fisher, *Ber.*, **28**, 2480 (1895). (b) Fisher and Ach, *Ber.*, **30**, 2208 (1897). (c) Adams and Whitmore, *J. Am. Chem. Soc.*, **67**, 1271 (1945). (d) Davoll and Lowy, *J. Am. Chem. Soc.*, **73**, 2936 (1951). (e) Robins and Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).

(6) *Cf.* (a) Fisher and Helferich, *Ber.*, **47**, 210 (1914). (b) Davoll, Lythgoe, and Todd, *J. Chem. Soc.*, 967, 1685 (1948). (c) Davoll and Lowy, *J. Am. Chem. Soc.*, **74**, 1563 (1952). (d) Brown and Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(7) Albert, Brown, and Cheeseman, *J. Chem. Soc.*, 474 (1951), converted 2-aminopyrazine-3-carboxamide to 4-hydroxypteridine by refluxing ethyl orthoformate and acetic anhydride.

(8) After completion of this investigation Richter and Taylor, *Angew. Chem.*, **67**, 303 (1955), described the cyclization of aminomalonamidamidine dihydrochloride by ethyl orthoformate and acetic anhydride to produce hypoxanthine.

(9) Montgomery, *J. Am. Chem. Soc.*, in press, has independently found that chloro-4,5-diaminopyrimidines are cyclized to chloropurines by ethyl orthoformateacetic anhydride (private communication).

(10) Baker, Joseph, and Schaub, *J. Org. Chem.*, **19**, 631 (1954).

(11) Traube, *Ber.*, **33**, 1371 (1900).

(12) Cavalieri, Bendich, Tinker, and Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948).

4-Chloro-5,6-diaminopyrimidine[2b] gave, after hydrolysis, 72% of 6-chloropurine,[3] m.p. 178–180° (dec.). Calc'd for $C_5H_3ClN_4$: C, 38.8; H, 1.96; Cl, 22.9. (Found: C, 39.0; H, 2.25; Cl, 22.7; N, 36.6.)

4,5-Diamino-2,6-dichloropyrimidine[13] (III) gave, after hydrolysis, 89% of crude 2,6-dichlorpurine (IV), m.p. 166–174°; colorless crystals, m.p. 180–181.5°, from water. Calc'd for $C_5H_2Cl_2N_4$: C, 31.8; H, 1.07; Cl, 37.5; N, 29.6. (Found: C, 31.8; H, 1.46; Cl, 37.4; N, 29.2); $\lambda_{max.}^{0.1\ N\ HCl}$ 250 mμ (inflection, ε 3,780), 274 mμ (ε 8,600); $\lambda_{max.}^{EtOH}$ 252 mμ (inflection, ε 3,400), 274 mμ (ε 8,100); $\lambda_{max.}^{0.1\ N\ NaOH}$ 281 mμ (ε 8,290). The condensation product from III, extracted with boiling heptane and chloroform, left 20% of IV, m.p. 173–175°. The heptane solution yielded 10% of crude N-acetyl-2,6-dichloropurine, m.p. 152–155°. Calc'd for $C_7H_4Cl_2N_4O$· C, 36.4; H, 1.74, Cl, 30.7; N, 24.2. (Found: C, 36.6; H 2.13; Cl, 30.5; N, 25.4; $\lambda_{max.}^{0.1\ N\ HCl}$ 257 mμ (inflection, ε 6,150); 273 mμ (ε 8,120); $\lambda_{max.}^{EtOH}$ 255–262 mμ (plateau, ε 6,940), 272 mμ (ε 7,590); $\lambda_{max.}^{0.1\ N\ NaOH}$ 281 mμ (ε 8,550).

4-Chloro-5,6-diamino-2-methylpyrimidine, 0.500 g., gave 0.656 g. of a mixture of 6-chloro-2-methylpurine[14] (V) and N-acetyl-6-chloro-2-methylpurine, hydrolyzed to yield 0.470 g. (88%) of V as colorless crystals, m.p. 206–207° (dec.), m.p. unchanged from water. Calc'd for $C_6H_5ClN_4$: C, 42.7; H, 2.99, Cl, 21.0; N, 33.2. (Found: C, 43.2; H, 3.13; Cl, 21.0; N, 33.4).

4,5-Diamino-6-dimethylaminopyrimidine,[15] 0.500 g., gave 0.729 g. of a mixture of 6-dimethylaminopurine[10] (VI) and N-acetyl-6-dimethylaminopurine (VII), recrystallized from ethanol to give 0.134 g. (20%) of VII, m.p. 129–130°; ethanol filtrate gave, after hydrolysis, 0.353 g. (66%) of VI, m.p. 256.5–257° from chloroform and ethyl acetate-hexane. Calc'd for $C_7H_9N_5$: C, 51.5; H, 5.56; N, 42.9. (Found: C, 51.7; H, 5.99; N, 42.8.)

2-Methyl-4,5-diamino-6-dimethylaminopyrimidine gave, after hydrolysis, 6-dimethylamino-2-methylpyrine, m.p. 285–287° from ethanol. Calc'd for $C_8H_{11}N_5$: C, 54.2; H, 6.26; N, 39.5. (Found: C, 54.5; H, 6.44; N, 39.8); $\lambda_{max.}^{0.1\ N\ HCl}$ 282.5 mμ (ε 17,100); $\lambda_{max.}^{EtOH}$ 275 mμ (ε 19,600); $\lambda_{max.}^{0.1\ N\ NaOH}$ 282.5 mμ (ε 17,100).

4,5-Diamino-2-(methylthio)-6-pyrimidinol[16] gave, after hydrolysis, 64% of 2-(methylthio)-6-purinol,[17] m.p. 278°, m.p. 289–291° from water ($^1/_4$ H_2O; Calc'd for $C_6H_6N_4OS \cdot {}^1/_4H_2O$: C, 38.6; H, 3.51; N, 30.0; S, 17.2. Found: C, 38.8; H, 3.82; N, 28.4; S, 16.8); $\lambda_{max.}^{0.1\ N\ HCl}$ 263 mμ (ε 14,500); $\lambda_{max.}^{EtOH}$ 259 mμ (ε 11,700); $\lambda_{max.}^{0.1\ N\ NaOH}$ 274 mμ (ε 11,200).

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(13) Bitterli and Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951).

(14) Hitchings and Elion, U. S. Patent 2,697,709 (Dec. 21, 1954), not characterized.

(15) Elion, Burgi, and Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(16) Johnson, Johns, and Heyl, *Am. Chem. J.*, **36**, 160 (1906).

(17) Mentioned by Elion, Hitchings, and VanderWerff, *J. Biol. Chem.*, **192**, 505 (1951), but neither synthesis nor characterization given.