acetone-Skellysolve B, m.p. 217–220° after recrystallization from acetone (lit.[2] m.p. 221–222°). The infrared absorption spectrum (Nujol mull) was identical with that of an authentic sample,[3] as was the mobility (R_f 0.41) on silica gel developed as above.

Tomentosic Bromo Lactone.—A 77-mg. sample of the *Bixa* acid was brominated in acetic acid containing sodium acetate essentially as in ref. 3. The crude product, 88 mg., was chromatographed on Florisil and the major peak, eluted with 15% acetone in methylene chloride, was recrystallized twice from methanol, m.p. 233–235°, $[\alpha]_D$ +49° ($CHCl_3$). These data, as well as the infrared absorption spectra and behavior on silica gel thin layer plates, are substantially identical with those of an authentic sample of tomentosic bromo lactone.[3]

Anal. Calcd. for $C_{30}H_{47}BrO_5$: C, 64.14; H, 8.73. Found: C, 63.48; H, 8.35.

Tomentosic Acid Triacetate.—A 50-mg. sample of the *Bixa* acid was treated overnight at 25° with 1 ml. each of acetic anhydride and pyridine. Slow dilution with water gave an amorphous solid which was filtered, washed with water, and dried to yield 57 mg., m.p. about 150°. It could not be satisfactorily recrystallized. The n.m.r. spectrum in deuteriochloroform solution is summarized in the discussion section. Optical rotatory dispersion data indicated a positive plain curve: $[\alpha]_{589}$ +100°, $[\alpha]_{350}$ +175°, $[\alpha]_{310}$ +1565°.

Anal. Calcd. for $C_{36}H_{54}O_9$: C, 68.54; H, 8.63. Found: C, 69.00; H, 8.83.

Acknowledgment.—The authors are indebted to Mr. Harold Hartgerink for samples of *B. orellana*, to Mr. L. Bayard Spaulding for performing alcohol and ether extractions of the ground root, and to Dr. J. L. Johnson, Dr. W. A. Struck, and associates for analyses and ultraviolet and infrared spectra.

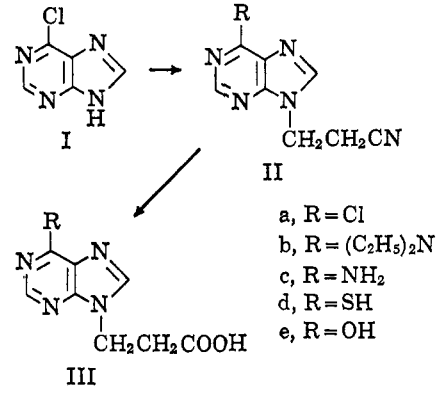
A Michael Addition with 6-Chloropurine[1]

B. R. BAKER AND PRAFULLCHANDRA M. TANNA

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, New York 14214

Received March 2, 1965

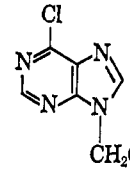
Since 6-chloropurine (I) is readily alkylated primarily at the 9-position,[1a,2,3] it is a versatile precursor for the synthesis of 6-substituted purines bearing a 9-alkyl group; this class of compounds has been of interest for a variety of biological studies.[3] Furthermore, 6-chloropurine will add to dihydropyran with acid catalysis in the usual orientation of addition to this enol ether.[4] For some biological studies related to those previously described,[3a,b] some 6-substituted 9H-purin-9-ylpropionic acids (III) were needed. If 6-chloropurine (I) could be added to acrylonitrile by base-catalyzed Michael addition, the product IIa would be a suitable precursor for the desired purin-9-ylpropionic acids (III).



Initial study on the addition of 6-chloropurine (I) to acrylonitrile in N,N-dimethylformamide catalyzed by potassium carbonate failed to give the desired adduct IIa; it was noted that an insoluble potassium salt formed which was apparently too insoluble to react. In contrast, the potassium salt was relatively soluble in dimethyl sulfoxide and initial conditions for addition gave a 14% yield of 6-chloro-9H-purin-9-ylpropionitrile (IIa, Table I, run 1); a study of the reaction variables finally led to optimum conditions which gave a 73% yield of IIa when a catalytic amount (6 mole %) of potassium carbonate was employed.

TABLE I

REACTION CONDITIONS *vs.* YIELDS FOR PREPARATION OF IIA[a]



Run	Molar ratio of I–acrylonitrile–K_2CO_3	Reaction time, hr.	% yield
1	1:1:0.06	40	14
2	1:2:0.06	72	59
3	1:5:0.12	1.5	18[b]
4	1:5:0.12	20	48
5	1:5:0.06	48	63
6	1:5:0.06	74	73
7	1:10:0.06	70	78[c]

[a] All runs were made with 3.3 mmoles of 6-chloropurine (I) in 5 ml. of dimethyl sulfoxide at room temperature, then processed as described for IIa. The yields are recorded for once-recrystallized product melting no more than 10° below the analytical sample, unless otherwise indicated. [b] This product contained some unchanged 6-chloropurine. [c] This product was impure and appeared to contain some polymeric material.

That IIa was a 9-substituted and not a 7-substituted purine was shown by reaction with diethylamine in boiling methanol[3a]; the resultant 6-diethylaminopurine (IIb) showed ultraviolet peaks in agreement with a 9-substituted purine,[5] but not a 7-substituted purine.

By reaction with thiourea in boiling ethanol,[2,3] the 6-chloropurine (IIa) was converted to the corresponding 6-purinethiol (IId) in 76% yield. A 1-hr. reaction of

(1) (a) Paper XXI of the series on Nonclassical Antimetabolites; for paper XX, see B. R. Baker, P. M. Tanna, and G. D. F. Jackson, *J. Pharm. Sci.*, in press. (b) This work was generously supported by Grant No. CA-05867 from the National Cancer Institute, U. S. Public Health Service.

(2) (a) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961); (b) H. J. Schaeffer and R. D. Weimar, Jr., *ibid.*, **81**, 197 (1959); (c) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953); (d) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957); (e) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *ibid.*, **22**, 954 (1957).

(3) (a) B. R. Baker and H. S. Sachdev, *J. Pharm. Sci.*, **52**, 933 (1963), paper XIII of this series; (b) B. R. Baker and P. M. Tanna, *ibid.*, in press, paper XIX of this series; (c) H. J. Schaeffer and R. Vince, *J. Med. Chem.*, **8**, 33 (1965); (d) H. J. Schaeffer and P. S. Bhargava, *Biochemistry*, **4**, 71 (1965); H. J. Schaeffer, S. Marathe, and V. Alks, *J. Pharm. Sci.*, **53**, 1368 (1964).

(4) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. L. Lewis, and A. Jackson, *J. Am. Chem. Soc.*, **83**, 2574 (1961).

(5) (a) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954); (b) L. B. Townsend, R. K. Robins, R. N. Leoppky, and N. J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964).

IIa with alcoholic ammonia at 110° under pressure[2,3] gave the corresponding adenine derivative (IIc) in 82% yield. Direct hydrolysis of the 6-chloropurine (IIa) with 12 *N* hydrochloric acid afforded 9H-hypoxanthin-9-ylpropionic acid (IIIe) in 43% yield; a similar acid hydrolysis of IIc gave the adeninepropionic acid (IIIc), isolated as a crystalline, quite water-soluble zwitterion. The less soluble 6-mercaptopurine-9-propionic acid (IIId) was isolated at 66% yield.

Experimental[6]

6-Chloro-9H-purin-9-ylpropionitrile (IIa).—To a magnetically stirred mixture of 10.3 g. (66 mmoles) of 6-chloropurine (I) (Burroughs Wellcome and Co.) and 100 ml. of dimethyl sulfoxide was added 22.2 ml. (330 mmoles) of acrylonitrile followed by 0.55 g. (4 mmoles) of anhydrous potassium carbonate. The mixture was stirred until solution was complete, then it was allowed to stand for 70 hr. protected from moisture. Diluted with 250 ml. of water, the mixture was extracted with five 100-ml. of chloroform. The combined extracts were washed with 100 ml. of water, dried with anhydrous magnesium sulfate, then spin evaporated *in vacuo;* the last of the dimethyl sulfoxide was removed at 1 mm. (bath 90°). Recrystallization from ethyl acetate gave 6.66 g. (48%) of light yellow crystals, m.p. 144–145°; a second crop of 1.83 g. (total 61%), m.p. 136–139°, was obtained that was suitable for further transformations. A second recrystallization of a pilot run gave light yellow crystals: m.p. 145–146°; ν_{max} 2250 (C≡N), 1915, 1765 (weak purine fine structure), 1590, 1560, 1500 cm.$^{-1}$ (C=C, C=N); λ_{max} 266 mμ.

Anal. Calcd. for $C_8H_6ClN_5$: C, 46.3; H, 2.91; Cl, 17.1. Found: C, 46.5; H, 3.05; Cl, 16.9.

Other conditions are listed in Table I.

6-Diethylamino-9H-purin-9-ylpropionitrile (IIb) Hydrochloride.—A solution of 104 mg. (0.5 mmole) of IIa and 110 mg. (1.5 mmoles) of diethylamine in 5 ml. of methanol was refluxed for 2 hr., then spin evaporated *in vacuo*. To a solution of the sirupy residue in 10 ml. of water was added 500 mg. of anhydrous potassium carbonate. The mixture was extracted with three 10-ml. portions of chloroform, then the combined extracts were washed with water, dried with magnesium sulfate, and spin evaporated *in vacuo*. The residue was dissolved in reagent ether and treated with hydrogen chloride. A gummy hydrochloride separated that solidified on standing overnight. Recrystallization from acetone–ethyl acetate gave 75 mg. (40%) of product, m.p. 168–170°. Recrystallization from the same solvent pair afforded the analytical sample as colorless needles: m.p. 173–176°; ν_{max} 3360 (NH+), 2700–2300 (broad acidic H), 2250 (C≡N), 2130, 1940 (weak purine fine structure), 1625, 1560 and 1540 cm.$^{-1}$ (C=C, C=N); λ_{max} (pH 1) 270 mμ (ε 17,500), (MeOH) 276 (18,000), (pH 13) 276 (18,200).[5] Since the compound lost hydrogen chloride on being dried at 100° under high vacuum, it was dried at room temperature under high vacuum for analysis.

Anal. Calcd. for $C_{12}H_{16}N_6 \cdot HCl$: C, 51.3; H, 6.10; N, 29.9. Found: C, 51.0; H, 6.20; N, 29.7.

6-Mercapto-9H-purin-9-ylpropionitrile (IId).—A solution of 207 mg. (1 mmole) of IIa and 76 mg. (1 mmole) of thiourea in 15 ml. of absolute ethanol was refluxed with magnetic stirring for 3 hr. during which time the product separated. The cooled mixture was filtered; the product was washed with water to yield 158 mg. (76%), m.p. 283–286° dec. Recrystallization from absolute ethanol gave buff-colored needles: m.p. 284–286° dec.; ν_{max} 2600–2300 (broad acidic H), 2250 (C≡N), 2000, 1850 (weak purine fine structure), 1590, 1560 (shoulder), 1540 cm.$^{-1}$ (C=C, C=N); λ_{max} 325 mμ.

Anal. Calcd. for $C_8H_7N_5S$: C, 46.8; H, 3.44; S, 15.6. Found: C, 46.8; H 3.30; S, 15.6.

9H-Adenin-9-ylpropionitrile (IIc).—To 2.08 g. (10 mmoles) of IIa in a steel bomb was added 44 ml. of ethanol saturated with ammonia at 0°. After being heated for 1 hr. in an oil bath at 110°, the bomb was cooled, and the mixture was spin evaporated *in vacuo*. Trituration of the residue with water gave 1.32 g. (71%) of white crystals, m.p. 243–247°. Recrystallization of a pilot run afforded the analytical sample: m.p. 247–250°; ν_{max} 3500, 3300, 3100 (NH), 2240 (C≡N), 1940, 1720 (weak purine fine structure), 1640, 1580, 1570, 1500 cm.$^{-1}$ (NH, C=C, C=N); λ_{max} 262 mμ.

Anal. Calcd. for $C_8H_8N_6$: C, 51.1; H, 4.28; N, 44.7. Found: C, 51.0; H, 4.39; N, 44.9.

9H-Hypoxanthin-9-ylpropionic Acid (IIIe).—A solution of 386 mg. (1.86 mmoles) of IIa in 12 ml. of 12 *N* hydrochloric acid was refluxed for 3 hr., then spin evaporated *in vacuo*. Trituration of the residue with 2 ml. of water gave 167 mg. (43%) of product, m.p. 275–280° dec.; no attempt was made to recover additional material from the filtrate. Recrystallization from water gave white crystals: m.p. 284–287° dec.; ν_{max} 2800–2300 (broad acidic H), 1720 (carboxyl C=O), 1660, 1580, 1550, 1510 (C=O, C=C, C=N), no C=N near 2250 cm.$^{-1}$; λ_{max} 251 mμ.

Anal. Calcd. for $C_8H_8N_4O_3$: C, 46.1; H, 3.87; N, 26.9. Found: C, 45.9; H, 3.73; N, 26.7.

6-Mercapto-9H-purin-9-ylpropionic Acid (IIId).—Hydrolysis of 390 mg. (1.9 mmoles) of IId as described for the preparation of IIIe gave 282 mg. (66%) of product, m.p. 261–262°. Recrystallization from water afforded opaque flakes: m.p. 262–264°; ν_{max} 2600–2200 (acidic H), 2000, 1925, 1875 (weak purine fine structure) 1710, (carboxyl C=O), 1640, 1600, 1575 (C=C, C=N), no C≡N near 2250 cm.$^{-1}$; λ_{max} 326 mμ.

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.8; H, 3.59; N, 25.0. Found: C, 42.7; H, 3.59; N, 252.

9H-Adenin-9-ylpropionic Acid (IIIc).—A solution of 217 mg. (1.15 mmoles) of IIc in 8 ml. of 12 *N* hyrochloric acid was refluxed for 8 hr., then spin evaporated *in vacuo*. Recrystallization from 2.5 ml. of water gave 94 mg. (34%) of IIIc hydrochloride: m.p. 225–227° dec.; ν_{max} 3400, 3250, 3080 (NH), 2800–2400 (broad acidic H), 1720 (carboxyl C=O), 1690 (C=NH$^+$), 1630, 1600, 1550, 1520 cm.$^{-1}$ (NH, C=C, C=N); no attempt was made to recover additional material from the filtrate. Recrystallization from 50% aqueous ethanol gave 24 mg. of the zwitterion of IIIc as white crystals: m.p. 279–280° dec.; ν_{max} 3200–2600 (broad NH and acidic H), 2200–1800 (broad NH$^+$), 1690 (C=NH$^+$), 1670, 1570 (NH, C=C, C=N), no carboxyl C=O near 1720 cm.$^{-1}$; the shape of the curve and the band intensitities are quite different from those of the hydrochloride. The compound had λ_{max} 262 mμ.

Anal. Calcd. for $C_8H_9N_5O_2$: C, 46.4; H, 4.38; N, 33.8. Found: C, 46.2; H, 4.59; N, 33.6.

(6) Melting points were determined in capillary tubes on a Mel-Temp block and those below 230° are corrected. Infrared spectra were run in KBr pellet with a Perkin-Elmer 137B spectrophotometer. Ultraviolet spectra were run with a Perkin-Elmer 202 spectrophotometer in ethanol, unless otherwise indicated.

Reaction of 2,3-Diphenylquinoxaline with Amide Ion. An Unusual Ring Contraction[1]

EDWARD C. TAYLOR AND ALEXANDER MCKILLOP

Department of Chemistry, Princeton University, Princeton, New Jersey

Received April 8, 1965

In 1931, Ogg and Bergstrom described a series of investigations designed to demonstrate possible analogies between heterocyclic systems and their acyclic and alicyclic counterparts.[2] Quinoxaline, for example, was described as an "ammono glyoxal," and 2,3-diphenylquinoxaline (**1**) was considered to be the heterocyclic equivalent of benzil. In an attempt to justify this hypothesis, the authors treated 2,3-diphenylquinoxaline (**1**) with potassium amide in liquid ammonia, anticipating a reaction similar to the benzil → benzilic acid rearrangement, which would lead to the formation of 2,2-diphenyl-3-amino-1,2-dihydroquinoxaline (**2**). The conditions chosen for

(1) This work was supported by a research grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) R. A. Ogg, Jr., and F. W. Bergstrom, *J. Am. Chem. Soc.*, **53**, 1846 (1931).