Reaction of 2-Aminobenzimidazole with Bifunctional Carboxylic Acid Derivatives. Formation of Pyrimido[1,2-a]benzimidazolones (I).

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2-Aminobenzimidazole reacts with α,β-unsaturated carboxylic acid chlorides or esters to give only pyrimido[1,2-a]benzimidazol-2-(1H)ones. β-Ethoxymethylenemalonic acid derivatives or β-ketocarboxylic acid derivatives give only pyrimido[1,2-a]benzimidazol-4-(1H)ones. Structural assignments based on nmr and chemical manipulations are discussed.

In the course of studying the biological data of 2-acylaminobenzimidazoles, attempts were made to synthesize several α,β-unsaturated derivatives. However, the expected products were not obtained. Rather, 2-aminobenzimidazole condensed with α,β-unsaturated carboxylic acid chlorides and esters to give the ring closed pyrimido-[1,2-a]benzimidazolones.

2-Aminobenzimidazole is reported to condense with diethyl ethoxymethylenemalonate (II) to give only ethyl 1,2-dihydro-2-oxopyrimido[1,2-a]benzimidazole-3-carboxylate (III) (2); and with ethyl ethoxymethylenecyanoacetate (V) to give only ethyl 2-aminopyrimido[1,2-a]-benzimidazole-3-carboxylate (VI) (2).
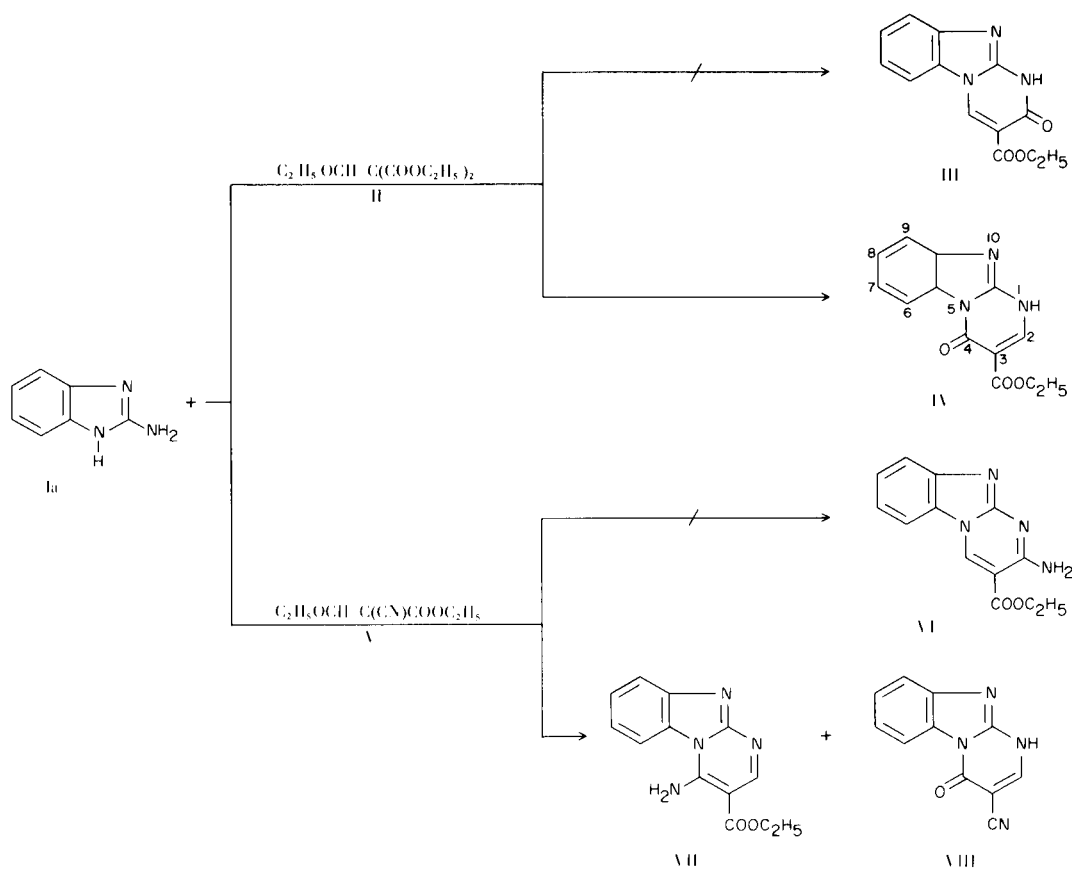
When these reactions were repeated by us, the reaction product between Ia and II was found to be the isomeric ethyl 1,4-dihydro-4-oxopyrimido[1,2-a]benzimidazole-3-carboxylate (IV); the reaction product between Ia and V was found to be a mixture of ethyl 4-aminopyrimido-[1,2-a]benzimidazole-3-carboxylate (VII), and 1,4-dihydro-4-oxopyrimido[1,2-a]benzimidazole-3-carbonitrile (VIII).

The assignment of the 4-oxo rather than the 2-oxo structure for compound IV was based on the observation that the nmr spectrum of the condensation product showed a three proton multiplet at δ 7.88 (H_{7-9}) and a a one proton multiplet at δ 8.72 (H_6). This downfield shift of 0.84 ppm for the H_6 proton from the main aromatic signal may be explained on the basis that the 4-oxo function is held in a rigid position, coplanar with and orientated toward the aromatic ring, thus exerting a deshielding effect on the H_6 proton. This consistent effect has been recognized in the literature (3,4). The assignment of the 4-oxo rather than the 2-oxo structure to compound VIII was also based on nmr interpretation, which showed a three proton multiplet centered at δ 7.92 (H_{7-9}) and a one proton multiplet centered at δ 8.72, a downfield shift of 0.80 ppm.

The nmr was less useful as a basis for structural assignment of the 4-amino compound VII which showed a three proton multiplet at δ 8.00 (H_{7-9}) and a one proton multiplet at δ 8.48 (H_6), clearly separated from the main aromatic envelope. Although it would be reasonable to expect the 2-amino structure VI to exhibit an nmr spectrum with all the aromatic protons appearing as an unresolvable multiplet, it is difficult to be certain whether this small (0.48 ppm) downfield shift observed with VII is compatible with the expected structure, mainly because similar systems are not as readily available in the literature. The tentative assignment of VII from the nmr data was confirmed by conversion of VII and IV to a common derivative IX. The nmr spectrum of IX showed a three proton multiplet at δ 7.39 (H_{7-9}) and a one proton multiplet at δ 8.36 (H_6), a downfield shift of 0.97 ppm. Thus VII is established as the structure for the reaction product between Ia and V.

The condensation of 2-aminobenzimidazole and β-ketocarboxylic acid derivatives to yield pyrimido[1,2-a]-benzimidazolones has also been reported in the literature. For example, 2-aminobenzimidazole has been reported to react with ethyl acetoacetate (5) and with ethyl 2-keto-cyclopentanecarboxylate to give 4-oxo compounds (6). These two reactions have been repeated by us. In both cases, the nmr spectra showed the H_6 proton signals to be 0.82-0.93 ppm downfield from the main aromatic protons, thus confirming the literature structures.

In contrast, our study showed that 2-aminobenzimidazole reacts with α,β-unsaturated carboxylic acid chlorides and esters (Xa,b,c and XII) to give only the 2-oxo products (XIa,b,c and XIII).

Nmr spectra of compounds XIa,b,c and XIII showed unresolvable signals in δ 7.6-7.9 region for four aromatic protons. No downfield shift of H_6, characteristic of 4-oxo structures, was observed. The reaction between 2-methylaminobenzimidazole (Ib) and ethyl propiolate (XII) gave XIV whose nmr spectrum, in comparison with those of XIa,b,c and XIII, showed a complex aromatic signal at δ 7.1-7.8 making the assignment of a 2-oxo structure uncertain. However, this 2-oxo structure for XIV was confirmed by methylation of XIII to XIV.

In contrast, the condensation between 2-methylamino-benzimidazole (Ib) and ethyl acetoacetate gave the expected 4-oxo structure XV. The nmr spectrum of XV showed a downfield shift of 0.87 ppm for H_6.

The formation of compounds IV, VII, and VIII between 2-aminobenzimidazole and ethoxymethylenemal-onic acid derivatives may involve an initial 1,4-addition and elimination of an ethoxide, the resulting crotonate (7a) may then cyclize to give pyrimido[1,2-a]benzimid-azoles (7b).

The formation of XIa,b,c, XIII, and XIV may involve an initial nucleophylic attack of the ring nitrogen on the acid chloride followed by a rearrangement to the more stable 2-acylamino derivative (8). This is then followed by a Michael-type condensation of the ring nitrogen anion with the electron deficient β-carbon of the α,β-unsaturated double bond (9).
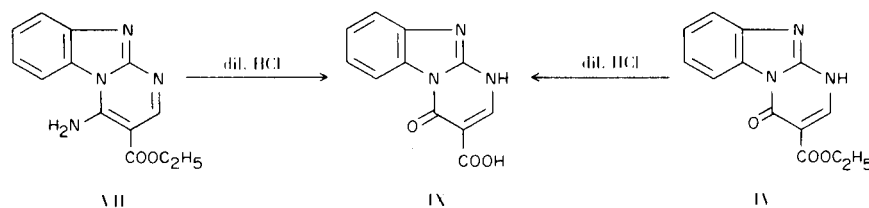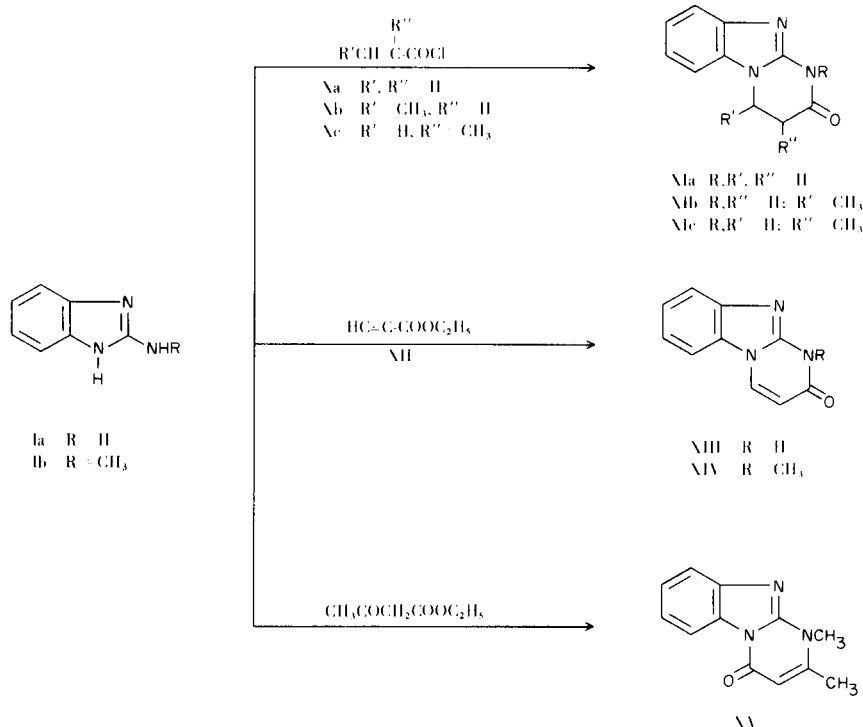
EXPERIMENTAL (10)

Ethyl 1,4-Dihydro-4-oxopyrimido[1,2-a]benzimidazole-3-carboxylate (IV).

A mixture of 7.5 g. (0.056 mole) of 2-aminobenzimidazole and 10.9 g. (0.05 mole) of diethyl ethoxymethylenemalonate (II) was heated neat (11) in an oil bath at 110° for 0.5 hour. After cooling, the resulting white solid was filtered to give 11.0 g. of crude product. Recrystallization from acetic acid gave 4.7 g. (36.5%) of purified IV, m.p. 280-282° dec. A further recrystallization from the same solvent and drying at 155° in vacuo furnished an analytical sample, m.p. 292-294° dec.; lit. m.p., 270-271° (2); uv λ max mμ (ϵ max): 231, 247, 276, shs; 331 (18,210), 341 (18,130), 358 sh; nmr (trifluoroacetic acid): 1.54 (3H, t, CH$_3$); 4.63 (2H, q, CH$_2$); 7.88 (3H, m, H$_{7-9}$); 8.72 (1H, m, H$_6$); 9.21 (1H, s, H$_2$).

Anal. Calcd. for C$_{13}$H$_{11}$N$_3$O$_3$: C, 60.70; H, 4.31; N, 16.34. Found: C, 60.61; H, 4.45; N, 16.58.

Ethyl 4-Aminopyrimido[1,2-a]benzimidazole-3-carboxylate (VII) and 1,4-Dihydro-4-oxopyrimido[1,2-a]benzimidazole-3-carbonitrile (VIII).

A mixture of 16.8 g. (0.1 mole) of ethyl ethoxymethylenecyanoacetate (V) and 13.4 g. (0.1 mole) of 2-aminobenzimidazole was heated neat in an oil bath at 120° for 1.25 hours. After cooling, the resulting solid was filtered to yield 18.7 g. of a crude product whose nmr and ir spectra indicated the presence of compounds VII and VIII. This crude solid was extracted with 500 ml. of boiling DMF. Upon cooling, the DMF extract deposited 9.1 g. (35.5%) of VII as a light orange solid, m.p. 270-272° dec., lit. m.p. 248-250° (2); tlc (solvent A): one spot, R$_f$ 0.85; ir: 5.94 μ (chelated β-amino-α,β-unsaturated ester) (12); 3.05 μ, sh, 3.20 μ (NH); uv λ max mμ (ϵ max): 236 sh, 247 (31,490), 256 (30,060), 263 sh, 310 (12,780) broad peak, 370 sh; nmr (tri-

fluoroacetic acid): 1.55 (3H, t, CH$_3$); 4.66 (2H, q, CH$_2$); 8.00 (3H, m, H$_{7-9}$); 8.48 (1H, m, H$_6$); 9.39 (1H, s, H$_2$).

Anal. Calcd. for C$_{13}$H$_{12}$N$_4$O$_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.78; H, 4.71; N, 22.17.

After filtering compound VII, the DMF mother liquor was evaporated in vacuo to a yellow solid. Crystallization from 650 ml. of acetic acid gave 3.0 g. (14.4%) of VIII as a tan solid, m.p. 355-360° dec. Recrystallization from the same solvent gave 2.25 g. of analytical sample, m.p. 358-362° dec.; tlc (solvent A): one spot, R$_f$ 0.57; ir: 4.48 μ (C≡N); uv λ max mμ (ϵ max): 228 (ϵ, 21,900) sh, 244 (19,100) sh; 264, 276, 284, 296, shs; 322 (17,300), 345 (16,800); nmr (trifluoroacetic acid): 7.92 (3H, m, H$_{7-9}$) 8.72 (1H, m, H$_6$); 8.89 (1H, s, H$_2$).

Anal. Calcd. for C$_{11}$H$_6$N$_4$O: C, 62.85; H, 2.88; N, 26.66. Found: C, 62.87; H, 2.96; N, 26.61.

1,4-Dihydro-4-oxopyrimido[1,2-a]benzimidazole-3-carboxylic Acid (IX).

A. By Hydrolysis of Ethyl 4-Aminopyrimido[1,2-a]benzimidazole-3-carboxylate (VII).

A stirred mixture of 1 g. (3.9 mmoles) of VII in 50 ml. of dilute hydrochloric acid was heated at reflux. A solution was obtained followed by the precipitation of a white solid. Heating was continued for another 0.5 hour and the solid was filtered to give 0.7 g. (79%) of the crude IX; m.p. 250° dec. Recrystallization from acetic acid gave an analytical sample, m.p. 280-282° dec.; ir: 5.80 μ (COOH); nmr (deuterium oxide/potassium): 7.39 (3H, m, H$_{7-9}$); 8.36 (1H, m, H$_6$); 8.79 (1H, s, H$_2$).

Anal. Calcd. for C$_{11}$H$_7$N$_3$O$_3$: C, 57.64; H, 3.08; N, 18.33. Found: C, 57.85; H, 3.44; N, 17.82.

B. By Hydrolysis of Ethyl 1,4-Dihydro-4-oxopyrimido[1,2-a]-benzimidazole-3-carboxylate (IV).

A stirred suspension of 0.5 g. of IV in 25 ml. of dilute hydrochloric acid was refluxed for 1 hour and cooled. The remaining white solid was filtered, washed with water and dried, m.p. 260-262° dec. Recrystallization from 125 ml. of acetic acid gave a purified sample, m.p. 267-268° dec. This was dried at 155°, under high vacuum, to give a solid, m.p. 280-282° dec. Mixed m.p. of the samples from A and B runs showed no depression; uv λ max mμ (ϵ max): 228 (26,300); 248, 256, shs; 330 (17,100), 342 (16,300). Nmr and ir were identical to those obtained in A run; tlc (solvent B); one spot, R$_f$ 0.63.

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.33. Found: C, 57.82; H, 3.25; N, 18.01.

3,4-Dihydropyrimido[1,2-a]benzimidazol-2(1H)one (XIa).

Acrylyl chloride (20 g., 0.22 mole) was added to a stirred mixture of 26.6 g. (0.2 mole) of 2-aminobenzimidazole and 23.7 g. (0.24 mole) of triethylamine in 1 l. of acetonitrile, keeping the temperature below 25°. Stirring was continued for 1.5 hours at room temperature. The resulting solid was filtered, washed with acetonitrile and dried to give 41 g. of crude product. This was suspended in 400 ml. of 50% ethanol and 40% sodium hydroxide was added to adjust the pH to 11.5. Water was added to dissolve all of the solid. The pH was lowered to 7.1 with acetic acid and the resulting solid was filtered, washed with 50% aqueous ethanol and dried to give 19.6 g. of XIa, m.p. 253-256°. Recrystallization from DMF gave 13.0 g. (35%) of an off-white solid, m.p. 260.5-262°; tlc (solvent C): one spot, R$_f$ 0.61; ir: 5.95 μ (amide); uv λ max mμ (ϵ max): 252 (11,400), 260 sh, 284 (13,200), 292 (13,400); λ max (pH 1): 234 (13,500), 279 (14,000), 287 (15,000); λ max (pH 13): 263 (7,700), 272 (7,400), 302 (21,000); nmr (trifluoroacetic acid): 3.43 (2H, t, J = 8 Hz, H$_3$); 4.72 (2H, t, J = 8 Hz, H$_4$); 7.68 (4H, s, H$_{6-9}$).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.21; H, 5.08; N, 22.48.

4-Methyl-3,4-dihydropyrimido[1,2-a]benzimidazol-2(1H)one (XIb).

During a period of 15 minutes, crotonyl chloride (41.8 g., 0.40 mole) was added dropwise to a stirred and cooled solution of 50.0 g. (0.38 mole) of 2-aminobenzimidazole, 38.0 g. (0.38 mole) of triethylamine in a mixture of 1250 ml. of acetone and 250 ml. of THF. The mixture was stirred an additional 6 hours at room temperature and filtered to yield 30.7 g. of an off-white solid, m.p. 234-242°. Recrystallization from ethanol gave 21.7 g. (28.8%) of XIb as a white crystalline solid, m.p. 260-261.5°; ir: 5.94 μ (amide); uv λ max mμ (ϵ max): 252 (11,600), 260 sh, 285 (13,500), 292 (13,800); λ max (pH 1): 234 (13,800), 279 (14,500), 287 (15,400); λ max (pH 13): 262 (12,700), 272 (11,700), 303 (23,400); nmr (trifluoroacetic acid): 1.72 (3H, d, J 7 Hz, CH$_3$); 3.0-3.8 (2H, octet, ABX position of ABX (13), δ A $\sim$ 3.2, δ_B $\sim$ 3.6, J$_{AB}$ = 17 Hz, J$_{AX}$ $\sim$ 2 Hz, J$_{BX}$ $\sim$ 7 Hz), 5.0-5.7 (1H, m, X position of ABX, δ_X $\sim$ 5.3), 7.73 (s, 4H) aromatic H.

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.44; H, 5.59; N, 20.83.

3-Methyl-3,4-dihydropyrimido[1,2-a]benzimidazol-2(1H)one (XIc).

Methacrylyl chloride (41.75 g., 0.40 mole) was added to a stirred solution of 50.0 g. (0.38 mole) of 2-aminobenzimidazole and 38.0 g. (0.38 mole) of triethylamine in a mixture of 1250 ml. of acetone and 250 ml. of THF. After the addition, the reaction mixture was stirred 5 hours at room temperature and filtered to give 80.8 g. of crude product. Crystallization from ethanol-water yielded 10.8 g. (14.5%) of purified XIc, m.p. 264-266°; uv λ max mμ (ϵ max): 251 (11,300), 258 sh, 284 (13,400), 291 (13,600);

λ max (pH 1): 234 (13,800), 279 (14,300), 287 (15,500); λ max (pH 13): 263 (10,000); 272 (9,400), 302 (22,300); nmr (14) (trifluoroacetic acid): 1.58 (3H, d, J = 7 Hz, CH$_3$); 3.3-3.7 (1H, m, C position of ABC, δ_C $\sim$ 3.5). 4.0-5.0 (octet, AB position of ABC, δ A $\sim$ 4.3, δ_B $\sim$ 4.8, J$_{AB}$ $\sim$ 13 Hz, J$_{AC}$ $\sim$ 10 Hz, J$_{BC}$ $\sim$ 8 Hz); 7.67 (4H, s, aromatic H).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.80; H, 5.48; N, 20.55.

Pyrimido[1,2-a]benzimidazol-2(1H)one (XIII).

A solution of 15.0 g. (0.11 mole) of 2-aminobenzimidazole and 11.5 g. (0.11 mole) of ethyl propiolate in 690 ml. of acetone was refluxed 4.5 hours. After cooling, the white solid was filtered to give 8.6 g. (41.5%) of crude product. Two recrystallizations from DMF gave 3.1 g. (15%) of purified XIII, m.p. 336-339° dec.; uv λ max mμ (ϵ max): 239 (29,400); 248, 264 shs; 298 (10,700); λ max (pH 1): 236 (30,500), 289 (9,100); λ max (pH 13): 253 (50,700), 268 (11,600) sh; nmr (trifluoroacetic acid): 7.00 (1H, d, J = 8 Hz, H$_3$); 7.86 (4H, m, H$_{7-9}$); 8.86 (1H, d, J = 8 Hz, H$_4$).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.65; H, 3.75; N, 22.53.

1-Methylpyrimido[1,2-a]benzimidazol-2(1H)one (XIV).

A. From 2-Methylaminobenzimidazole.

A solution of 3.0 g. (0.02 mole) of 2-methylaminobenzimidazole and 2.2 g. (0.022 mole) of ethyl propiolate in 125 ml. of acetone was refluxed for 20 hours. The solvent was removed and the residual solid was triturated with cold ethyl acetate to give 0.7 g. (17.6%) of crude product. Recrystallization from ethyl acetate gave XIV as long needles, m.p. 178-180°; uv λ max mμ (ϵ max): 249 (29,500), 263 (15,900), 290 (9,000); nmr (deuterochloroform): 3.67 (3H, s, CH$_3$); 6.12 (1H, d, J = 8 Hz, H$_3$); 7.1-7.8 (4H, m, aromatic H); 8.00 (1H, d, J = 8 Hz, H$_4$).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.24; H, 4.68; N, 21.21.

B. From Pyrimido[1,2-a]benzimidazol-2(1H)one (XIII).

The methylation reaction (15) was carried out by treating a solution of 0.5 g. (27 mmoles) of pyrimido[1,2-a]benzimidazol-2(1H)one (XIII) in a mixture of 70 ml. of methanol and 50 ml. of DMF with an ethereal solution of diazomethane (from 1 g. of N-nitrosomethylurea and 40% potassium hydroxide). The resulting mixture was allowed to stand in an ice bath for 4.5 hours and then concentrated *in vacuo* to remove all solvents. The residue was recrystallized from ethyl acetate (charcoal) to give 0.25 g. (47%) of XIV, m.p. 176-178°. The ir and nmr spectra of this product were identical to those obtained for product prepared under Procedure A.

1,2-Dimethylpyrimido[1,2-a]benzimidazol-4(1H)one (XV).

A mixture of 1.5 g. (0.01 mole) of 2-methylaminobenzimidazole, 1.5 g. (0.011 mole) of ethyl acetoacetate was heated in a 160° oil bath for 21 hours. The brown mixture was dried on a clay plate to give 2.05 g. (96.5%) of crude product. Two recrystallizations from ethyl acetate (charcoal) gave 0.7 g. of XV as white needles, m.p. 165-167°; tlc (solvent D): R$_f$ 0.58; uv λ max mμ (ϵ max): 233 (16,600), 248 (9,775) sh, 316 (2,800) broad peak; λ max (pH 1): 229 (13,300), 244 (8,800) sh, 306 (3,200); λ max (pH 13): 231 (16,300) sh, 250 (9,050) sh, 318 (2,750) broad peak; nmr (trifluoroacetic acid): 2.73 (3H, s, CH$_3$); 4.13 (3H, s, NCH$_3$); 6.67 (1H, s, H$_3$); 7.85 (3H, m, H$_{7-9}$); 8.72 (1H, m, H$_6$).

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(10) Decomposition points, whose values vary depending upon the rate of heating, were determined in capillary tubes with a Thomas-Hoover apparatus and were uncorrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer Infracord. Ultraviolet spectra were obtained in ethanol on a Cary Model 14 Spectrophotometer. Nmr spectra were obtained on a Varian A-60, Varian T-60, and Jeolco C60H Spectrophotometers; chemical shifts, δ, are expressed in ppm downfield from TMS. Tlc were carried out on Silica Gel G by ascending method: Solvent A, ethanol-DMF (80:20); Solvent B, ethanol-formic acid (95:5), Solvent C, chloroform-methanol (50:50); Solvent D, chloroform-methanol (90:10).

(11) The same product was obtained in comparable yield when the reaction was carried out in acetic acid as described in Reference (2).

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(13) Analyzed as an ABX system according to J. A. Pople, W. G. Schneider, and H. J. B. Bernstein, "High Resolution Nuclear Magnetic Resonance," Chapter 6, McGraw-Hill, New York, 1959.

(14) If we assume XIb and XIc are conformationally homogeneous, then nmr data indicates that the methyl substituent in XIb (4-methyl) assumes a *quasi-axial* orientation (Hx lies between the *gem*-protons; $J_{AX} \sim 2$ Hz, $J_{BX} \sim 7$ Hz). This orientation is necessary to avoid crowding between methyl and H_6 protons. The methyl substituent in XIc (3-methyl) is that of *quasi-equatorial* orientation (Hx lies outside the *gem*-protons; $J_{AC} \sim 10$ Hz, $J_{BC} \sim 8$ Hz. See N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p. 145.

(15) The same product was obtained in poor yield by methylation with methyl iodide.