hand, oxidation of tetracaine to tetracaine N-oxide by the urine or the extraction solvents were not occurred in our experimentals. This result shows that the tetracaine N-oxide obtained from the urine samples is not an artificial product.

Kalow[3] reported that tetracaine was also hydrolyzed by the procaine esterase in serum, and that it was hydrolyzed four to five times more slowly than procaine. On the other hand, it was known that the procaine esterase activity in the blood of various animals including horses were lower than man.[9,10] Therefore, presence of the tetracaine N-oxide in the urine of various animals, it may be considered that tetracaine was slowly hydrolyzed in body.

9) M.H. Aren, A. Light, and F.F. Foldes, *Fed. Proc.*, 12, 299 (1953).
10) P. Terp, *Acta Pharm. Toxicol.*, 9, 374 (1953).

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Studies on Ketene and Its Derivatives. LXXIX.[1] Reaction of Diketene with Benzimidazole and 2-Methylbenzimidazole Derivatives

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Reaction of benzimidazole and N-acetylbenzimidazole with diketene in acetic acid or acetic anhydride at room temperature resulted in the formation of 2-acetonyl-1,3-diacetyl-2,3-dihydrobenzimidazole (II), and 5-acetyl-4a,5-dihydropyrido[1,2-*a*]benzimidazol-1,3(2H,4H)-dione. On the other hand, reactions of 2-ethoxycarbonylmethylbenzimidazole (XIIIa), 2-carbamoylmethylbenzimidazole (XIIIb), 2-cyanomethylbenzimidazole (XIIIc) with diketene in acetic acid at room temperature resulted in the formation of 4-substituted-3-methylpyrido[1,2-*a*]benzimidazol-1(5H)-one (XIIIa—c) in good yields, respectively.

We have previously reported that[3,4] reaction of diketene with pyridine afforded the Wollenberg compounds. This reaction involves the addition of diketene to the C=N double bond of pyridine followed by acetoacetylation and cyclization to give the pyronoquinolizine derivative. Similarly, aromatic N-heterocycles such as quinoline, isoquinoline, and phenanthridine reacted with diketene to give Wollenberg type compounds.[5] Recently, Yamanaka, *et al.*[6] reported the reaction of isoquinoline with diketene in acetic acid to afford 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline.

However, reactions with five membered aromatic N-heterocycles, in view of the above reactions, have not been studied yet. In the present paper we wish to report the reaction of diketene with benzimidazole and its derivatives.

Reaction of Diketene with Benzimidazole in Acetic Acid

When benzimidazole was allowed to react with diketene in acetic acid or acetic anhydride, colorless prisms of mp 140—141°, $C_{14}H_{16}O_3N_2$ (II), were obtained together with pale yellow

1) Part LXXVIII: T. Kato, T. Chiba, and M. Daneshtalab, *Heterocycles*, 3, 723 (1975).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kato, T. Kitagawa, and Y. Yamamoto, *Yakugaku Zasshi*, 83, 267 (1963).
4) O. Wollenberg, *Chem. Ber.*, 67, 1675 (1934).
5) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), 14, 752 (1966).
6) H. Yamanaka, T. Shiraishi, and T. Sakamoto, *Heterocycles*, 3, 1069 (1975).

prisms of mp 217—219° (decomp.), $C_{13}H_{12}O_3N_2$ (III), in 33% and 40% yields, respectively. Based on the chemical behaviours and spectral data, compound II and III were characterized as 2-acetonyl-1,3-diacetyl-2,3-dihydrobenzimidazole, and 5-acetyl-4a,5-dihydropyrido[1,2-*a*]-benzimidazol-1,3(2H,4H)-dione, respectively. Namely, infrared (IR) spectrum of compound II shows absorptions at 1715 and 1660 cm^{-1} due to the carbonyl groups. The nuclear magnetic resonance (NMR) spectrum indicates three methyl signals, a methylene, a methine, and ring protons. Acid hydrolysis of this compound resulted in the formation of benzimidazole and acetone, while in alkali hydrolysis the C–N bond was completely cleaved and N-acetyl-*o*-phenylenediamine was obtained. These data are well consistent with the structure of II.

The IR spectrum of III shows absorptions at 1765 and 1654 cm^{-1} due to carbonyl groups, and NMR indicates the existence of a methyl, two methylene, a methine, and ring protons. Thermolysis reaction of this compound resulted in the formation of benzimidazole. By treatment with a mixture of Ac_2O–AcOH this compound didn't change to II. Observing these data the structure of this compound was assigned as III.

Attempts were made to prepare the authentic sample of compound II. Namely, 2-acetonylbenzimidazole ethylene ketal (IV) was prepared according to the literature.[7] This compound was hydrogenated in acetic anhydride over PtO_2 to afford 2-acetonyl-1,3-diacetyl-2,3-dihydrobenzimidazole ethylene ketal (V), acid hydrolysis of which gave rise to compound II.

Compounds II, and III were also obtained by the reaction of N-acetylbenzimidazole with diketene in acetic acid, in 20% and 41% yields, respectively.

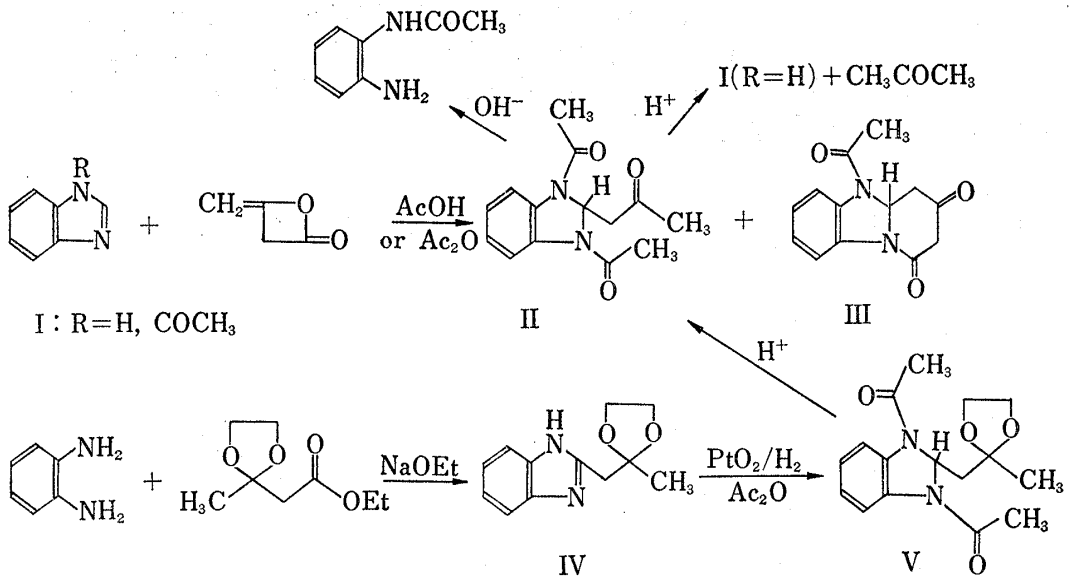

Chart 1

Although the details of the mechanism of the formation of these compounds is not clear at present, a likely pathway is suggested as following: electrophilic attack of the carbonyl carbon of diketene to the lone pair of nitrogen would result in the formation of dipolar intermediate A, which is in resonance form with B. Ring closure of B would give rise to compound III. The cyclization of dipolar intermediate C, formed by prototropy of B, results in the formation of the four membered α-acetyl-β-lactam D. The β-lactam ring would be cleaved by prototropy to form C-acetylketene derivative E. Further acetylation of E followed by hydrolysis and decarboxylation leads to the formation of II.

7) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim Acta*, 43, 1298 (1960).

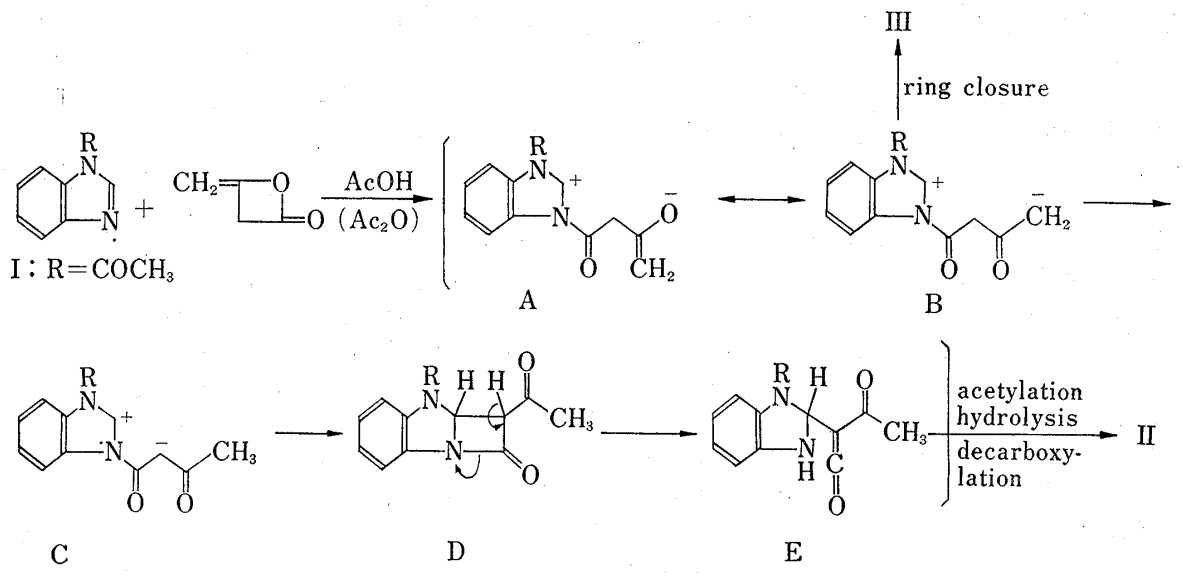

Chart 2

Reaction of Diketene with 2-Methylbenzimidazole Derivatives

Concerning the reaction of the heterocycles posessing active methylene, at side chain in α-position to nitrogen, with diketene, we have already reported[8] the reaction of 2-cyanomethylpyridine (VI) with diketene to afford the C-acetoacetyl derivative VII, which easily cyclized to give the quinolizine derivative (VIII). On the other hand, reaction of imidazoline derivatives IX with diketene has been reported[9] to afford 7-hydroxy-7-methyl-5-oxo-2,3,5,-6,7,8-hexahydroimidazo[1,2-*a*]pyridine X, dehydration of which gave compound XI. The reaction suggested that diketene added to the nitrogen to give the N-acetoacetyl derivative as an intermediate, followed by cyclization to X.

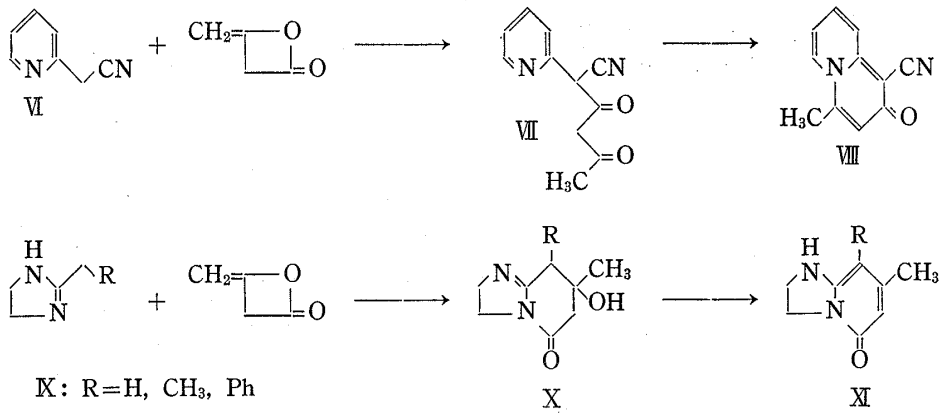

Chart 3

On the basis of these facts our interest was focused on the reaction of diketene with benzimidazole derivatives, having active methylene at 2-position, to see if diketene reacts with either the active methylene or ring nitrogen at first step.

2-Methylbenzimidazole derivatives (XII) used in this reaction were 2-ethoxycarbonylmethylbenzimidazole (XIIa), 2-carbamoylmethylbenzimidazole (XIIb), 2-cyanomethylbenzimidazole (XIIc), 2-methyl, and 2-ethylbenzimidazole (XIId, e). When diketene was allowed to react with XIIa in acetic acid at room temperature, colorless prisms of mp 225—

8) T. Kato and T. Atsumi, *Yakugaku Zasshi*, **87**, 961 (1967).
9) T. Kato and T. Sakamoto, *Yakugaku Zasshi*, **91**, 1174 (1971).

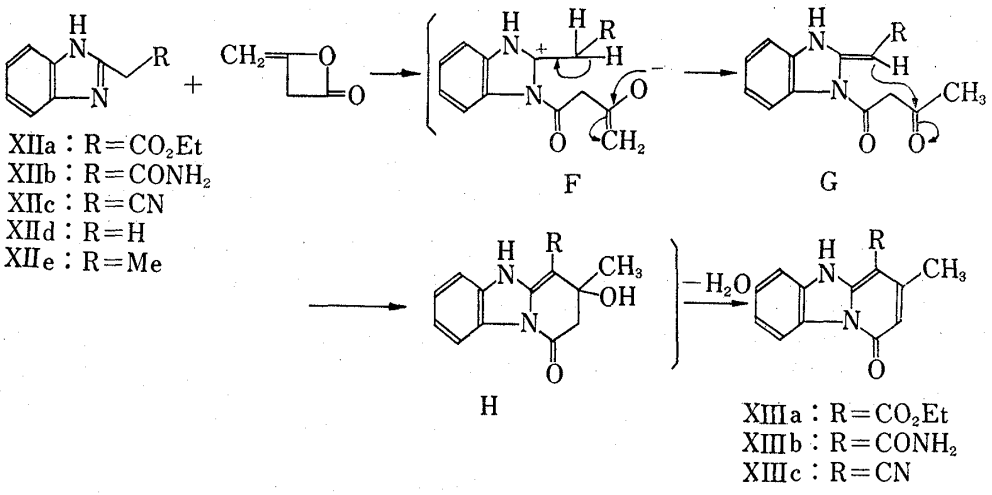

Chart 4

227° (decomp.), $C_{15}H_{14}O_3N_2$ (XIIIa), were obtained in 97% yield. Based on the spectral data the structure of this compound was assigned as 4-ethoxycarbonyl-3-methylpyrido[1,2-*a*]-benzimidazol-1(5H)-one. Namely, in the NMR spectrum of XIIIa the proton of 9-position was shifted to the lower field (8.72—8.97 ppm), to compare with C_6, C_7, C_8 protons (7.40—7.55 ppm), by the effect of anisotropy of the carbonyl group of 1-position. In the meantime, olefin and methyl protons as singlets together with chemical shifts related to ethoxycarbonyl group, were also observed. Similarly, reaction of diketene with XIIb and XIIc afforded a 91% yield of 4-carbamoyl-3-methylpyrido[1,2-*a*]benzimidazol-1(5H)-one (XIIIb), and a 50% yield of 4-cyano-3-methylpyrido[1,2-*a*]benzimidazol-1(5H)-one (XIIIc), respectively. Treatment of XIIIb with polyphosphoric acid resulted in the formation of XIIIc in 36% yield.

No reaction was observed when 2-methyl and 2-ethylbenzimidazole (XIId, e) were treated with diketene.

Although the precise mechanism of the formation of these products remains obscure, the reaction is presumed to proceed as following: electrophilic attack of the carbonyl carbon of diketene to the lone pair of nitrogen leads to the dipolar intermediate F, prototropy of which would make the intermediate G. This intermediate undergoes cyclization reaction to form intermediate H, dehydration of which results in the formation of compound XIIIa—c.

Experimental

All melting points were uncorrected. IR spectra were measured by a JASCO DS-301 spectrometer. NMR spectra were measured on a Hitachi-Perkin Elmer R-20 spectrometer, and reported as δ value (ppm) relative to tetramethylsilane (TMS) or sodium 3-trimethylsilyl-1-propane sulfonate (DSS) as internal standards. Abbreviations: s–singlet, d–doublet, t–triplet, q–quartet, m–multiplet, br–broad. Mass spectra were obtained on a Hitachi double focusing Mass Spectrometer RMU-7L.

Reaction of Benzimidazole with Diketene in Acetic Acid——To a solution of benzimidazole (2 g, 0.017 mole) in acetic acid (12 ml), was added diketene (5.76 g, 0.068 mole) dropwise. An exothermic reaction with the evolution of carbon dioxide occurred. After ceasing the evolution of carbon dioxide, the reaction mixture was kept at room temperature for three days, then condensed under reduced pressure. The residual oil was submitted to silica gel column chromatography using ether, and ethyl acetate as eluants. The ether eluate was condensed, and the residual solid was purified by recrystallization from benzene to give 1.050 g (23%) of colorless prisms, mp 140—141°. *Anal.* Calcd. for $C_{14}H_{16}O_3N_2$ (II): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.37; H, 6.13; N, 10.59. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1660. NMR ($CDCl_3$) ppm: 2.22 (3H, s, –CO–CH_3), 2.38 (6H, s, N–$COCH_3$), 2.92 (2H, d, J=6 Hz, –CH_2–), 6.67 (1H. t, J=6 Hz, –CH–), 6.98—7.53 (4H, m, ring protons). Mass Spectrum *m/e*: 260 (M^+).

The ethyl acetate eluate was condensed, and the residual solid was purified by recrystallization from acetone to give pale yellow prisms, mp 217—219° (decomp.), 0.4 g (10%). *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$ (III): C, 63.92; H, 4.95; N, 11.47. Found: C, 63.73; H, 5.05; N, 11.30. IR ν_{max}^{KBr} cm^{-1}: 3440, 1765, 1670 (shoulder), 1654. NMR (CF_3COOH, DSS) ppm: 2.56 (2H, ABq, J=19 Hz, –CH_2–), 2.61 (3H, s, N–$COCH_3$), 3.02—3.95

(2H, m, $-CH_2-$), 5.88—6.62 (1H, m, >CH–), 7.10—7.50 (3H, m, C_6, C_7, C_8, protons), 7.90—8.40 (1H, m, C_9–proton). Mass Spectrum *m/e*: 244 (M^+).

Reaction of Benzimidazole with Diketene in Acetic Anhydride——To a solution of benzimidazole (2 g, 0.017 mole) in acetic anhydride (20 ml) was added diketene (2.88 g, 0.034 mole) dropwise. The reaction mixture was kept at room temperature for four days. Crystals obtained were filtered, washed with ether, and purified by recrystallization from acetone to pale yellow prisms of mp 217—219° (decomp.), whose IR spectrum was identical in every respect with that of a sample of III obtained from the above run. Yield 1.67 g (40%).

The filtrate was condensed under reduced pressure. The residual solid was purified by recrystallization from benzene to give colorless prisms of mp 140—141°, IR spectrum of which was identical in every respect with that of a sample of II obtained in the above run. Yield 1.5 g (33%).

Reaction of 1-Acetylbenzimidazole with Diketene——To a solution of 1-acetylbenzimidazole (1 g, 0.0062 mole) in acetic acid (6 ml) was added diketene (2.1 g, 0.025 mole) dropwise. The reaction mixture was kept at room temperature for 5 days. The crystals obtained were filtered, and purified by recrystallization from acetone to pale yellow prisms of mp 217—219° (decomp.), 0.360 g, undepressed on admixture with an authentic sample of II obtained in the above run. The filtrate was condensed under reduced pressure, and the oily residue was dissolved in a small amount of benzene and submitted to silica gel column chromatography using ether and ethyl acetate as eluants. The ether eluate was condensed and the residue was purified by recrystallization from benzene to give colorless prisms of mp 140—141°, 0.330 g (20%), undepressed on admixture with an authentic sample of II obtained in the above run. From the ethyl acetate eluate after condensation, and purification of the residue by recrystallization from acetone, 0.260 g of compound III was obtained (total yield 41%).

Alkali Hydrolysis of Compound II——A suspension of II (0.300 g) in 10% NaOH solution (10 ml) was stirred at room temperature for 24 hr. The reaction mixture was extracted with ether. The extract was dried over anhydrous Na_2SO_4, then condensed up to dryness. The residual solid was recrystallized from benzene to colorless pillars of mp 132—133°, 0.077 g (48%), which was identified as N-acetyl-*o*-phenylenediamine by comparison with an authentic sample of N-acetyl-*o*-phenylenediamine prepared according to the literature.[10]

Acid Hydrolysis of Compound II——A mixture of compound II (0.780 g) in 10% solution of HCl (30 ml) was refluxed for 1 hr. A 5 ml aliquot of the reaction mixture was distilled in order to identify the acetone liberated. The reaction mixture was cooled, neutralized with $NaHCO_3$, and extracted with chloroform. The extract was dried over $CaCl_2$. After removal of the solvent, the crystalline residue was purified by recrystallization from EtOH–H_2O to give 0.130 g (37%) of colorless prisms of mp 172—174°, undepressed on admixture with an authentic sample of benzimidazole.

The acetone liberated during the reaction was identified from the distilate by making acetone 2,4-dinitrophenylhydrazone, identical with an authentic sample prepared by the reaction of acetone with 2,4-dinitrophenylhydrazine.

Thermolysis Reaction of Compound III——Compound III (0.061 g) was heated on an oil bath at 203° for 15 min. After cooling, the residue was dissolved in a small amount of methanol and submitted to alumina column chromatography using ethyl acetate as an eluant. First fraction was condensed under reduced pressure. The residue was extracted with hot ether. The extract was condensed, and the crystals obtained were purified by recrystallization from EtOH–H_2O to give 0.015 g (52%) of colorless prisms of mp 172—174°, undepressed on admixture with an authentic sample of benzimidazole.

2-Acetonyl-1,3-diacetyl-2,3-dihydrobenzimidazole Ethylene Ketal (V)——2-Acetonylbenzimidazole ethylene ketal (prepared according to the literature[7]) (0.218 g, 0.001 mole) was dissolved in acetic anhydride (7 ml) and hydrogenated over platinum oxide (0.050 g) at room temperature for 6 hr. The reaction mixture was poured into an ice-water mixture. The resulting mixture was condensed under reduced pressure. The crystalline residue was purified by recrystallization from ether to give colorless pillars of mp 109—110°, 0.220 g (72%). *Anal.* Calcd. for $C_{16}H_{20}O_4N_2$ (V): C, 63.14; H, 6.62; N, 9.21. Found: C, 63.11; H, 6.73; N, 8.96. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 1660. NMR ($CDCl_3$) ppm: 1.32 (3H, s, $-CH_3$), 2.22 (2H, d, J=6 Hz, $-CH_2-$). 2.34 (6H, s, N–$COCH_3$), 3.80 (4H, br.s, $-CH_2-CH_2-$), 6.54 (1H, t, J=6 Hz, >CH–), 6.92—7.18 (4H, m, ring protons).

Acid Hydrolysis of Compound V to give Compound II——A suspension of compound V (0.070 g) in 2 N HCl (5 ml) was stirred at room temperature for 2 hr. The reaction mixture was extracted with chloroform. The extract was dried over anhydrous Na_2SO_4, and condensed. The crystalline residue was purified by recrystallization from benzene to give colorless prisms of mp 140—141°, whose IR spectrum was identical in every respect with that of a sample of compound II obtained from the above run. Yield 0.05 g (84%).

4-Ethoxycarbonyl-3-methylpyrido[1,2-*a*]benzimidazol-1(5H)-one (XIIIa)——To a solution of 2-ethoxycarbonylmethylbenzimidazole (prepared according to the literature[11]) (0.204 g, 0.001 mole) in acetic acid (2 ml) was added diketene (0.336 g, 0.004 mole) dropwise. The reaction mixture was kept at room temperature

10) F. Bell and J. Kenyon, *J. Chem. Soc.*, **1926**, 854.
11) J.J. Ursprung, U.S. Patent 3105837 (1963) [*C.A.*, **60**, 1763g (1964)].

for 5 days. The crystals obtained were filtered, and purified by recrystallization from benzene to give colorless prisms of mp 225—227° (decomp.), 0.262 g (97%). *Anal.* Calcd. for $C_{15}H_{14}O_3N_2$ (XIIIa): C, 66.65; H, 5.22; N, 10.37. Found: C, 66.65; H, 5.00; N, 10.39. IR ν_{max}^{KBr} cm^{-1}: 3390, 1683, 1640. NMR ($CDCl_3$) ppm: 1.44 (3H, t, J=7 Hz, CH_2–$C\underline{H}_3$), 2.60 (3H, s, $-CH_3$), 4.42 (2H, q, J=7 Hz, $-C\underline{H}_2$–CH_3), 6.07 (1H, s, $\rangle$CH), 7.40—7.55 (3H, m, C_6, C_7, C_8 protons), 8.72—8.97 (1H, m, C_9–proton), 12.06—12.40 (1H, br, –NH).

4-Carbamoyl-3-methylpyrido[1,2-*a*]benzimidazole-1 (5H)-one(XIIIb)——To a solution of 2-carbamoylmethylbenzimidazole (prepared according to the literature[12]) (0.175 g, 0.001 mole) in acetic acid (2 ml) was added diketene (0.336 g, 0.004 mole) dropwise. The reaction mixture was kept at room temperature for 5 days. The crystals obtained were filtered, washed with water, and purified by recrystallization from AcOH–H_2O to give colorless prisms of mp 273—275° (decomp.), 0.220 g (91%). *Anal.* Calcd. for $C_{13}H_{11}O_2N_3$ (XIIIb): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.50; H, 4.52; N, 17.45. IR ν_{max}^{KBr} cm^{-1}: 3380, 3220, 1660 (shoulder), 1645, 1612. NMR (CF_3COOH, DSS) ppm: 2.90 (3H, s, $-CH_3$), 6.92 (1H, s, $\rangle$CH), 7.50—7.95 (5H, m, C_6, C_7, C_8 protons and $CONH_2$), 8.50—8.75 (1H, m, C_9–H).

4-Cyano-3-methylpyrido[1,2-*a*]benzimidazol-1 (5H)-one(XIIIc)——To a solution of 2-cyanomethylbenzimidazole (prepared according to the literature[13]) (0.300 g, 0.0019 mole) in acetic acid (3 ml) was added diketene (0.170 g, 0.002 mole) dropwise. The mixture was kept at room temperature overnight. The crystals obtained were filtered, and purified by recrystallization from EtOH to give colorless needles of mp$>$315° (decomp.), 0.215 g (50%). *Anal.* Calcd. for $C_{13}H_9ON_3$ (XIIIc): C, 69.94; H, 4.06; N, 18.83. Found: C, 70.31; H, 4.10; N, 18.59. IR ν_{max}^{KBr} cm^{-1}: 3480, 3120—2720, 2240, 1670. NMR (CF_3COOH) ppm: 2.80 (3H, s, $-CH_3$), 6.95 (1H, s, $\rangle$CH), 7.50—7.92 (3H, m, C_6, C_7, C_8 protons). 8.44—8.73 (1H, m, C_9 proton).

Dehydration of XIIIb to give Compound XIIIc——Compound XIIIb (0.055 g) was mixed with polyphosphoric acid (0.8 g), and the mixture was heated at about 90—95° for 5 min. The reaction mixture was decomposed by ice-water mixture, and the precipitate was filtered off. The precipitate was suspended in 5 ml saturated solution of $NaHCO_3$, and filtered again, and purified by recrystallization from EtOH to colorless needles of mp 315° (decomp.), 0.018 (36%). The product obtained in this reaction was identical with a sample of XIIIc obtained in the above run.

Acknowledgement The authors are indebted to all the staffs of the Central Analyses Room of this Institute for elemental analyses, and spectral measurements.

12) Ralph A.B. Copeland and Allan R. Day, *J. Am. Chem. Soc.*, **65**, 1072 (1943).
13) J. Büchi, H. Zwicky, and A. Aeki, *Arch. Pharm.*, **293**, 758 (1960) [*C.A.*, **55**, 518g. (1961)].