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Photochemical Synthesis of a Pyridopyrrolo[2,1-*a*]isoindole System by Cyclization of N-Methylpyridylphthalimides[1,2]

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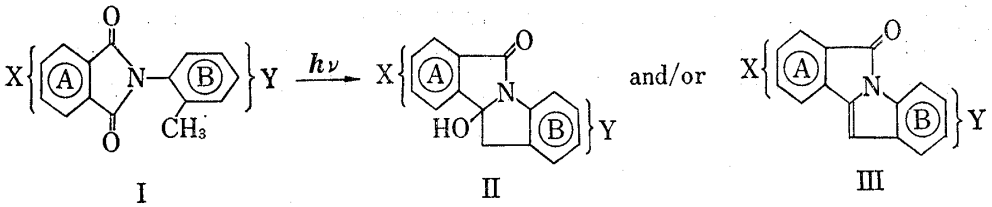
Photochemical reactions of N-methylpyridylphthalimides (VII—IX) were investigated. Although irradiation of VII in an acetone solution gave only the dihydro product, 3-hydroxy-2-(3-methyl-2-pyridyl)phthalimidine (X), VIII afforded the expected cyclized product, 10b,11-dihydro-10b-hydroxy-6*H*-pyrido[4′,3′: 4,5]pyrrolo[2,1-*a*]isoindol-6-one (XII) and dihydro product, 3-hydroxy-2-(4-methyl-3-pyridyl)phthalimidine (XI). Under similar conditions, the cyclized product, 10b,11-dihydro-10b-hydroxy-6*H*-pyrido[3′,4′: 4,5]-pyrrolo[2,1-*a*]isoindol-6-one (XIII) was obtained from the photolysis of IX and none of the reduced product was isolated.

Keywords——pyridopyrrolo[2,1-*a*]isoindole; N-methylpyridylphthalimide; Norrish type II reaction; photochemical syntheses of heterocycles; 2-substituted azaindole

In our exploration of the photochemistry of carbonyl derivatives, participation of an aromatic imide carbonyl in the Norrish type II reaction has been first found by observing that N-*o*-tolylphthalimide (I: X=Y=H) on irradiation cyclized to form the cyclopentanol (II; X=Y=H)[4] which was readily dehydrated to give an indoloisoindole (III; X=Y=H) as shown in Chart 1.

This finding led us to investigate synthetic possibilities of the photochemical reaction of a variety of the phthalimides, *e.g.*, the cyclic aromatic imide system.[5]



I II III

Chart 1

In hope of providing the scope and limitation of the reaction, the photocyclization of N-*o*-tolylphthalimides (I) possessing various substituents on the A or B ring was examined.[6] Photolysis of the phthalimides with an electron-withdrawing group on the A ring afforded the corresponding cyclized products (II and/or III), whereas those which have an electron-donating substituent resisted to the cyclization. In contrast, the phthalimides which possess either an electron-withdrawing or electron-donating group on the B ring smoothly underwent

1) Photoinduced Reactions. XXVII. Part XXVI: Y. Kanaoka, S. Nakao, and Y. Hatanaka, *Heterocycles*, **5**, 261 (1976).
2) Photochemistry of the Phthalimide System. XIV. Part XIII: Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi, and Y. Kanaoka, *Tetrahedron Lett.*, **1976**, 1889.
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4) Y. Kanaoka and K. Koyama, *Tetrahedron Lett.*, **1972**, 4517.
5) *a*) For a leading reference see: Y. Kanaoka, *J. Syn. Org. Chem.* (Yūkigōseikagaku Kyōkai-shi), **33**, 949 (1975) (in Japanese); *b*) ref. 2) and earlier papers cited therein.
6) Y. Kanaoka, C. Nagasawa, H. Nakai, Y. Sato, H. Ogiwara, and T. Mizoguchi, *Heterocycles*, **3**, 553 (1975).

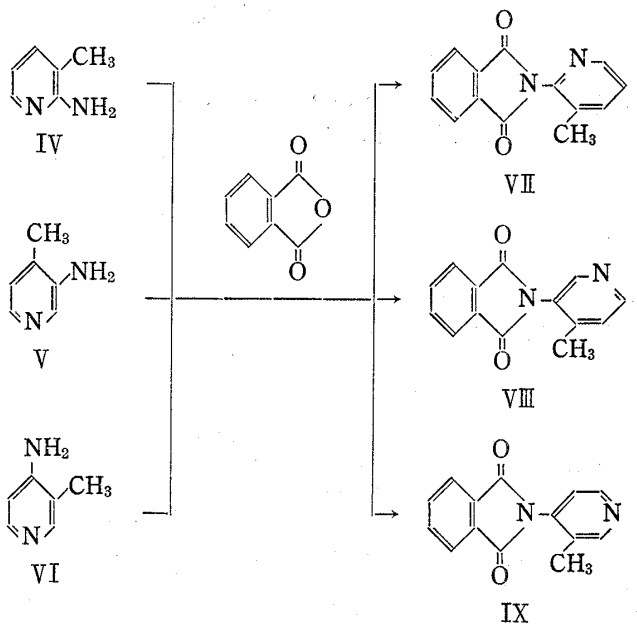


Chart 2

the photoreaction giving rise to the cyclized products (II and/or III).[6] These results indicate a possibility of wide structural variation of the B ring of the substrates and therefore encourage us to explore photoreactions of the phthalimides in which the B ring is a heteroaromatic ring system. As part of research on photochemical syntheses of heterocycles, the present paper describes the synthesis of a pyridopyrrolo[2,1-*a*]isoindole system (XII and XIII) by the photocyclization of N-pyridylphthalimides containing an *o*-methyl group on the pyridine ring.

The preparation of the methylpyridylphthalimides (VII—IX) used in this study was accomplished by thermal condensation of aminopicolines (IV—VI) with phthalic anhydride as shown in Chart 2.

Irradiation of an acetone solution of VII with a 500W high-pressure mercury lamp gave only the dihydro product (X), in 14% yield, together with VII. None of the cyclized product was isolated. Characterization of (X) was based on the elemental analysis and the spectral data [infrared spectrum (IR), 3270 cm^{-1} (OH), 1670 cm^{-1} (amide C=O); NMR, δ 6.70(C_3-H)], and established by comparison with an authentic sample prepared by reduction of VII with sodium borohydride. However, photolysis of VIII under similar conditions afforded, after preparative thin-layer chromatography (TLC), the expected cyclized compound (XII), 10b, 11-dihydro-10b-hydroxy-6*H*-pyrido[4′,3′: 4,5]pyrrolo[2,1-*a*]isoindol-6-one in a low yield, accompanied by the reduced product (XI). The compound (XII) has the same composition ($C_{14}H_{10}N_2O_2$: elemental analysis and mass spectrum) as the starting phthalimide (VIII). The absence of imide carbonyl absorption in the IR spectrum and the presence of an absorption of lactam carbonyl (1710 cm^{-1}) and a methylene peak (δ 3.47) as a singlet in the nuclear

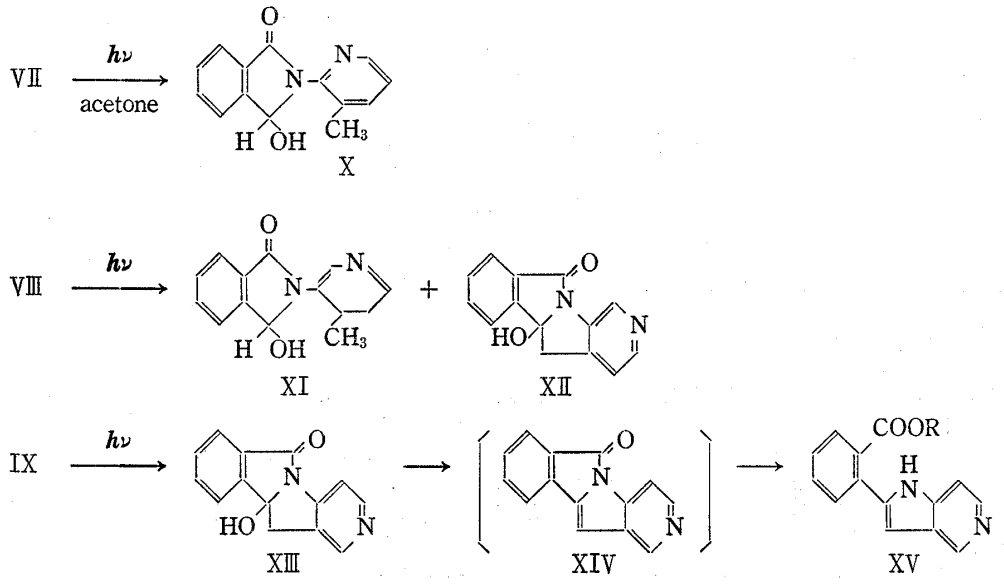
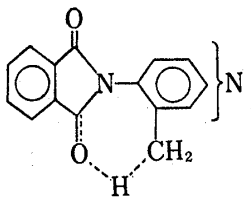


Chart 3

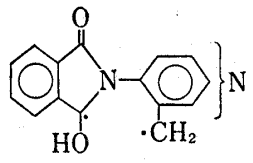
magnetic resonance (NMR) spectrum in place of a methyl in VIII, are all in accord with the proposed structure which indicates that a new bond has been intramolecularly formed between the imide carbonyl carbon and the methyl group on the pyridine ring. In a similar manner, photolysis of IX afforded the expected ring compound (XIII), 10b,11-dihydro-10b-hydroxy-6*H*-pyrido[3′,4′: 4,5]pyrrolo[2,1-*a*]isoindol-6-one, in 9% yield. A characteristic reaction of a tertiary alcohol of the tetracyclic system (II) is facile dehydration on acid treatment leading to the indoloisoindole (III).[4] However, the dehydration of XIII proceeded rather slowly and after prolonged heating in ethanol containing sulfuric acid, the 2-substituted azaindole (XVb) was ultimately isolated. Apparently the initially formed indole (XIV) underwent subsequent hydrolysis of the amide bond to afford XVb.

From the analogy to the currently accepted mechanism for the type II reaction of phenyl ketone triplets,[7] intermediacy of the biradical (XVII) has been assumed for the photoreactions of the imide carbonyl.[2,4,5] Thus the excited carbonyl abstracts a hydrogen from the picolyl methyl by way of a transition state (XVI) to form the biradical intermediate (XVII), which readily undergoes cyclization following the well-known pattern of the type II reaction to afford a pentanol derivative (II).

According to the postulated mechanism, the substituent on the B ring influences only the stability of the benzyl radical and would have no substantial effect on the excited state



XVI



XVII

of the carbonyl.[6] One might argue that the presence of an electro-negative ring-nitrogen (VII—IX) could lower the reactivity of the methyl towards the triplet carbonyl oxygen which is of an electrophilic radical nature.[7,8] However, this seems at least not important because the cyclization has well occurred for the imide with such an electron-withdrawing substituent as chlorine.[6]

The reason of the reluctance of VII to react is unknown. The interaction between lone-pair of α-nitrogen and imide carbonyl would disturb the co-planarity of the molecule which is necessary for smooth cyclization to occur. Further application of this reaction for photochemical synthesis of heterocycles is still in progress.

Experimental

All melting points are uncorrected. IR and ultraviolet (UV) spectra were recorded on a Shimadzu IR-400 and a Hitachi Model-124 spectrophotometers, respectively. NMR spectra were measured with a Hitachi R-24 spectrometer (60 MHz) and chemical shifts were given on δ (ppm) scales with tetramethylsilane as an internal standard. The following abbreviations are used: d=doublet; t=triplet; q=quartet. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 GC-Mass spectrometer with a direct inlet system. For preparative TLC, silica gel (Merck, GF_{254}) and aluminum oxide (Merck, SI 1000 Å) was used for column chromatography.

UV irradiation was carried out in a Pyrex vessel at room temperature, using a Eikosha 500 W high-pressure mercury lamp.

4-Amino-3-methylpyridine (VI)——4-Nitro-3-methylpyridine 1-oxide (5.61 g) in AcOH (100 ml) and Ac_2O (5.5 ml) was hydrogenated over 10% Pd-C (4 g) at 3 atm for 15 hr and worked up according to the procedure of Herz, *et al.*[9] to yield VI (2.953 g), mp 107—108.5° (Lit.[9] mp 107.4—108.6°).

7) P.J. Wagner, *Accounts Chem. Res.*, **4**, 168 (1971).
8) P.J. Wagner and A.E. Kemppainen, *J. Am. Chem. Soc.*, **94**, 7495 (1972).
9) W. Herz and L. Tsai, *J. Am. Chem. Soc.*, **76**, 4184 (1954).

N-(3-Methyl-2-pyridyl)phthalimide (VII)——A mixture of 2-amino-3-methylpyridine (IV)[10] (2.947 g) and phthalic anhydride (4.042 g) was heated at 150° for 2 hr. The crude product obtained was recrystallized from acetone to give VII (6.12 g, 94%) as colorless needles, mp 223—225°. *Anal.* Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.73; H, 4.18; N, 11.77. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). UV λ_{max}^{EtOH} nm (ε): 263 (8000), 293 (2460). NMR ($CDCl_3$) δ: 2.26 (3H, s, Ar-CH_3). MS *m/e* (%): 238 (M^+, 100), 220 (M^+-H_2O, 6), 210 (M^+-CO, 19.5), 199 (20.5), 194 (30), 181 (26).

N-(4-Methyl-3-pyridyl)phthalimide (VIII)——A mixture of 3-amino-4-methylpyridine[11] (V) (1.435 g) and phthalic anhydride (1.97 g) was heated at 150—180° for 4 hr. Recrystallization of the resulting crude product from EtOH gave VIII (3.20 g, 88.2%) as colorless needles, mp 176.5—177°. *Anal.* Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.53; H, 4.23; N, 11.82. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). UV λ_{max}^{EtOH} nm (ε): 292 (1920). NMR ($CDCl_3$) δ: 2.24 (3H, s, Ar–CH_3). MS *m/e* (%): 238 (M^+, 100), 220 (M^+-H_2O, 84), 194 (28), 105 (22), 104 (21), 76 (66).

N-(3-Methyl-4-pyridyl)phthalimide (IX)——A mixture of 4-amino-3-methylpyridine (VI) (5.61 g) and phthalic anhydride (4.00 g) was heated at 160° for 20 hr. The crude solid obtained was recrystallized from EtOH to give IX (5.89 g, 86.5%) as colorless needles, mp 178—179.5°. *Anal.* Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.89; H, 4.31; N, 11.84. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). UV λ_{max}^{EtOH} nm (ε): 263 (4950), 293 (1940). NMR ($CDCl_3$) δ: 2.26 (3H, s, Ar–CH_3). MS *m/e* (%): 238 (M^+, 100), 220 (M^+-H_2O, 97), 210 (5), 194 (20), 130 (4), 105 (20), 76 (37).

Reduction of VII with $NaBH_4$——To a solution of VII (1.00 g) in MeOH (50 ml) was added $NaBH_4$ (160 mg) and stirred overnight at room temperature. After addition of AcOH to decompose excess reagent the resulting solution was concentrated *in vacuo*. Water was added to the residue, and the precipitates were collected by filtration and recrystallized from MeOH to give X (800 mg) as colorless needles, mp 223—225°. *Anal.* Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.89; H, 5.02; N, 11.69. IR ν_{max}^{Nujol} cm^{-1}: 3270 (OH), 1670 (C=O). UV λ_{max}^{EtOH} nm (ε): 270 (8910). NMR (CD_3OD) δ: 2.38 (3H, s, Ar–CH_3), 6.70 (1H, s, C_3–H). MS *m/e* (%): 240 (M^+, 31), 222 (M^+-H_2O, 60), 197 (100).

Reduction of VIII with $NaBH_4$——To a solution of VIII (238 mg) in EtOH (10 ml) was added $NaBH_4$ (20 mg) and stirred at room temperature for 2 hr. The resulting solution was concentrated *in vacuo* below 35° and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhyd. Na_2SO_4 and concentrated. The crude product obtained was recrystallized from EtOH to give XI (152 mg) as colorless needles, mp 208—208.5°. *Anal.* Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.10; H, 5.01; N, 11.64. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). UV λ_{max}^{EtOH} nm (ε): 251 (7250). NMR (CD_3OD) δ: 2.31 (3H, s, Ar–CH_3), 6.25 (1H, s, C_3–H). MS *m/e* (%): 240 (M^+, 100), 196 (19), 132 (59), 119 (16), 105 (80), 78 (31).

Irradiation of N-(Methylpyridyl)phthalimides (VII, VIII, IX)——A solution of phthalimide (VII, VIII or IX) (800 mg, 3.36 mmol) in acetone (500 ml) was irradiated (VII: 3.5 hr, VIII: 2.5 hr, IX: 1.5 hr) under N_2 atmosphere. The solution was evaporated *in vacuo*, the residual reaction mixture was purified by TLC or column chromatography as described below.

3-Hydroxy-2-(3-methyl-2-pyridyl)phthalimidine (X)——After irradiation the reaction mixture was separated by preparative TLC (silica gel, AcOEt) to afford the recovered VII (483 mg) and crude X which was recrystallized from MeOH to give pure X (121 mg, 14%) whose spectral (IR, NMR) and TLC behaviors were identical with those of X prepared by the reduction of VII with $NaBH_4$.

3-Hydroxy-2-(4-methyl-3-pyridyl)phthalimidine (XI) and 10b,11-Dihydro-10b-hydroxy-6*H*-pyrido[4′,3′:-4,5]pyrrolo[2,1-*a*]isoindol-6-one (XII)——The reaction mixture separated by preparative TLC (Al_2O_3, AcOEt) afforded the recovered VIII (268 mg), XI (35 mg, 4%) and XII (134 mg, 17%). The crude XI was further purified by recrystallization from EtOH to give XI (10 mg) as colorless needles, identified by comparison of IR spectrum and TLC behavior with those of an authentic sample prepared by the reduction of VIII with $NaBH_4$. The crude XII was recrystallized from MeOH to furnish colorless needles (27 mg), mp 219.5—220.5°. *Anal.* Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.45; H, 4.16; N, 11.65. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). UV λ_{max}^{EtOH} nm (ε): 229 (12910), 276 (7580). NMR (CD_3OD) δ: 3.47 (2H, s, Ar–CH_2). MS *m/e* (%): 238 (M^+, 89), 220 (M^+-H_2O, 100), 194 (22).

10b,11-Dihydro-10b-hydroxy-6*H*-pyrido[3′,4′: 4,5]pyrrolo[2,1-*a*]isoindol-6-one (XIII)——The crude product was chromatographed on silica gel with *n*-hexane–acetone (5: 2, v/v) as an eluent to afford the unreacted IX (607 mg) and XIII (71 mg, 9%) as colorless needles, mp 220.5°, by recrystallization from acetone. *Anal.* Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.57; H, 4.19; N, 11.64. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). UV λ_{max}^{EtOH} nm (ε): 229 (14350), 267 (8700), 276 (8540). NMR (CD_3OD) δ: 3.44 (2H, s, Ar–CH_2). MS *m/e* (%): 238 (M^+, 84), 220 (M^+-H_2O, 100), 194 (13).

Ethyl *o*-(1*H*-Pyrrolo[3,2-*c*]pyridin-2-yl)benzoate (XVa) and *o*-(1*H*-Pyrrolo[3,2-*c*]pyridin-2-yl)benzoic Acid (XVb)——A solution of XIII (40 mg) in EtOH (6 ml) containing conc. H_2SO_4 (3.4 mg) was refluxed for 29 hr. After addition of Na_2CO_3 (3.8 mg), the solvent was evaporated *in vacuo* and the residual mixture was extracted

10) Product of Aldrich Chemical Co.

11) *a*) H.E. Baumgarten, H. Chien-fan Su and A.L. Krieger, *J. Am. Chem. Soc.*, **76**, 596 (1954); *b*) W. Herz and D.R.K. Murty, *J. Org. Chem.*, **25**, 2242 (1960).

with CH_2Cl_2. The organic layer was washed with water, dried over anhyd. Na_2SO_4 and concentrated. The residue was separated by preparative TLC (Al_2O_3, CH_2Cl_2: EtOH=40: 3) to afford the unreacted XIII (15 mg) and crude XVa (22 mg). IR ν_{max}^{Nujol} cm^{-1}: 1723 (ester). UV λ_{max}^{EtOH} nm: 237, 265, 274, 295, 347. NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz, O-$CH_2\underline{CH}_3$), 4.21 (2H, q, J=7 Hz, O-$\underline{CH}_2CH_3$), 6.70 (1H, s, C_3-H). MS *m/e* (%): 266 (M^+, 26), 220 (M^+−EtOH, 100), 192 (13), 139 (5).

The crude XVa was readily hydrolyzed while recrystallizing from water to furnish XVb as colorless fine plates, mp 295—300.5° (dec.). *Anal.* Calcd. for $C_{14}H_{10}N_2O_2 \cdot H_2O$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.59; H, 4.62; N, 11.00. IR ν_{max}^{Nujol} cm^{-1}: 3340 (OH), 1673 (C=O), 1636, 1620, 1570. NMR (CF_3-COOD) δ: 6.73 (1H, s, C_3-H), 8.57 (1H, s, C_4-H). MS *m/e* (%): 238 (M^+, 20), 220 (M^+-H_2O, 100).

XVb was converted to XVa by treatment with EtOH-$SOCl_2$ mixture[12] at 75° overnight in good yield.

12) *cf.* M. Brenner and W. Huber, *Helv. Chim. Acta.*, **36**, 1109 (1953).