Chem. Pharm. Bull.
21(5)1118—1123(1973)

UDC 547.833.1.04 : 547.314.2.04

Studies on the Reactions of Heterocyclic Compounds. X.[1] 1,3-Dipolar Cycloaddition Reaction of Isoquinolinium Ylides and Dicyanoacetylene[2]

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(Received August 31, 1972)

The 1,3-dipolar cycloaddition of dicyanoacetylene (IIb) to isoquinolinium ylides did not give the primary adduct but the aromatized and/or isomerized products. Further, in the reaction of isoquinolinium bis(methoxycarbonyl)methylide (Ia), possibly a rearranged addition product, 1,10b-dihydropyrrolo[2,1-*a*]isoquinoline (VII), was obtained beside 2,3-dihydropyrrolo[2,1-*a*]isoquinoline (Va) and pyrrolo[2,1-*a*]isoquinoline (VIa). In the reaction of isoquinolinium cyano(methoxycarbonyl)methylide (Ib), 2,3-dihydropyrrolo[2,1-*a*]isoquinoline (VIII), formed by the liberation of a methoxycarbonyl group, was obtained in addition to VIa and pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarbonitrile (VIb).

We have already reported that the reaction of various isoquinolinium ylides (I) with dimethyl acetylenedicarboxylate (IIa) afforded 3,10b-dihydropyrrolo[2,1-*a*]isoquinolines (III) as a primary adduct, 1,10b-dihydropyrrolo[2,1-*a*]isoquinolines (IV) and 2,3-dihydropyrrolo[2,1-*a*]isoquinolines (V) both as proton migration products, and pyrrolo[2,1-*a*]isoquinolines (VI) as an aromatized product.[1,4,5]

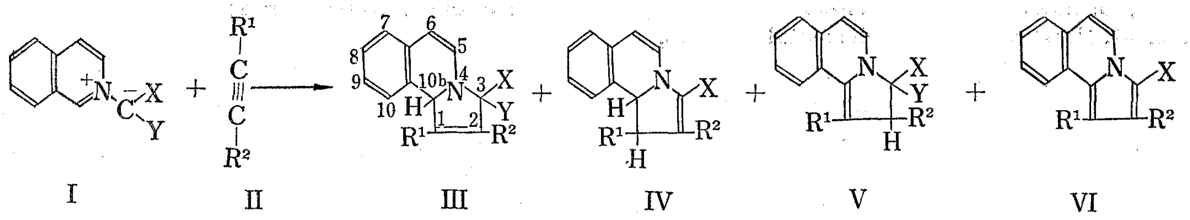

Chart 1

In the present paper, dicyanoacetylene (IIb) was used as a dipolarophile in the reaction with various isoquinolinium ylides and the effect of the substituent of the dipolarophile was examined. The results were summarized in Table I.

Reaction of isoquinolinium bis(methoxycarbonyl)methylide[6] (Ia) with IIb in a mixture of acetonitrile and dichloromethane, for 1 hr under ice cooling, afforded dimethyl 1,2-dicyano-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-3,3-dicarboxylate (Va), aromatized product (VIa), and a novel rearrangement product (VII), but the primary adduct (IIIa) was not isolated.

It is assumed that the facile formation of Va and VIa is due to the strong electron-attracting cyano group in the initially formed adduct (IIIa), which activates the hydrogen atom

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[1] Part IX: T. Kutsuma, Y. Sekine, K. Fujiyama, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2701 (1972).

[2] Presented at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971.

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[4] T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1558 (1972).

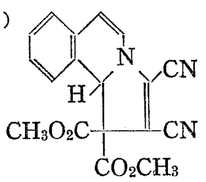
[5] T. Kutsuma, K. Fujiyama, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1809 (1972).

[6] Y. Kobayashi, T. Kutsuma, K. Morinaga, M. Fujita, and Y. Hanzawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 2489 (1970).

Table I

Starting material	X	Y	Product (%) III	IV	V	VI	VII	VIII
Ia	CO_2CH_3	CO_2CH_3	—	—	41.9	12.7	4.5[a]	
Ib	CN	CN	—	—	—	74.6		
Ic	CN	CO_2CH_3	—	—	—	10.9[b] 0.5[d]		10.3[c]
Id	H	CO_2CH_3	—	—	—	10.2		
Ie	H	CN	—	6.8	—	17		
If	H	COC_6H_5	—	—	—	20		

a)



; b) X: CN; c) V ($R^1=R^2=X=CN, Y=H$); d) X: CO_2CH_3

in 10b-position, resulting in easy isomerization and progress of elimination reaction. VIa is thought to have been formed by *cis*-elimination[5] of methyl formate from IIIa. The ultraviolet (UV) absorption spectrum of Va shows a characteristic curve of this type of compounds, having absorption maxima at 390 (ε: 7.2×10^3), 411 (ε: 8.62×10^3), and 436 nm (ε: 5.38×10^3). Treatment of Va with alumina or heating at 250° results in liberation of methyl formate to give VIa. The UV spectrum of VIa also shows a characteristic curve with maxima at 323 (ε: 8.92×10^3), 339 (ε: 9.43×10^3), and 356 nm (ε: 1.02×10^4). Heating of VII at 200° changes it into methyl 2,3-dicyanopyrrolo[2,1-*a*]isoquinoline-1-carboxylate (IX) but treatment with alumina produces no change. The UV spectrum of VII exhibits absorption at 416 nm (ε: 1.03×10^4), suggesting the possibility of its being an ylide but the ylide form cannot be accepted from the fact that its absorption is not affected by the solvent effect. The structure of IX was determined from the similarity of its UV spectral curve to those of aromatized VI's, evidence for the presence of a cyano and a carbonyl groups in its infrared (IR) spectrum, the shift of the hydrogen atom at 10-position to a lower magnetic field (δ=9.30 ppm) by magnetic anisotropic effect of the carbonyl group[7] in its nuclear magnetic resonance (NMR) spectrum, and the presence of M^+ 275 in its mass spectrum. There seems to be two possibilities for the formation of VII; one is the formation of an intramolecular three-membered ring (X) and addition of IIb to its C-N single bond, and the other is cleavage of the C-N bond in the three-membered ring followed by addition of IIb to the rearranged product. However, formation of a three-membered ring would be sterically prohibited in thermal reaction from the Woodward-Hoffmann rule,[8] while in the presence of a metal ion some rearrangement reactions are said to progress with formation of a three-membered ring.[8] An attempt was therefore made to isolate the intermediate by the presence of sodium ion as the metal ion and carrying out the reaction in dimethylformamide, but neither the objective rearrangement product nor the three-membered ring compound (X) was obtained; only diemthyl pyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (XI) and isoquinoline were found to have been formed (Chart 2).

From the formation of isoquinoline and the presence of a methoxycarbonyl group in 1-position of XI, the carbon atom in the 1-position was thought to have been derived from the second ylide (Ia). Since XI was not formed when solvents other than dimethylformamide were used, the carbon atom in 2-position of XI should have been derived from dimethylfor-

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[7] From the observation of the molecular model, both *cis* and *trans* carbonyl groups were found to be quite near the 10b-hydrogen atom.

[8] R.B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

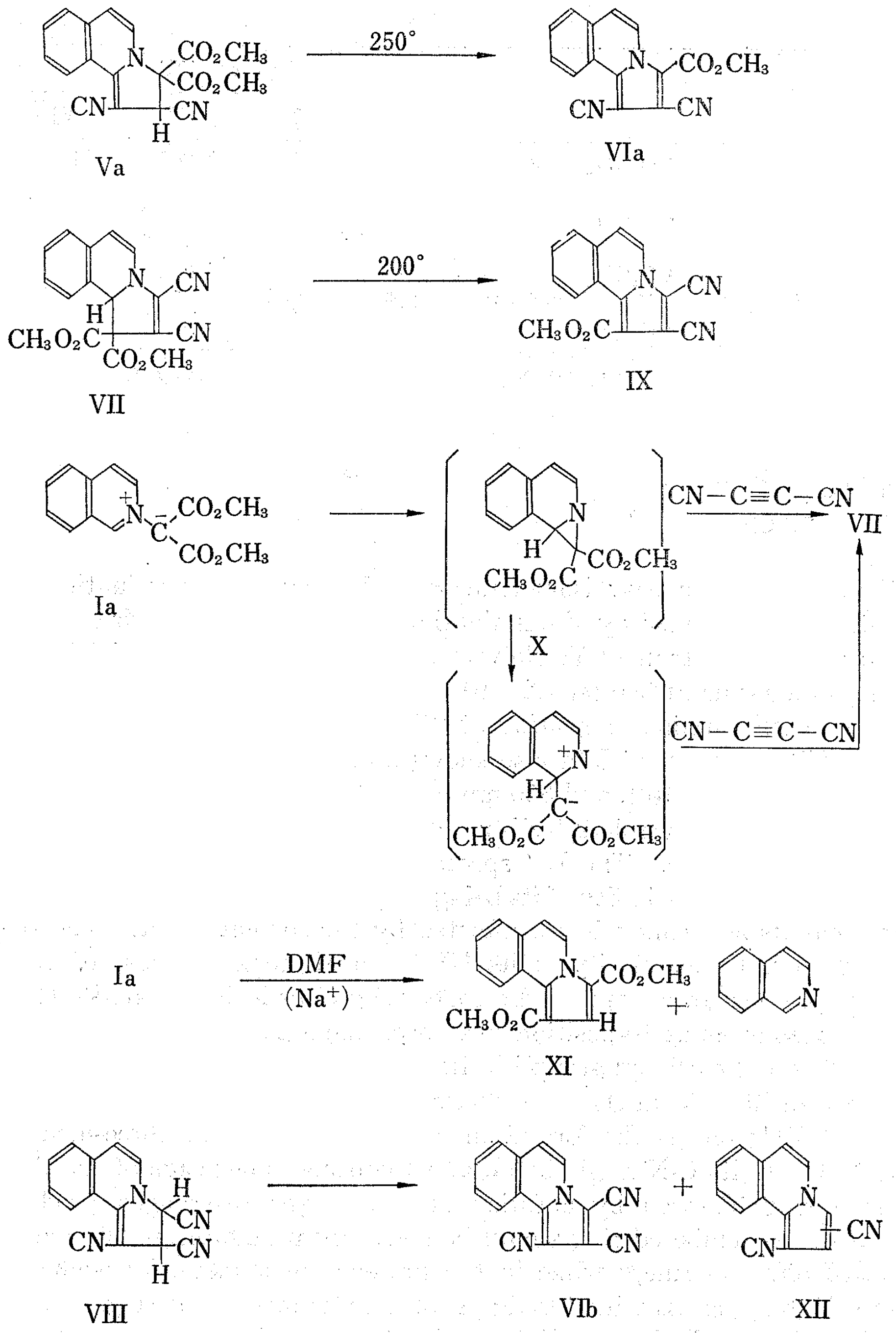

Chart 2

mamide. These results suggest that the formation of VII need not necessarily pass through intramolecular rearrangement and could have also been formed through intermolecular rearrangement.

Reaction of isoquinolinium dicyano methylide[4] (Ib) with IIb in a mixture of dimethylformamide and acetonitrile for 0.5 hr under chilling in ice-salt bath afforded only the aromatized compound (VIb) and not any primary adduct. Substitution of four cyano groups must have activated the primary adduct and accelerated the progress of isomerization reaction and aromatization.

Reaction of isoquinolinium cyano(methoxycarbonyl)methylide[4] (Ic) and IIb in a mixture of dichloromethane and acetonitrile for 1 hr under ice cooling afforded VIa, VIb and 2,3-

dihydropyrrolo[2,1-*a*]isoquinoline (VIII). The structure of VIII was determined from the similarity of its UV spectral curve to that of Va, presence of M^+ 244 in its mass spectrum, and its conversion to VIb and dicyano compound (XII) by treatment with silica gel for *ca.* 3 hr, by which dehydrogenation and elimination of hydrogen cyanide were made to progress. It is interesting that the methoxycarbonyl group liberated in the present reaction under a mild condition of being stirred at room temperature. This is probably due to the effect of the cyano group which made it easy for the methoxycarbonyl group to liberate.

Reaction of 2-(methoxycarbonylmethyl)isoquinolinium bromide (Id′) with IIb in dimethylformamide, in the presence of triethylamine for 1.2 hr under chilling with ice-salt mixture, afforded only VIa, the dehydrogenation product. This result seems to be due to the electron-attracting effect of the cyano group in 1-position of the primary adduct which activated the hydrogen atom in 10b-position and resulted in facile dehydrogenation reaction.

Reaction of 2-(cyanomethyl)isoquinolinium bromide (Ie′) with IIb in dichloromethane-acetonitrile mixture in the presence of triethylamine for 1 hr under ice cooling afforded the isomer (IVe) of the primary adduct and VIb. The UV spectrum of IVe shows a characteristic curve similar to that of VII with an absorption maximum at 410 nm. Presence of absorption in such a long wavelength region is probably due to the delocalization of the π-electrons by the presence of a cyano group in 3-position. The NMR spectrum of the 1,10b-dihydro compound (IVe) indicates that the hydrogen atoms at 1- and 10b-positions are in *cis* configuration[9] ($J_{1,10b}=16.17$ Hz).

Reaction of N-phenacylisoquinolinium bromide (If′) with IIb in acetonitrile-dichloromethane mixture in the presence of triethylamine for 1.2 hr under chilling in ice-salt mixture afforded only the aromatized compound (VIf) and not the primary adduct, as in the case of Id′. The UV spectrum of VIf was different from that of VIa and showed absorption at 379.5 nm. The structure of VIf was determined from its elemental analysis and from its IR, UV, and NMR spectra.

These results, compared with those of dimethyl acetylenedicarboxylate, showed that the strong electron-attracting cyano group promoted isomerization and elimination reaction and prevented isolation of the primary adducts. Further, a novel rearrangement and elimination reactions were observed.

Experimental[10]

Dimethyl 2,3-Dicyano-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,1-dicarboxylate (VII), Dimethyl 1,2-Dicyano-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-3,3-dicarboxylate (Va), and Methyl 1,2-Dicyanopyrrolo[2,1-*a*]-isoquinoline-3-carboxylate (VIa)——To a solution of isoquinolinium bis(methoxycarbonyl)methylide (Ia) (519 mg) dissolved in CH_2Cl_2 (20 ml), stirred with ice cooling, a solution of dicyanoacetylene (IIb) (152 mg) dissolved in MeCN (20 ml) was added dropwise, at which the mixture turned reddish black and then black by the end of the addition. The mixture was stirred for 1 hr at room temperature, CH_2Cl_2 and MeCN were evaporated under a reduced pressure, and the residue was submitted to chromatography over silica gel. Development of the silica gel column with CH_2Cl_2 afforded a mixture of VII and VIa, and Va. The mixture was separated into MeOH-soluble and -insoluble fractions, and VII was obtained from the former and VIa from the latter. Recrystallization of VII from MeOH gave 30 mg (4.5%) of orange prisms, mp 127°. IR cm^{-1}: $\nu_{C\equiv N}$ 2213, $\nu_{C=O}$ 1745 (KBr). UV λ_{max}^{MeCN} nm($\varepsilon \times 10^{-3}$): 416 (10.25). NMR ($CDCl_3$) δ: 3.58 (3H, s), 4.01 (3H, s), 5.92 (1H, d, $J=7.5$ Hz, 6-H), 6.65 (1H, d, $J=7.5$ Hz, 5-H), 7.25 (5H, m, 7-H, 8-H, 9-H, 10-H, 10b-H). Mass Spectrum *m/e*: 335 (M^+). *Anal.* Calcd. for $C_{18}H_{13}O_4N_3$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.15; H, 4.11; N, 12.57.

Recrystallization of Va from CH_2ClCH_2Cl–MeOH (1 : 2) mixture gave 209 mg (41.9%) of yellow prisms, mp 177°. IR cm^{-1}: $\nu_{C\equiv N}$ 2193, $\nu_{C=O}$ 1758 (KBr). UV λ_{max}^{MeOH} nm($\varepsilon \times 10^{-3}$); 390 (7.21), 411 (8.62), 436 (5.38). NMR ($CDCl_3$) δ: 3.92 (3H, s), 3.99 (3H, s), 5.18 (1H, s, 2-H), 6.27 (1H d, $J=7.5$ Hz, 6-H), 7.08 (1H, d, $J=$

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[9] *a*) R. Huisgen, *Angew. Chem. Internal. Edit.*, **2**, 633 (1963); *b*) A. Hassner and M.J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).

[10] All the melting points are uncorrected.

7.5 Hz, 5-H), 7.46 (3H, m, 7-H, 8-H, 9-H), 8.49 (1H, m, 10-H). *Anal.* Calcd. for $C_{18}H_{13}O_4N_3$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.40; H, 3.75; N, 12.16.

Recrystallization of VIa from CH_2ClCH_2Cl gave 70 mg (12.7%) of colorless prisms, mp 288°. IR cm^{-1}: $\nu_{C\equiv N}$ 2242, $\nu_{C=O}$ 1722 (KBr). UV λ_{max}^{MeCN} nm($\varepsilon \times 10^{-3}$): 323 (8.92), 339 (9.43), 356 (10.21). *Anal.* Calcd. for $C_{16}H_9O_2N_3$: C, 69.39; H, 3.30; N, 15.27. Found: C, 69.39; H, 3.23; N, 15.52.

Pyrolysis of Va——Va (23 mg) was heated in a microtube at 250° for *ca.* 1 min, the content was dissolved in CH_2Cl_2, and the solution was chromatographed over silica gel. Fraction eluted with CH_2Cl_2 afforded 12 mg (63.5%) of VIa, mp 288°.

Pyrolysis of VII——VII (109 mg) was heated in a microtube at 200° for *ca.* 1 min, the content was dissolved in CH_2Cl_2, and the solution was chromatographed over silica gel. The fraction eluted with CH_2Cl_2 was evaporated and the residue was recrystallized from CH_2ClCH_2Cl, affording methyl 2,3-dicyanopyrrolo[2,1-*a*]isoquinoline-1-carboxylate (IX) as cream-colored prisms, mp 218.5°. Yield, 25 mg (28%). IR cm^{-1}: $\nu_{C\equiv N}$ 2226, $\nu_{C=O}$ 1730 (KBr). NMR (d_6-DMSO) δ: 3.96 (3H, s), 7.86 (4H, m, 6-H, 7-H, 8-H, 9-H), 8.45 (1H, d, J=8.73 Hz, 5-H), 9.30 (1H, m, 10-H). Mass Spectrum m/e: 275 (M$^+$). *Anal.* Calcd. for $C_{16}H_9O_2N_3$: C, 69.81; H, 3.30; N, 15.27. Found: C, 69.60; H, 3.09; N, 15.24.

Pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarbonitrile (VIb)——To a solution of isoquinolinium dicyano methylide (Ib, 193 mg) dissolved in $HCONMe_2$ (13 ml), a solution of IIb (76 mg) dissolved in MeCN (7 ml) was added dropwise under stirring and chilling with ice-NaCl. The mixture turned reddish black and then black by the end of the addition. The mixture was stirred for further 30 min, $HCONMe_2$ and MeCN were evaporated under a reduced pressure (below 40°), and the residue was chromatographed over silica gel. The fraction eluted with CH_2Cl_2 was evaporated and the residue was recrystallized from CH_2ClCH_2Cl to give VIb as colorless needles, mp 256°. Yield, 181 mg (74.6%). IR cm^{-1}: $\nu_{C\equiv N}$ 2236 (KBr). NMR (d_6-DMSO) δ: 7.71 (1H, d, J=7.5 Hz, 6-H), 7.98 (3H, m, 7-H, 8-H, 9-H), 8.45 (1H, d, J=7.5 Hz, 5-H), 8.58 (1H, m, 10-H). *Anal.* Calcd. for $C_{15}H_6N_4$: C, 74.38; H, 2.48; N, 23.14. Found: C, 74.53; H, 2.32; N, 23.20.

2,3-Dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarbonitrile (VIII), VIa, and VIb——A solution of IIb (76 mg) dissolved in MeCN (10 ml) was added dropwise into a solution of isoquinolinium cyano(methoxycarbonyl)methylide (Ic, 226 mg) dissolved in CH_2Cl_2 (10 ml), while stirring under ice cooling, and the dark orange mixture was stirred for further 1 hr, by which some crystals were precipitated out. CH_2Cl_2 and MeCN were evaporated under a reduced pressure and the crystals were washed with MeOH and chromatographed over silica gel. The fraction eluted with CH_2Cl_2 afforded 55 mg of VIa and 50 mg of VIII. MeOH was evaporated and the residue was submitted to column chromatography over silica gel. The fraction eluted with CH_2Cl_2 gave 5.7 mg of VIa and 2.5 mg of VIb.

Recrystallization of VIII from CH_2ClCH_2Cl gave some yellow prisms. UV spectrum of VIII showed a curve similar to that of Va while its mass spectrum showed m/e 244 (M$^+$). Yield: 10.3% of VIII, 0.5% of VIa, 10.9% of VIb.

Treatment of VIII with silica gel for *ca.* 3 hr changed it to VIb and its dicyano compound (XII). IR cm^{-1}: $\nu_{C\equiv N}$ 2212 and 2232 (KBr). Mass Spectrum m/e: 217 (M$^+$).

VIa——A solution of NEt_3 (101 mg) in $HCONMe_2$ (5 ml) was added dropwise into a solution of 2-(methoxycarbonyl methyl)isoquinolinium bromide (Id′, 282.2 mg) dissolved in $HCONMe_2$ (5 ml) while stirring at room temperature. The mixture was then chilled with ice-NaCl mixture and a solution of IIb (76 mg) dissolved in $HCONMe_2$ (10 ml) was added dropwise. The mixture was stirred for 1.2 hr, purified water and ice were added, and the mixture was extracted with $CHCl_3$ (150 ml). The extract was washed with water (500 ml) and dried over Na_2SO_4, and $CHCl_3$ was evaporated under a reduced pressure. Addition of MeOH to the residue precipitated some crystals whose recrystallization from CH_2ClCH_2Cl gave VIa, mp 288°. Yield, 28 mg (10.2%).

VIb and 1,10b-Dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarbonitrile (IVe)——To a solution of 2-(cyano methyl)isoquinolinium bromide (Ie′, 249 mg) suspended in CH_2Cl_2 (7 ml), being stirred under ice cooling, a solution of NEt_3 (101 mg) dissolved in CH_2Cl_2 (3 ml) was added dropwise, then a solution of IIb (76 mg) dissolved in MeCN (10 ml) was added dropwise, and the mixture was stirred for 1 hr. CH_2Cl_2 and MeCN were evaporated under a reduced pressure, the residue was chromatographed over silica gel, and the fraction eluted with CH_2Cl_2 afforded VIb, mp 256°, and IVe, which formed orange needles, mp 171°, by recrystallization from MeOH. Yield, 17 mg (6.8%). IR cm^{-1}: $\nu_{C\equiv N}$ 2219 (KBr). Its UV spectral curve was similar to that of VII. NMR ($CDCl_3$) δ: 4.53 (1H, d, J=16.25 Hz), 5.46 (1H, d, J=16.25 Hz), 6.11 (1H, d, J=7.5 Hz, 6-H), 6.71 (1H, d, J=7.5 Hz, 5-H), 7.33 (4H, m, 7-H, 8-H, 9-H, 10-H). *Anal.* Calcd. for $C_{15}H_8N_4$: C, 73.76; H, 3.30; N, 22.94. Found: C, 73.72; H, 3.00; N, 22.69. Yield of VIb, 41.2 mg (17%).

3-Benzoylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarbonitrile (VIf)——To a suspension of N-phenacylisoquinolinium bromide (If′, 656 mg) in CH_2Cl_2 (15 ml), stirred under chilling with ice-NaCl, a solution of NEt_3 (202 mg) dissolved in CH_2Cl_2 (5 ml) was added dropwise, then a solution of IIb (152 mg) dissolved in MeCN (10 ml) was added dropwise, and the mixture was stirred for 1.2 hr. CH_2Cl_2 and MeCN were evaporated under a reduced pressure (below 40°) and addition of MeOH to the residue precipitated some crystals. The crystals were collected by filtration and chromatographed over silica gel and the fraction eluted by CH_2Cl_2

gave VIf. Yield, 128.6 mg (20%). IR cm^{-1}: $\nu_{C\equiv N}$ 2221, $\nu_{C=O}$ 1644 (KBr). UV λ_{max}^{EtOH} nm: 375. *Anal.* Calcd. for $C_{21}H_{11}ON_3$: C, 78.49; H, 3.45; N, 13.08. Found: C, 78.40; H, 3.38; N, 13.15.

Dimethyl Pyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (XI)——NaCl (29 mg) was added to a solution of Ia (130 mg) dissolved in $HCONMe_2$ (10 ml) and the mixture was stirred at 106—121° for 22 hr. The mixture was passed through a column of silica gel and the fraction eluted by CH_2Cl_2 afforded XI, mp 214.5°, and isoquinoline. Yield of XI, 2 mg (1.4%). IR cm^{-1}: $\nu_{C=O}$ 1711 (KBr). Its UV spectral curve was similar to that of VIa. NMR (CF_3COOH) δ: 4.08 (3H, s), 4.10 (3H, s), 7.10 (1H, d, $J=7.5$ Hz, 6-H), 7.88 (4H, m, 2-H, 7-H, 8-H, 9-H), 8.93 (1H, d, $J=7.5$ Hz, 5-H), 9.08 (1H, m, 10-H). *Anal.* Calcd. for $C_{16}H_{13}O_4N$: C, 67.84; H, 4.63; N, 4.95. Found: C, 68.15; H, 4.56; N, 4.89. Yield of isoquinoline, 17 mg (25.9%).

Acknowledgement We express our sincere gratitude to the analytical center of our college for elemental analyses and mass spectrum measurement and to Dr. A. Ohsawa of our laboratory for his helpful suggestions.