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# Studies on the Reactions of Heterocyclic Compounds. VI.[1] 1,3-Dipolar Cycloaddition Reaction of Disubstituted Methylides of Isoquinoline and Pyridine with Acetylenic Compounds[2]

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Tetramethyl 3,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate (VI) was isolated for the first time as the primary addition product of a reaction between isoquinolinium bis(methoxycarbonyl)methylide (V) and dimethyl acetylenedicarboxylate (IV). Treatment of VI with hydrogen chloride and then with potassium carbonate resulted in its isomerization into 2,3-dihydropyrrolo[2,1-*a*]isoquinoline derivative (VII). In the reaction of isoquinolinium dicyanomethylide (XI) with IV, the isomerized 2,3-dihydro compound (XIII) and the eliminated product (XIV) were produced, instead of their primary adduct (XII). The relation between a substituent group in the 2,3-dihydro-type compounds and their reactivity was examined. On the other hand, in the reaction of disubstituted pyridinium methylides with acetylenic compounds, only aromatized products were obtained.

There have been many reports published on 1,3-dipolar cycloaddition reaction of nitrogen ylides of aromatic amines with acetylenic esters. However, all the products isolated were not the primary adduct (I), but compounds (II) formed by 1,4-elimination[1,4] or other compounds (III) formed by recyclization to a six-membered ring.[5] Consequently, there can be found no report on the isolation of a primary adduct (I) of an ylide and a dipolarophile.

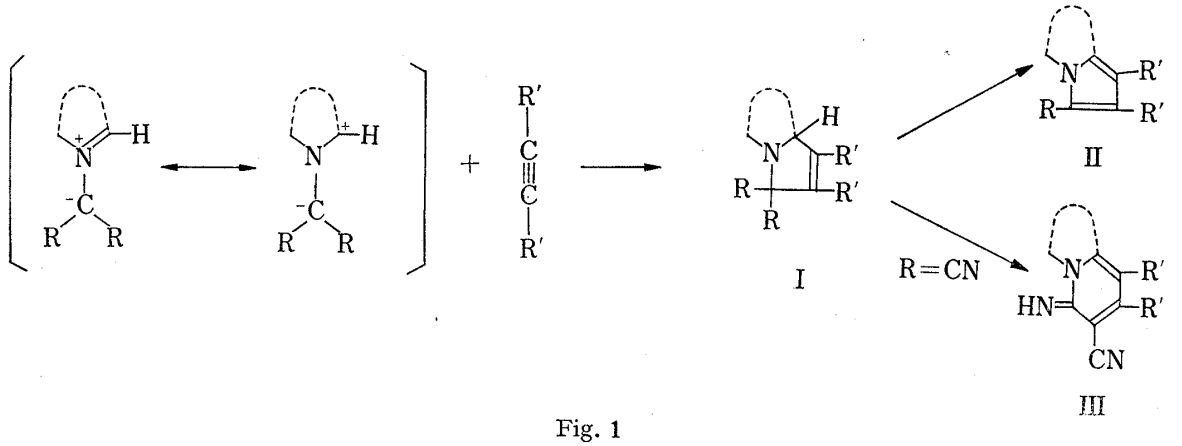



Fig. 1

We have succeeded in separating the primary adduct, or at least its isomer retaining the five-membered ring, by the reaction of isoquinolinium ylides with dimethyl acetylenedicarboxylate (IV). With pyridinium ylides, however, these products could not be isolated.

1) Part V: Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **19**, 2106 (1971).
2) Presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April 1969.
3) Location: *Kitashinjuku-3, Shinjuku-ku, Tokyo, 160, Japan* (All requests are to be sent to this author); *a*) Present Address: *Research Laboratories, Ohta Seiyaku Co., Ltd., Namiki-cho, Kawaguchi, Saitama-ken, 332, Japan.*
4) C.A. Henrick, E. Rittie, and W.C. Taylor, *Aust. J. Chem.*, **20**, 2467 (1967).
5) *a*) W.J. Linn, O.W. Webster, and R.E. Benson, *J. Am. Chem. Soc.*, **87**, 3651 (1965); *b*) V. Boeckelheide and N.A. Fedoruk, *J. Am. Chem. Soc.*, **90**, 3830 (1968).

When isoquinolinium bis(methoxycarbonyl)methylide[6] (V) was treated with IV in acetonitrile, the primary adduct (VI) was obtained besides a small amount of yellow crystals (VII) and colorless crystals (VIII). The structures of VI and VII were respectively assigned as tetramethyl 3,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate and tetramethyl 2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate from their ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR) and mass spectra. The structure of VIII was found to be trimethyl pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate from its melting point, UV[7] and NMR[8] spectra which agreed with those in literature. The structures of VI, VII, and VIII can also be explained from reactions described below without any contradiction. By following the reaction with the UV spectrum, we found that VI was initially formed and that it was converted into VII and VIII during the separation process. When VI was dissolved in benzene and dry hydrogen chloride was saturated in this solution, an oily product (IX) precipitated. The UV spectrum of IX agreed fairly well with that of 2-bis(methoxycarbonyl)methylisoquinolinium bromide (X).[6] When IX was treated with aqueous potassium carbonate, 2,3-dihydrocompound (VII) was obtained. A small amount of triester (VIII) was obtained from the benzene layer after IX was separated.

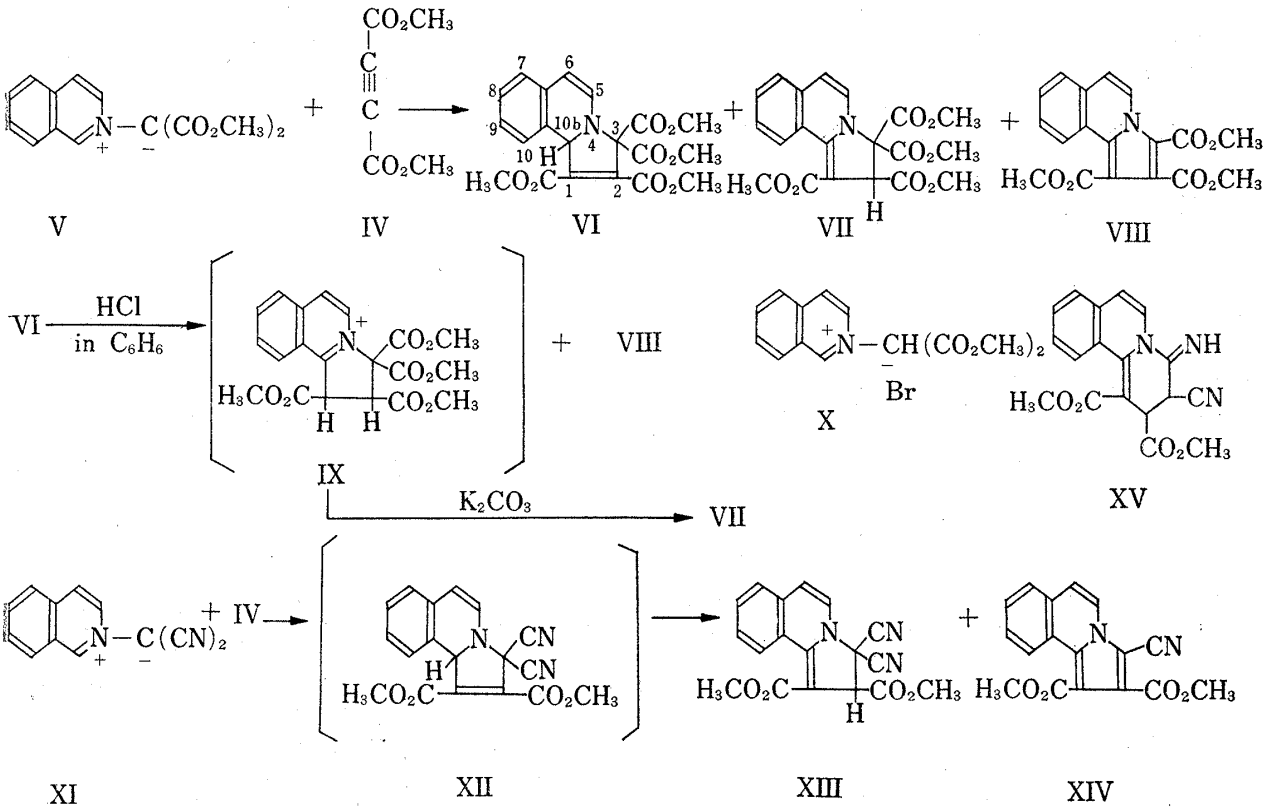



Chart 1

On the other hand, a similar reaction of isoquinolinium dicyanomethylide (XI) with IV afforded yellow crystals (XIII) of type VII and colorless crystals (XIV) after elimination of hydrogen cyanide in approximately 1:1 ratio, instead of the primary adduct (XII). This can be attributed to the effect of two strongly electronegative cyano groups at 3-position of the adduct (XII) formed first, which activated the hydrogen atom at 10b-position on isomeri-

6) Y. Kobayashi, T. Kutsuma, K. Morinaga, M. Fujita, and Y. Hanzawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 2489 (1970).
7) R.H. Wiley and L.H. Knabeschuk, *J. Org. Chem.*, **18**, 836 (1953).
8) R.M. Acheson and D.A. Robinson, *J. Chem. Soc.* (*C*), **1968**, 1633.

zation or elimination reaction. Although the above reaction was already reported by Linn, Webster, and Benson,[5a] they assigned a different formula (XV) to the yellow crystals (XIII). The NMR spectrum of XIII (*cf.* Table I) shows a singlet signal at $\delta$ 4.675, which is not affected by treatment with deuterium oxide, and its NMR and UV spectra are quite similar to those of the tetraester (VII), both facts supporting the formula XIII and denying the

Table I. NMR Spectra[a] of Dihydropyrrolo [2,1-*a*] isoquinolines and Pyrrolo [2,1-*a*] isoquinolines

| Compound | Solvent[b] | Chemical shift ($\delta$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_1$ | $H_2$ | $H_3$ | $H_5$ | $H_6$ | $H_7$ | $H_8$ | $H_9$ | $H_{10}$ | $H_{10}$[b] |
| VI | C | — | — | — | 6.48 | 5.82 | 7.16——6.80 | | ($H_7$-$H_{10}$) | | 5.88 |
| VII | C | — | 4.94 | — | 7.03 | 6.27 | 7.31 | 7.52 | 7.35 | 9.68 | — |
| XIII | C | — | 4.67 | — | 6.88 | 6.45 | 7.35 | 7.60 | 7.46 | 9.72 | — |
| XVI | C | — | 4.33 | 4.87 | 6.80 | 6.27 | 7.33 | 7.52 | 7.37 | 9.80 | — |
| XVII | DM | — | 4.57 | — | 7.26 | 6.57 | 7.70——7.40 | | ($H_7$-$H_9$) | 9.72 | — |
| XVIII | DM | — | 3.84 | 4.86 | 7.13 | 6.42 | 7.62——7.30 | | ($H_7$-$H_9$) | 9.73 | — |
| XXI | C | — | 4.93 | — | 7.08 | 6.27 | 7.34 | 7.45 | 7.40 | 9.68 | — |
| XXIII | DM | — | 4.54 | — | 7.23 | 6.54 | 7.70——7.42 | | ($H_7$-$H_9$) | 9.66 | — |
| XXIV[h] | TFA | 5.73 | 5.16 | — | 8.93 | 8.55——8.15 | | ($H_6$-$H_{10}$) | | | — |
| | | 5.67 | 5.04 | — | 8.69 | 8.55——8.15 | | ($H_6$-$H_{10}$) | | | — |
| XXV[i] | TFA | 5.82 | 4.76 | 6.52 | 8.78——8.15 | | ($H_5$-$H_{10}$) | | | | — |
| | | 5.83 | 4.78 | 6.64 | 8.78——8.15 | | ($H_5$-$H_{10}$) | | | | — |
| VIII | C | — | — | — | 9.27 | 7.19 | 7.75——7.50 | | ($H_7$-$H_9$) | 9.41[j] | — |
| XXII | C | — | — | — | 9.32 | 7.27 | 7.75——7.60 | | ($H_7$-$H_9$) | 9.44[j] | — |

| Compound | Other signal | Coupling constant (Hz) |
|---|---|---|
| VI | 3.91 3.82 3.99 3.54 ($CH_3$)[c] | $J_{5,6}$=7.5 |
| VII | 3.84 3.82 3.70 3.68 ($CH_3$)[c] | $J_{5,6}=J_{7,8}=J_{8,9}=J_{9,10}$=7.5; $J_{8,10}$=2.0 |
| XIII | 3.86 3.74 ($CH_3$)[c] | $J_{5,6}=J_{7,8}=J_{8,9}=J_{9,10}$=7,5; $J_{8,10}$=2.5 |
| XVI | 3.80 3.74 3.70 ($CH_3$)[c] | $J_{2,3}$=4.0; $J_{5,6}=J_{7,8}=J_{8,9}=J_{9,10}$=7.5; $J_{8.10}$=2.5 |
| XVII | 3.72 ($CH_3$)[c] 8.21 7.89 ($NH_2$)[d] *ca.* 12.0 (NH)[e] | $J_{5,6}$=7.5 |
| XVIII | 3.72 ($CH_3$)[c] 7.77 7.62 7.28 7.05 ($NH_2$)[d] | $J_{2,3}$=4.0; $J_{5,6}$=7.5; $J_{9,10}$=7.5 |
| XXI | 3.88 3.86 ($CH_3$)[c] 1.26 1.24 ($CH_3$)[f] 4.18 4.14 ($CH_2$)[g] | $J_{5,6}=J_{7,8}=J_{8,9}=J_{9,10}$=7.5; $J_{8,10}$=2,0; $J_{CH_3\text{-}CH_2}$=7.0 |
| XXIII | 1.28 ($CH_3$)[f] 4.18 ($CH_2$)[g] 8.18 7.90 ($NH_2$)[d] *ca.* 12.0 (NH)[e] | $J_{5,6}=J_{9,10}$=7.5; $J_{8,10}$=2.0; $J_{CH_3\text{-}CH_2}$=7.5 |
| XXIV[h] | 4.05 4.01 3.89 3.86 ($CH_3$)[c] | $J_{1,2}$=2.0; $J_{5,6}$=7.5 |
| | 4.14 4.03 4.00 3.88 ($CH_3$)[c] | $J_{1,2}$=9.0; $J_{5,6}$=7.5 |
| XXV[i] | 4.05 4.03 3.87 ($CH_3$)[c] | $J_{1,2}$=1.7; $J_{2,3}$=2.0 |
| | 4.10 4.03 3.87 ($CH_3$)[c] | $J_{1,2}$=9.2; $J_{2,3}$=2.0 |
| VIII | 3.96 3.90 3.90 ($CH_3$)[c] | $J_{5,6}$=7.5 |
| XXII | 1.43 1.40 ($CH_3$)[f] 4.46 4.44 ($CH_2$)[g] | $J_{5,6}$=7.5; $J_{CH_3\text{-}CH_2}$=7.0 |

*a*) All the spectra were measured at 100 MHz by JNM-4H-100 spectrometer (Japan Electron Optics Lab. Co., Ltd.) in *ca.* 5% (w/v) solution with TMS as an internal standard.
*b*) abbreviation: C-$CDCl_3$; DM DMSO-$d_6$; TFA $CF_3COOH$.
*c*) methyl group of methyl ester
*d*) broad signal
*e*) very broad signal
*f*) methyl group of ethyl ester
*g*) methylene group of ethyl estrer
*h*) VII in TFA Contribution of trans form ($J_{1,2}$=9.0 Hz) is about 85% and that of cis form ($J_{1,2}$=2.0 Hz) about 15% by evaluation of area of the signals.
*i*) XVI in TFA Contribution of trans form ($J_{1,2}$=9.2 Hz) is about 83% and that of cis form about 17% by evaluation of the siganls.
*j*) multiplet

formula XV. The same effect of 3-substituents (-COOMe and -CN) as mentioned above on different stability of the primary adducts (VI and XII) was also observed in the cases of 2,3-dihydrocompounds, VII and XIII.

Although tetraester (VII) is stable against heat (180—200°) and weak bases (*e.g.* alumina or dilute aqueous ammonia), its cyano derivative (XIII) was instantly converted into an aromatized compound by elimination of hydrogen cyanide when treated under the same conditions. The above difference is plainly due to the difference in electron-withdrawing effect of the substituent at 3-position, ester group, or (and) cyano group towards the hydrogen atom at 2-position. Esterification of XIII in methanol saturated with hydrogen chloride, to obtain the tetraester (VII) resulted in the formation of a triester (XVI) instead.[9] Since the tetraester (VII) is stable under the same condition, the change from XIII to XVI was not *via* VII. XVI can be obtained by treating the tetraester (VII) with one molar equivalent of sodium hydroxide in methanol. NMR spectrum of XVI showed two doublets at $\delta$ 4.33 and 4.87 and from their coupling constant value[10] ($J$=4.0 Hz), the hydrogen atoms at 2- and 3-positions are in *trans*.

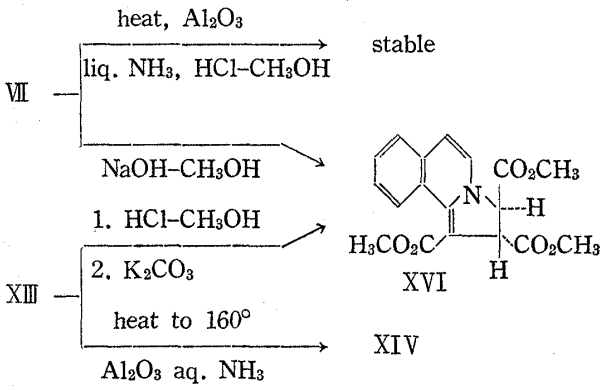



Chart 2

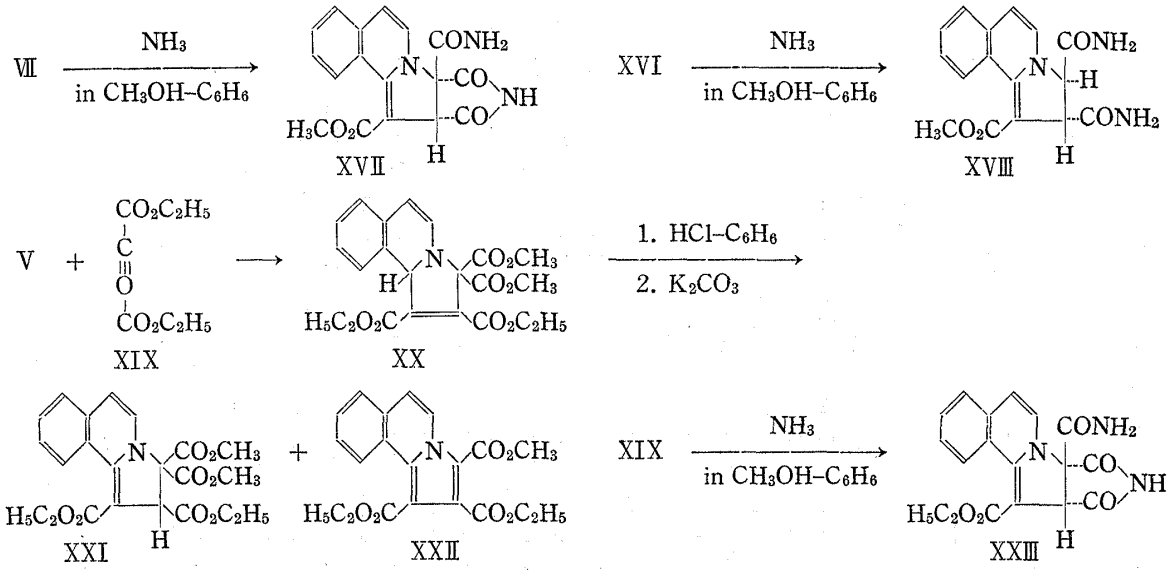



Chart 3

While an imido-ester (XVII) was obtained by the treatment of VII with ammonia in methanol, a similar treatment of XVI gave a diamide (XVIII), thereby proving chemically that hydrogen atoms at its 2- and 3-positions are in *trans*.

9) Trimethyl 2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (XVI) was reported to have been obtained from the reaction of 2-(methoxycarbonyl)methylisoquinolinium bromide with IV by a group (D.G. Farnum, R.J. Alaime, and J.M. Dunston, *J. Org. Chem.*, **32**, 1130 (1967) in the presence of triethylamine. However, its melting point and UV, IR, and NMR spectra did not agree with those of XVI obtained here. Further investigation of this difference will be reported in the next paper.

10) *a*) Huisgen has reported that *cis* and *trans* coupling constants between two hydrogen atoms at 4- and 5-positions of dimethyl 1,3-diphenyl-2-pyrazoline-4,5-dicarboxylate are 13 and 4.5 Hz, respectively. R. Huisgen, *Angew. Chem. Internal. Edit.*, **2**, 633 (1963); *b*) A. Hassner and M.J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).

TABLE II. Ultraviolet and Infrared Spectra of Dihydropyrrolo[2,1-*a*]isoquinolines and Pyrrolo[2,1-*a*]isoquinolines

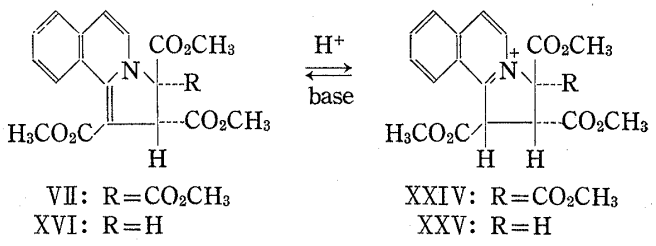
| Compound | UV spectrum | | | | | | | | | | IR spectrum | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Solvent[a] | $\lambda_{max}$ nm $10^{-4}$ | | | | | | | | | Condition | $\nu_{CN}$ | $\nu_{CO}$ | | | | $\nu_{C=C}$ |
| VI | E | 311 | 225[b] | | | | | | | | KBr | — | 1755 | 1738 | | | |
| | | 9.50 | 15.70[b] | | | | | | | | | | | | | | |
| VII | E | 441[b] | 420 | 400[b] | 358 | 344[b] | 298 | 288 | 260 | 219 | $CHCl_3$ | — | 1768 | 1758 | 1743 | 1685 | 1528 |
| | | 8.20 | 11.60 | 9.30[b] | 7.80 | 6.70[b] | 11.20 | 9.30 | 8.60 | 35.00 | | | | | | | |
| | EA[c] | 353 | 344 | 285 | 275[b] | 242 | | | | | | | | | | | |
| | | 4.90 | 4.90 | 3.46 | 3.10[b] | 48.00 | | | | | | | | | | | |
| | TFA[c] | 353 | 343 | 296[b] | 285 | 275[b] | | | | | | | | | | | |
| | | 3.40 | 3.45 | 1.18[b] | 2.75 | 2.35[b] | | | | | | | | | | | |
| X | E | 348 | 338 | 280 | 270[b] | 263 | | | | | | | | | | | |
| | | 4.88 | 4.70 | 3.90 | 3.65[b] | 46.00 | | | | | | | | | | | |
| XIII | E | 436[b] | 415 | 396[b] | 359 | 344 | 326[b] | 297 | 288 | 264 | 220 | $CHCl_3$ | — | 1755 | 1695 | | | 1538 |
| | | 4.65[b] | 7.00 | 6.10[b] | 6.10 | 5.70 | 4.10[b] | 10.40 | 9.70 | 14.00 | 34.40 | | | | | | | |
| XVI | E | 440[b] | 419 | 400[b] | 364 | 298 | 288 | 262 | 220 | | | $CHCl_3$ | — | 1750 | 1680 | | | 1518 |
| | | 8.60[b] | 12.20 | 10.00[b] | 8.10 | 11.00 | 8.10 | 7.50 | 36.80 | | | KBr | — | 1753 | 1730 | 1655 | | 1513 |
| | EA[d] | 348 | 338 | 284 | 273 | 239 | | | | | | | | | | | | |
| | | 4.84 | 4.70 | 2.80 | 2.65 | 47.40 | | | | | | | | | | | | |
| XXI | E | 440[b] | 421 | 401[b] | 360 | 344[b] | 298 | 290[b] | 260 | | | $CHCl_3$ | — | 1768 | 1758 | 1743 | 1680 | 1528 |
| | | 8.40 | 11.20 | 8.80 | 7.30 | 6.60 | 10.90 | 9.00 | 8.30 | | | KBr | — | 1770 | 1756 | 1743 | 1682 | 1528 |
| VIII | E | 354 | 337 | 315 | 287 | 270 | 241 | 222.5 | | | | $CHCl_3$ | — | 1745 | 1713 | | | — |
| | | 13.20 | 12.20 | 10.00 | 24.00 | 46.50 | 20.90 | 19.70 | | | | | | | | | | |
| XIV | AN | 359 | 343 | 320 | 264 | 244[b] | | | | | | $CHCl_3$ | 2220 | 1740 | 1733 | | | — |
| | | 7.00 | 7.90 | 6.50 | 48.00 | 23.40[b] | | | | | | | | | | | | |
| XXII | E | 355 | 339 | 316 | 288 | 271 | 242 | 222 | | | | $CHCl_3$ | — | 1740 | 1716 | 1710 | | — |
| | | 11.70 | 10.90 | 9.00 | 23.60 | 46.30 | 21.60 | 20.50 | | | | | | | | | | |

*a*) abbreviation: E 95% EtOH; EA 0.1 N HCl–EtOH; TFA $CF_3COOH$; AN acetonitrile
*b*) numerals indicate inflexion
*c*) VII in acidic ethanol or trifluoroacetic acid takes a structure shown as XXIV.
*d*) XVI in acidic ethanol takes a structure shown as XXV.

The position of the ester group in XVII which was not converted to an amide was determined as 1-position from the structure of the imido-ester (XXIII) obtained by a similar treatment of the ethyl ester (XXI). The NMR spectra of the pyrrolo[2,1-*a*]isoquinolines are shown in Table I, and their IR and UV spectra, in Table II.

It was found that 2,3-dihydro-esters (VII and XVI) take the respective isoquinolinium structures (XXIV and XXV) under acidic condition from the resemblance of their UV spectra in ethanol to that of 2-bis(methoxycarbonyl)methylisoquinolinium bromide (X). These spectra returned to those in neutral medium when the acidic solution was neutralized with ammonia. UV spectrum of VII in trifluoroacetic acid also agreed with that in acidic ethanol. NMR spectrum also supports the assumption that VII and XVI take the isoquinolinium structure (XXIV and XXV) in trifluoroacetic acid. Protonation of VII and XVI was found to occur at 1-position (Table I).

The UV spectra of 2,3-dihydro-pyrrolo[2,1-*a*]isoquinolines (VII, XIII, XVI, and XXI) have three specific absorption bands with inflexions in longer wavelength regions (from 400 to 440 nm) than those of pyrrolo[2,1-*a*]-isoquinolines (VIII, XIV, and XXII). As regards their IR spectra, dihydro derivatives have a conjugated ester carbonyl group and specific absorptions which can be assigned to the enamino-ester grouping[11] in regions of 1680—1695 and 1518—1538 $cm^{-1}$ (strongest absorption bands). Their NMR spectra show that the proton at 10-position is strongly deshielded by the ester group at 1-position.




VII: R=$CO_2CH_3$
XVI: R=H

XXIV: R=$CO_2CH_3$
XXV: R=H

Chart 4

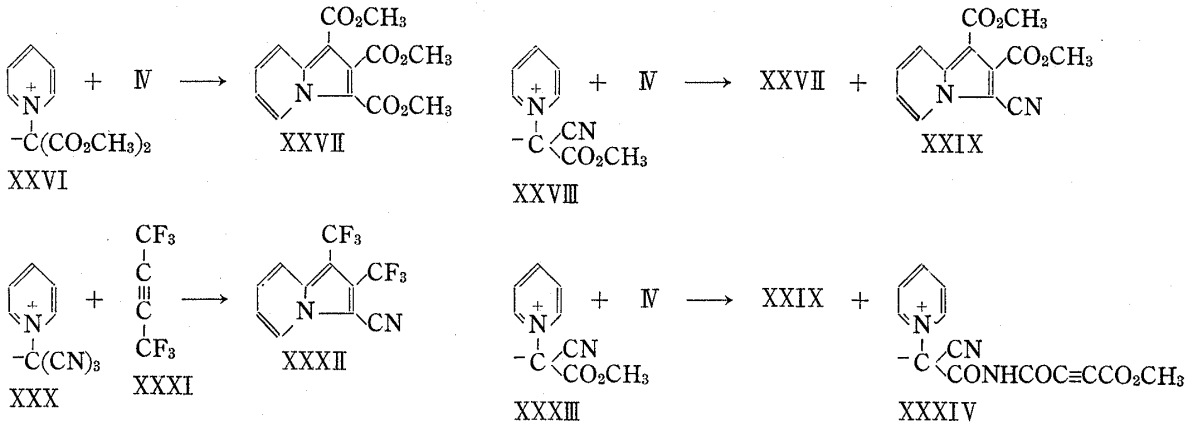



Chart 5

Pyridinium ylides[6] (XXVI, XXVIII, XXX, and XXXIII) gave corresponding indolizines (XXVII, XXIX, and XXXII) when treated with acetylenic compounds (IV and XXXI) after elimination of methyl formate or hydrogen cyanide depending on the structure of ylides.

In the reaction of asymmetrically disubstituted methylide (XXVIII) with IV, 1,4-elimination of the primary adduct was found to give XXVII with elimination of hydrogen cyanide and XXIX with that of methyl formate in about 1: 1.5 ratio.

In the reaction of pyridinium carbamoylcyano-methylide (XXXIII) with IV, an ylide (XXXIV), which was simply formed by condensation of XXXIII and IV, was produced

11) R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966); Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2230 (1969).

besides cyanoindolizine (XXIX). The structure of XXXIV was determined by elemental analysis, and from its UV, IR, and NMR spectra.

The above results show that the dihydro-type indolizines cannot exist with stability; that is, the benzene part of isoquinoline ring contributes to the stabilization of dihydro-type compounds.

## Experimental[12]

**Reaction of Isoquinolinium Bis(methoxycarbonyl)methylide (V) with Dimethyl Acetylenedicarboxylate (IV)**——To a solution of V (0.259 g) in $CH_2Cl_2$ (10 ml), a solution of IV (0.142 g) in $CH_3CN$ was added dropwise with stirring under ice cooling and the mixture was allowed to stand overnight at room temperature. The UV spectrum of the reaction mixture showed absorption at only 311 nm (broad). Concentration of the reaction mixture *in vacuo* gave an orange residue, which was chromatographed over $SiO_2$ (25 g) using $CH_2Cl_2$ as a solvent. From the first fraction (40 ml), a pale yellow resinous substance (0.30 g) was obtained, which crystallized by addition of MeOH. Rectysrallization from MeOH (2 ml) gave tetramethyl 3,10b-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate (VI) as pale yellow prisms (0.243 g), mp 111—112°. *Anal.* Calcd. for $C_{20}H_{19}O_8N$: C, 59.85; H, 4.77; N, 3.49. Found: C, 59.73; H, 4.89; N, 3.51. Mol. wt. Calcd.: 401. Found: 401 (by mass analysis).

From the second fraction (60 ml), a pale yellow resinous substance (0.067 g) was obtained. Its recrystallization from MeOH (1 ml) gave VIII as colorless needles (0.012 g), mp 150—151°. *Anal.* Calcd. for $C_{18}H_{15}O_6N$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.22; H, 4.47; N, 3.97.

When the mother liquor of VIII was allowed to stand, yellow crystals (0.008 g), mp 140—142°, were obtained. Recrystallization from 90% EtOH gave tetramethyl 2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate (VII) as yellow prisms, mp 145—146°. *Anal.* Calcd. for $C_{20}H_{19}O_8N$: C, 59.85; H, 4.77; N, 3.49. Found: C, 59.71; H, 4.73; N, 3.44. Mol. wt. Calcd.: 401. Found: 401 (by mass analysis.).

**Trimethyl Pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (VIII) and Tetramethyl 2,3-Dihydropyrrolo-[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate (VII)**——VI (0.060 g) was dissolved in dry benzene and dry HCl gas was passed through it, the solution changed from yellow to colorless, and pale yellow oil precipitated. The oil and the benzene layer were separated by decantation, and the latter was washed with dil. $K_2CO_3$ and then with $H_2O$, and dried over $MgSO_4$. Evaporation of benzene *in vacuo* afforded faintly yellow crystals (0.004 g). Recrystallization from MeOH gave colorless needles, mp 150—151°. It was identified with VIII, obtained from the reaction of V with IV, by mixed melting point and comparison of IR spectra.

The oil separated from the benzene layer was dissolved in $CH_2Cl_2$ and neutralized with dil. $K_2CO_3$, by which the pale orange solution became yellow. After the solution was washed with $H_2O$ and dried over $MgSO_4$, $CH_2Cl_2$ was evaporated to give a yellow residue (0.055 g), which solidified on addition of MeOH. Recrystallization from MeOH gave yellow prisms (0.046 g), mp 145—146°. It was identified with VII, obtained from the reaction of V and IV, by a mixed fusion and comparison of IR spectra.

**Reaction of Isoquinolinium Dicyanomethylide (XI) and Dimethyl Acetylenedicarboxylate (IV)**——To a suspension of XI[5a] (0.97 g) in $CH_3CN$ (60 ml), IV (0.71 g) in $CH_3CN$ (5 ml) was added with stirring at room temperature. After about 20 min, all the solid was dissolved and then new crystals began to precipitate out. The reaction mixture was allowed to stand overnight at room temperature, and pale pink crystals were collected by filtration and washed with cold $CH_3CN$ to give the desired object (0.80 g), mp 224—225°. Recrystallization from ethylene dichloride gave colorless prisms (XIV), mp 224—225° (reported[5a] mp 228—228.5°).

After the removal of XIV, the filtrate was concentrated to give a resinous orange substance (0.79 g), which crystallized when warmed with EtOH. Recrystallization from EtOH afforded orange-yellow needles (XIII), mp 156—157° (reported[5a] mp 154.5—155.5°, whose structure has been reported as XV). *Anal.* Calcd. for $C_{18}H_{13}O_4N_3$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.40; H, 3.80; N, 12.56. Mol. wt. Calcd.: 335. Found: 335 (by mass analysis).

**Dimethyl 3-Cyanopyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (XIV)**——i) When heated at 160—170°, XIII (0.030 g) melted and instantly bubbled violently. After the bubbling was over, the content solidified. Recrystallization of the solid from ethylene dichloride with active carbon afforded colorless crystals (0.020 g), mp 224—225°.

ii) XIII (0.050 g) was dissolved in EtOH (5 ml) with warming and dil. aq. $NH_3$ (0.1 ml) was added. Instantly, colorless crystals precipitated out, which were collected and washed with EtOH to colorless crystals (0.41 g), mp 223—224°.

iii) A solution of XIII (0.050 g) in $CHCl_3$ was passed through $Al_2O_3$ (5 g) column and colorless crystals (0.042 g), mp 224—225°, were obtained.

12) All the melting points are uncorrected.

The crystals obtained by methods (i), (ii), and (iii) were identified with XIV, obtained from the reaction of XI with IV, mentioned above, by mixed melting point and comparison of IR spectra.

**Trimethyl 2,3-*trans*-Dihydropyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (XVI)**——i) A solution of XIII (0.15 g) in abs. MeOH (10 ml) was saturated with dry HCl gas at room temperature and allowed to stand overnight. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ice water. The aqueous solution was neutralized with aq. $K_2CO_3$ and the crystals produced were extracted with benzene. The extract was dried over $Na_2SO_4$ and concentrated to afford yellow crystals. Recrystallization from MeOH gave yellow prisms (XVI, 0.12 g), mp 155—156°. *Anal.* Calcd. for $C_{18}H_{17}O_6N$: C, 62.97; H, 4.99; N, 4.08. Found: C, 62.83; H, 4.98; N, 4.18. Mol. wt. Calcd.: 343. Found: 343 (by mass analysis).

ii) To a solution of Na (0.06 g) in abs. MeOH (5 ml) with $H_2O$ (0.047 ml), a solution of the tetraester (VII, 1.0 g) in abs. MeOH (45 ml) was added and allowed to stand for 30 min at room temperature. The reaction mixture was poured into ice water and the precipitated crystals were extracted with $CH_2Cl_2$ to give a yellow solid (0.44 g). Recrystallization from MeOH afforded yellow prisms, mp 155—156°, undepressed by admixture with XVI obtained by method (i).

**Methyl 3-Carbamoyl-2,3-(iminodicarbonyl)pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (XVII)**——A solution of VII (0.40 g) in MeOH–benzene (30 ml, 3:2) was saturated with dry $NH_3$ gas in an ice bath and allowed to stand overnight at 0°. Concentration of the solution under a reduced pressure gave a yellow solid, which was washed with cold acetone to afford fine yellow crystals (XVII, 0.23 g), mp 225.5° (decomp.). A sample for elemental analysis was prepared by dissolving the crystals in pyridine and reprecipitating it by the addition of petr. ether. Its melting point did not change. *Anal.* Calcd. for $C_{17}H_{13}O_5N_3$: C, 60.17; H, 3.86; N, 12.39. Found: C, 60.07; H, 3.90; N, 12.33.

**Methyl 2,3-*trans*-Dicarbamoyl-2,3-dihydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate (XVIII)**——A solution of XVI (0.28 g) in MeOH–benzene (40 ml, 3:1) was saturated with dry $NH_3$ gas under ice cooling. After the same treatment as with XVII, yellow crystals of XVIII (0.10 g), mp 190—190.5°, were obtained. *Anal.* Calcd. for $C_{16}H_{15}O_4N_3$: C, 61.33; H, 4.83; N, 13.41. Found: C, 60.97; H, 4.66; N, 13.09.

**1,2-Diethyl 3,3-Dimethyl 2,3-Dihydro-pyrrolo[2,1-*a*]isoquinoline-1,2,3,3-tetracarboxylate (XXI) and 1,2-Diethyl 3-Methyl Pyrrolo[2,1-*a*]isoquinoline-1,2,3-tricarboxylate (XXII)**——A solution of V (1.30 g) and diethyl acetylenedicarboxylate (XIX, 0.85 g) in MeCN (30 ml) was stirred for 2 hr at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in $CH_2Cl_2$ and passed through a column of $SiO_2$ (10 g) to remove a brown resinous substance. A reddish orange resinous substance (2.05 g) obtained was dissolved in benzene (50 ml) and dry HCl gas was passed into the solution to separate the reddish orange oil from the benzene layer. The oil dissolved in $CH_2Cl_2$ was washed with aq. dil. $K_2CO_3$ solution and then with $H_2O$ and dried over $Na_2SO_4$. Evaporation of $CH_2Cl_2$ *in vacuo* afforded a reddish orange resinous oil (1.32 g), which solidified on addition of MeOH. Recrystallization from MeOH (20 ml) afforded yellow needles (XXI), mp 139°. *Anal.* Calcd. for $C_{22}H_{23}O_8N$: C, 61.53; H, 5.40; N, 3.26. Found: C, 65.13; H, 5.26; N, 3.85.

The benzene layer separated from XXI was washed with aq. solution of $NaHCO_3$ and dried over $Na_2SO_4$. Evaporation of benzene *in vacuo* afforded a reddish orange resinous oil (0.69 g), which solidified on addition of MeOH. Recrystallization from MeOH afforded faintly yellow needles (XXII, 0.12 g), mp 120°. *Anal.* Calcd. for $C_{20}H_{19}O_6N$: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.13; H, 5.26; N, 3.85.

**Ethyl 3-Carbamoyl-2,3-dihydro-2,3-(iminodicarbonyl)pyrrolo[2,1-*a*]isoquinoline-1-carboxylate (XXIII)**——A solution of XXI (0.15 g) in MeOH–benzene (15 ml, 2:1) was treated in the same way as XVI to afford yellow crystals (XXIII, 0.015 g), mp 220° (decomp.). *Anal.* Calcd. for $C_{18}H_{15}O_5N_3$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.80; H, 4.13; N, 11.93.

**Trimethyl 1,2,3-Inodolizinetricarboxylate (XXVII)**——The ylide[6] (XXVI, 1.05 g) and IV (0.71 g) were stirred in MeCN (10 ml) at room temperature for 3 hr. The dark red residue obtained after the evaporation of MeCN was chromatographed over $Al_2O_3$ (70 g) with benzene to give a pale yellow solid (0.39 g). Recrystallization from MeOH afforded colorless needles, mp 148—149° (reported[4] mp 146—147°). *Anal.* Calcd. for $C_{14}H_{13}O_6N$: C, 57.73; H, 4.50; N, 4.82. Found: C, 57.72; H, 4.49; N, 4.93. NMR ($CDCl_3$) $\delta$: 9.48 (1H, d, $J_{5,6}$=7.0 Hz, $H_5$), 8.34 (1H, d, $J_{7,8}$=9.0 Hz, $H_8$), 7.36 (1H, m, $H_7$), 7.03 (1H, m, $H_6$), 3.97 (3H, s, $CH_3O_2C$), 3.87 (6H, s, 2 $CH_3O_2C$).

**Reaction of Pyridinium Cyano(methoxycarbonyl)methylide (XXVIII) with IV**——A mixture of the ylide[5a,6] (XXVIII, 1.76 g) and IV (1.42 g) in MeCN was allowed to stand at room temperature for 6 hr and then concentrated *in vacuo*. The dark brown resinous oil was chromatographed three times over $Al_2O_3$ (100 g) with benzene–cyclohexane (2:1). From the faster moving yellow band, colorless crystals (XXIX, 0.48 g), mp 127—129°, were obtained, whose recrystallization from MeOH gave crystals of mp 130—131°. This substance was identified by mixed melting point and comparison of IR spectra with dimethyl 3-cyanoindolizine-1,2-dicarboxylate obtained by the procedure of Linn and others[5a] with pyridinium dicyanomethylide (XXX) and IV.

From the slower moving pale yellow-orange band, colorless crystals (0.32 g), mp 135—140°, were obtained. Recrystallization from MeOH gave colorless needles, mp 148—149°. The substance was identified with the triester (XXVII) obtained from the reaction of XXVI with IV by mixed melting point.

**1,2-Bis(trifluoromethyl)indolizine-3-carbonitrile (XXXII)**——A solution of the ylide[5a] (XXX, 0.72 g) in MeCN (15 ml) was charged into an autoclave with hexafluoro-2-butyne (XXXI, *ca.* 1.5 ml) liquefied with dry ice–acetone under dry ice–acetone chilling and the mixture was stirred for 20 hr at room temperature. The reaction mixture was concentrated and the residue was distilled *in vacuo*. A faintly yellow liquid distilled at 130—134°/8 mmHg, which, on cooling, solidified (mp 83—85°). Recrystallization from hexane afforded colorless needles (XXXII), mp 85—85.5°. NMR ($CDCl_3$) $\delta$: 8.41 (1H, d, $J_{5,6}=6.8$ Hz, $H_5$), 7.89 (1H, d, $J_{7,8}=9.5$ Hz, $H_8$), 7.40 (1H, dd, $J_{6,7}=7.5$, $J_{7,8}=9.5$ Hz, $H_7$), 7.16 (1H, dd, $J_{5,6}=6.8$, $J_{6,7}=7.5$ Hz, $H_6$). *Anal.* Calcd. for $C_{11}H_4N_2F_6$: C, 47.49; H, 1.45; N, 10.07. Found: C, 47.18; H, 1.62; N, 10.00.

**Reaction of Pyridinium Carbamoylcyanomethylide (XXXIII) with IV**——To a suspension of the ylide[6] (XXXIII, 0.81 g) in 50% MeOH (10 ml), a solution of IV (0.72 g) in MeOH (5 ml) was added with stirring in an ice bath. The solid gradually dissolved. After stirring was continued for 10 hr, the dark red solution was poured into ice water (50 ml), and the precipitated colorless crystals were collected and recrystallized from MeOH to colorless needles (0.26 g), mp 130—131°. This substance was identified with XXIX obtained from XXVIII and IV by mixed melting point.

The dark red filtrate separated from XXIX as above was concentrated *in vacuo* and a reddish orange solid (1.15 g) was recrystallized from AcOH (15 ml) to yellow needles (XXXIV, 0.14 g), mp 274—275° (decomp.). NMR (DMSO-$d_6$) $\delta$: 10.43 (1H, s, NH), 9.01 (2H, d, $J_{2,3}=7.5$ Hz, $H_2$ and $H_6$), 8.66 (1H, t, $J_{3,4}=J_{4,5}=7.5$ Hz, $H_4$), 8.08 (2H, t, $J_{2,3}=J_{3,4}=7.5$ Hz, $H_3$ and $H_5$), 3.66 (3H, s, $CH_3O_2C$). UV $\lambda_{max}^{95\%EtOH}$ nm($\varepsilon$): 449 (12700), 254 (15400). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3150—3000 (NH), 2210 (CN), 1742 ($CO_2CH_3$), 1660 ($CONH_2$). *Anal.* Calcd. for $C_{13}H_9O_4N_3$: C, 57.56; H, 3.34; N, 15.48. Found: C, 57.42; H, 3.62; N, 15.46.

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