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Studies on Pyridazines. XVIII.[1] Cyanation of 3,3'-Bipyridazines and Their N-Oxides *via* Their Quaternary Salts

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The reaction of quaternary salts of 3,3'-bipyridazines and their N-oxides with cyanide ion was carried out. 3,3'-Bipyridazine 1,1'-dioxides (I, II) gave the dihydro compounds having cyano groups at α-positions to the N-oxide groups (IV, V). The bipyridazines without N-oxide groups (VII, VIII) afforded the dihydro compounds having cyano groups at γ-positions to the N-CH_3 groups (X, XI). And 6,6'-dimethoxy-3,3'-bipyridazine (IX) afforded 1,1'-dimethyl-3,3'-bipyridazine-6,6'(1H,1'H)-dione (XII). As for the 2,2'-dioxide (III), the compound composed of both the dihydro type ring and the aromatic ring formed by the elimination of the methoxy group (VI), was obtained.

In the previous papers, we have reported the syntheses[3] of 3,3'-bipyridazines, N-oxidation of them, and the reactions of the N-oxides.[4] The present paper describes the reactions of quaternary salts of the bipyridazines and their N-oxides with cyanide ion.

As for the cyanation of the monomeric pyridazine N-oxides, the Reissert method[5] by means of benzoyl chloride–KCN, and Okamoto's method[6] by means of dimethyl sulfate–KCN have been examined. And subsequently, it has been reported[7] that when the pyridazine 1-oxides unsubstituted at the 6-positions, were submitted to these cyanation reactions, α-positions to the N-oxide groups were sensitive, affording the 6-cyanopyridazines.

Application of Reissert reaction to the several 3,3'-bipyridazine N-oxides resulted in the recovery of the starting materials, presumably due to their slight solubility in benzoyl chloride.

Using Okamoto's method, we obtained the corresponding Reissert compounds.

A mixture of the bipyridazine N-oxides and a large excess of dimethyl sulfate was heated and then an excess dimethyl sulfate was removed by extraction with ether. The quaternary

1) Part XVII: H. Ogura, S. Sugimoto, H. Igeta and T. Tsuchiya, *J. Heterocyclic Chem.*, in press.
2) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
3) Part XIV: H. Igeta, T. Tsuchiya, C. Okuda and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 1228 (1970).
4) Part XV: H. Igeta, T. Tsuchiya, C. Okuda and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 1347 (1970).
5) A. Reissert, *Ber.*, **38**, 1603, 3415 (1905).
6) T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 130, 925 (1959).
7) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **11**, 1472 (1963); M. Ogata, *ibid.*, **11**, 1522 (1963).

salts thus obtained were dissolved in a small amount of water, to which a solution of KCN was added with stirring under ice cooling.

Accoring to the procedure described above, 3,3′-bipyridazine 1,1′-dioxide (I), 6,6′-dimethyl-3,3′-bipyridazine 1,1′-dioxide (II), and 6,6′-dimethoxy-3,3′-bipyridazine 2,2′-dioxide (III) afforded 1,1′-dimethoxy-6,6′-dicyano-1,1′,6,6′-tetrahydro-3,3′-bipyridazine (IV), mp 90—92°, 1,1′-dimethoxy-6,6′-dicyano-6,6′-dimethyl-1,1′,6,6′-tetrahydro-3,3′-bipyridazine (V), mp 120—122°, and 2′,6,6′-trimethoxy-5,5′-dicyano-2′,5′-dihydro-3,3′-bipyridazine (VI), mp 166—167°, respectively. And the yields of them were about 10—20%.

The reactions of these N-oxides and dimethyl sulfate proceeded with difficulty and heating the mixture at 100—120° rendered the whole dark, and led to the lowering of the yields. But the reaction readily completed in 1 hr at 60—70° by addition of a small amount of water to the mixture.

The reaction of the quaternary salt and KCN in a water solution, finished in several minutes below 0°. The higher temperature, or the prolonged reaction time, caused the decomposition under evolution of gases, lowering the yield of the product.

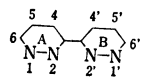
These dihydro compounds thus obtained were relatively unstable in the solution. In benzene gradually, and in MeOH or water rapidly, they decomposed to tarry substances.

Then, the similar procedure was applied to the bipyridazines without N-oxide groups. 3,3′-Bipyridazine (VII) gave 1,1′-dimethyl-4,4′-dicyano-1,1′,4,4′-tetrahydro-3,3′-bipyridazine (X), mp 160° (40—50%). And 6,6′-dimethoxy-3,3′-bipyridazine (IX) gave 1,1′-dimethyl-3,3′-bipyridazine-6,6′ (1H,1′H)-dione (XII), mp 240° (70%).

Table I. NMR Spectral Data[a)]

Compound	H_4	H_5	H_6	Miscellaneous (δ)		cps
IV	6.32	7.69	5.53	N-OCH_3	4.10	$J_{4,5}=12.0$, $J_{5,6}=16.0$
V	6.45	7.43	—	C-CH_3	2.06	$J_{4,5}=12.0$
				N-OCH_3	4.09	
X	4.73	4.73	6.30	N-CH_3	3.36	$J_{4,5}=15.0$, $J_{5,6}=6.0$
XI	4.65	4.58	—	C-CH_3	1.95	$J_{4,5}=12.0$
				N-CH_3	3.38	
XII	6.91	7.92	—	N-CH_3	3.80	$J_{4,5}=10.0$
	H_4	$H_{4'}$	$H_{5'}$			
VI	7.80	8.65	6.12	C-OCH_3	4.26	$J_{4',5'}=12.0$
				N-OCH_3	3.96	

a) 60 M/C in $CDCl_3$ with TMS as internal reference



The 4-cyano dihydro compounds (X, and XI) were more stable than the 5- and 6-cyano compounds (IV—VI).

Except XII, infrared (IR) spectra of these compounds exhibited absorption bands at around 2200 cm^{-1} due to the cyano groups.

As shown in Table I, except the case of VI, nuclear magnetic resonance (NMR) spectra of these compounds show the simple pattern, indicating the symmetrical structures, which were also confirmed by elemental analyses and molecular weight determination.

Thus, concerning the symmetrical compounds, discussion will conveniently be made on half moieties of the molecules, *i.d.*, on the rings A.

Since the signal (1H) at 7.69δ of the spectrum of IV is quartet, the common signals at around 6.4δ (1H) and 7.5δ (1H) of the spectra of IV and V, are apparently due to H_4 and H_5.

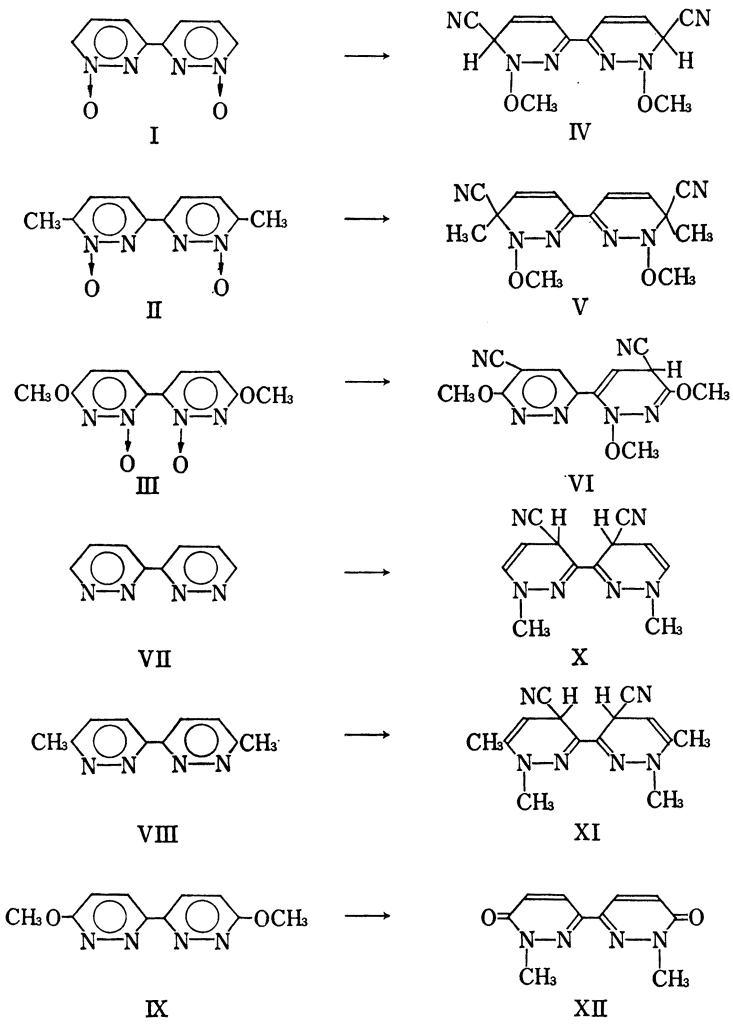


Chart 1

Accordingly, the signal at 5.53δ (d, J=16.0 cps) of IV, is due to $H_{(6)}$. Besides, the values of the chemical shifts of methyl protons and the coupling constants support the correctness of these structures, indicating the introduction of the cyano groups in the 6-positions.

Moreover, should these compounds be 4-cyano compounds, the signals of $H_{(5)}$-protons must be observed at higher field (4.5—5.0δ) because of the enamine structures, which are similar to those of the compounds X and XI. But, in fact, the signals are observed at lower field, the assumption of 4-cyano dihydro structures should be excluded.

The signal at 7.80δ (s) of the spectrum of VI is assigned to $H_{(4)}$, whose value is reasonable compared with those of $H_{(4)}$ and $H_{(5)}$ of pyridazines.[8]

The relative lower field shifts of $H_{(4')}$ and $H_{(5')}$ of B rings are presumably due to the effects of A rings.

In the case of X and XI, the relative higher field shift of $H_{(5)}$, as shown in Table I, is considered to be due to a increase of the electron density at $C_{(5)}$ on acocoun tof the effect of $N_{(1)}$.

8) K. Tori and M. Ogata, *Chem. Pharm. Bull.* (Tokyo), **12**, 272 (1964).

These values of the chemical shifts are approximately coincident with those of 3-cyano-1,4-dihydropyridines[9] and cyclic enol ethers.[10]

The assumption of 6-cyano dihydro structures for them has been disproved becasuse of the higher field shift of $H_{(5)}$. Furthermore, the assumption of $N_{(2)}$ $-CH_3$ and $C_{(5)}$ $-CN$ structures for them must also be abandoned because of the value of $J_{4,5}$ (6.0 cps) and of the higher field shift of the methyl protons at $C_{(6)}$.

IR spectrum of XII exhibited the strong absorption band at 1665 cm^{-1} (amide) and that of NMR showed the similar pattern to that of 2-methyl-3-(1H)-pyridazone.[11]

Thus, it is interestingly concluded that, regardless of the presence of the substituents, the 1,1'-dioxides afford the compounds having cyano groups at α-positions to the N-oxide groups. And the bipyridazines without N-oxide groups give the compounds having cyano groups at γ-positions to the $N\text{-}CH_3$ groups, regardless of the presence of the substituents at α-positions. Moreover, as for the 2,2'-dioxides, they afford the compounds composed of both the dihydro type rings and the aromatic rings formed by the elimination of the methoxyl groups.

Further investigations on the cyanation reaction are now underway.

Experimental

1,1'-Dimethoxy-6,6'-dicyano-1,1',6,6'-tetrahydro-3,3'-bipyridazine (IV)——To a solution of I (300 mg) and dimethyl sulfate (3 ml) a few drops of water were added and the whole was warmed at 50—60° for 0.5—1 hr to a clear solution. After cool, an excess dimethyl sulfate was removed by extraction with ether. To a solution of the quaternary salt dissolved in water (5 ml) a saturated aqueous solution of KCN (1.5 moles equivalents) was added dropwise in 1—2 minutes at −5—0° with stirring. Stirring was continued for further 1—2 minutes and the reaction mixture was extracted with CH_2Cl_2. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* below 40°. The crude thus obtained was dissolved in a small amount of CH_2Cl_2 and passed through a column of alumina. The solvent was again evaporated in vacuo and the residue was recrystallized from benzene to crystals, mp 90—92° (90 mg). *Anal.* Calcd. for $C_{12}H_{12}O_2N_6$: C, 52.93; H, 4.44; N, 30.89. Found: C, 52.68; H, 4.64; N, 30.39.

1,1'-Dimethoxy-6,6'-dicyano-6,6'-dimethyl-1,1',6,6'-tetrahydro-3,3'-bipyridazine (V)——This compound was prepared by the procedure quite similar to that described for IV. The residue was recrystallized from benzene to crystals, mp 120—122° (120 mg from 300 mg of II). *Anal.* Calcd. for $C_{14}H_{16}O_2N_6$: C, 55.99; H, 5.37; N, 27.99. Found: C, 55.72; H, 5.52; N, 28.18.

2',6,6'-Trimethoxy-5,5'-dicyano-2',5'-dihydro-3,3'-bipyridazine (VI)——The compound (III, 400 mg) was treated quite similarly to the procedure described for IV. The residue was recrystallized from AcOEt to crystals, mp 166—167° (160 mg). *Anal.* Calcd. for $C_{13}H_{12}O_3N_6$: C, 52.00; H, 4.03; N, 27.99. Found: C, 51.89; H, 4.11; N, 27.92.

1,1'-Dimethyl-4,4'-dicyano-1,1',4,4'-tetrahydro-3,3'-bipyridazine (X)——The compound (VII, 400 mg) was treated quite similarly to the procedure described for IV. The residue was recrystallized from AcOEt to crystals, mp 160° (210 mg). *Anal.* Calcd. for $C_{12}H_{12}N_6$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.76; H, 5.14; N, 34.67.

1,1',6,6'-Tetramethyl-4,4'-dicyano-1,1',4,4'-tetrahydro-3,3'-bipyridazine (XI)——The compound (VIII, 300 mg) was treated quite similarly to the procedure described for IV. The residue was recrystallized from AcOEt to crystals, mp 187° (200 mg). *Anal.* Calcd. for $C_{14}H_{16}N_6$: C, 62.66; H, 6.02; N, 31.32. Found: C, 62.55; H, 6.02; N, 31.24.

1,1'-Dimethyl-3,3'-bipyridazine-6,6'(1H,1'H)-dione (XII)——The compound (IX, 400 mg) was treated quite similarly to the procedure described for IV. The residue was recrystallized from benzene to crystals, mp 240° (280 mg). *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.22; H, 4.60; N, 25.51.

9) S. Yamada, M. Kuramoto, and Y. Kikugawa, *Tetrahedron Letters*, **1969**, 3101.
10) L.M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.
11) H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 763 (1969).