142~143°, NMR (nuclear magnetic resonance) peak at 6.21τ (1H, heptet, J_{ae}=5 c.p.s., J_{aa}=10 c.p.s). On the other hand, reduction of Ⅳ with a large excess of aluminum isopropoxide in benzene at 40° for 15 min. gave a mixture of Va, Ⅵa and the starting material (Ⅳ) in a ratio of 52:41:7. Acetylation of the mixture with acetic anhydride-pyridine followed by column chromatography on silica gel gave the acetate (Vb), m.p. 105°, NMR peak at 5.08τ (1H, heptet, J_{ae}=5 c.p.s., J_{aa}=10 c.p.s.), and the oily acetate (Ⅵb), NMR peak at 4.76τ (1H, quintet, $J_{ae}=J_{ee}$=3 c.p.s). Hydrolysis with sodium hydroxide converted Vb to Va and Ⅵb to Ⅵa, m.p. 142~143°, NMR peak at 5.78τ (1H, quintet, $J_{ae}=J_{ee}$=3 c.p.s.). Compounds (Va) and (Ⅵa) were treated with dimethyl sulfate and potassium hydroxide and then potassium iodide to give the methiodides (Ⅶ), m.p. 221~223° and (Ⅷ), m.p. 210~212°, respectively. The latter methiodide (Ⅷ) was found to be identical (infrared spectrum in chloroform) with the methiodide of Ⅲ.

The stereochemistry of compounds (V) and (Ⅵ) follows from comparison of the chemical shifts and coupling constants[5] of C-2 proton in their NMR spectra and also from the above mentioned behavior of the amino ketone (Ⅳ) towards the reducing agents.[6]

Parello, *et al.*[7] have recently isolated a new alkaloid, phyllanthine ($C_{14}H_{17}O_3N$, m.p. 96~98°, $[\alpha]_D$ −898°), from the roots of *Phyllanthus discoides*, suggesting the partial structure (Ⅸ).

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Reaction of Oxazoles with Dienophiles

We have recently shown that 4-methyloxazole (I) was treated with several dienophiles to afford 3-unsubstituted (type A) and 3-hydroxylated pyridine derivatives (type B and C).[1] Similar results were observed independently by Osbond.[2] The present communication deals with behaviors of some oxazole derivatives toward such reactants and with mechanism of the reactions.

1) T. Yoshikawa, F. Ishikawa, Y. Omura, T. Naito: This Bulletin, **13**, 873 (1965). cf. T. Naito, T. Yoshikawa, F. Ishikawa, Y. Omura: Japan. Pat., 65-22740 (Appl. 1963), 65-23908 (Appl. 1963).
2) J.M. Osbond: Fr. Pat., 1,343,270 (1963), (C.A., **60**, 11991 (1964)), Japan. Pat., 65-6466 (Appl. 1962).

As oxazole derivatives were employed the following seven compounds, *i.e.* I, 2,4-dimethyloxazole (II), 4-methyl-5-ethoxyoxazole (III), ethyl 4-methyl-5-oxazolecarboxylate (IV), 4-methyl-5-oxazolecarbonitrile (V), 4-methyl-5-oxazolecarboxylic acid (VI) and 2-amino-4,5-dimethyl oxazole (VII), and as dienophiles were used the following seven compounds, *i.e.* maleic anhydride (VIII), fumaronitrile (IX), acrylonitrile (X), diethyl maleate (XI), diethyl fumarate (XII), ethyl acrylate (XIII), and N-phenylmaleimide (XIV). The experiments described below refer to reaction of the oxazoles with the dienophiles and in each case the results are summarized in the following order : dienophile employed, product (yield), (type).

Reaction of II with dienophiles : VIII, 2,6-dimethyl-3,4-pyridinedicarboxylic acid (57%), (A); IX, 5-hydroxy-2,6-dimethyl-nicotinonitrile, (XV), (55%), (B); X, 2,6-dimethyl-3-pyridinol (8%), (B) and XV (2%), (C); XII, diethyl 5-hydroxy-2,6-dimethyl-3,4-pyridinedicarboxylate, (XVI), (7%), (C); XIII, ethyl 5-hydroxy-2,6-dimethyl-nicotinate, (XVII), (13%), (C).

Reaction of III with dienophiles : IX, 5-hydroxy-6-methyl-3,4-pyridinedicarbonitrile (24%), (C);X, 2-methyl-3-pyridinol, (XVIII), (PPC*[1]), (B), 2-methyl-3-hydroxyisonicotinonitrile, (XIX), (44%), (C) and 5-hydroxy-6-methylnicotinonitrile, (XX), (PPC), (C) ; XI, ethyl 5-hydroxy-6-methylnicotinate, (XXI), (PPC), (B) and diethyl 5-hydroxy-6-methyl-3,4-pyridinedicarboxylate, (XXII), (75%), (C) ;XII, XXI (PPC), (B) and XXII (60%), (C); XIII, ethyl 2-methyl-3-hydroxyisonicotinate, (XXIII), (67%), (C).

Reaction of IV with dienophiles : XI, XXII (trace), (C) ;XII, XXI (PPC), (B), XXII (PPC), (C) and diethyl 2-methyl-3,5-pyridinedicarboxylate, (XXIV), (trace), (D).

Reaction of V with dienophiles : IX, XX (PPC), (B) ;XI, XXI (6%), (B) and XXII (2%), (C); XII, XXI (4%), (B) and XXII (2%), (C) ;XIII, XXI (35%), (C).

Reaction of VI with dienophiles : IX, XX (PPC), (B) ;X, XVIII (6%), (B), XX (4%), (C) and XIX (trace), (C) ;XI XXI (trace), (B) and XXII (2%), (C); XII, XXI (trace), (B) and XXII (8%), (C); XIII, XXI (8%), (C) and XXIII (PPC), (C).

All above reactions were carried out in acetic acid, and the products were characterized by comparison with authentic sample except unknown compounds, *i.e.* XV, XVI, XIX, XXIII, and XXIV.

Product (XV), $C_8H_8ON_2$, m.p. 249~251°, IR ν_{max}^{KBr} cm^{-1} : 2230 (C≡N), was confirmed to be 5-hydroxy-2,6-dimethylnicotinonitrile by esterification with ethanolic hydrogen chloride to XVII. Alkaline hydrolysis of compound (XVI), $C_{13}H_{17}O_5N \cdot HCl$, m.p. 145~147°, to 5-hydroxy-2,6-dimethyl-3,4-pyridinedicarboxylic acid gave evidence for XVI being diethyl 5-hydroxy-2,6-dimethyl-3,4-pyridinedicarboxylate. Product (XIX), $C_7H_6ON_2$, m.p. 233°, IR ν_{max}^{KBr} cm^{-1} : 2200 (C≡N), or product (XXIII), $C_9H_{11}O_3N$, m.p. 51~54°, IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O), was considered to be 2-methyl-3-hydroxyisonicotinonitrile or ethyl 2-methyl-3-hydroxyisonicotinate because of their disagreement with isomeric XX or XXI, respectively. Identity of compound (XXIV), $C_{12}H_{15}O_4N$, m.p. 60~64°, IR ν_{max}^{KBr} cm^{-1} : 1720 (C=O), with diethyl 2-methyl-3,5-pyridinedicarboxylate was established by comparison with a specimen synthesized from diethyl 2-oxo-6-methyl-1,2-dihydro-3,5-pyridinedicarboxylate *via* diethyl 2-chloro-6-methyl-3,5-pyridinedicarboxylate, $C_{12}H_{14}O_4NCl$, m.p. 52~55°, and XXIV was recognized as a product of new type (type D).

Previous investigations concerned with the reaction between III,[3] IV[4] or V[5] and dienophiles have described formation of either compounds classified into type A or type C as the products. The results mentioned above, however, clarified that the

*1 The abbreviation " PPC " expresses the amount of compounds which were detected by paper partition chromatography of reaction mixture.

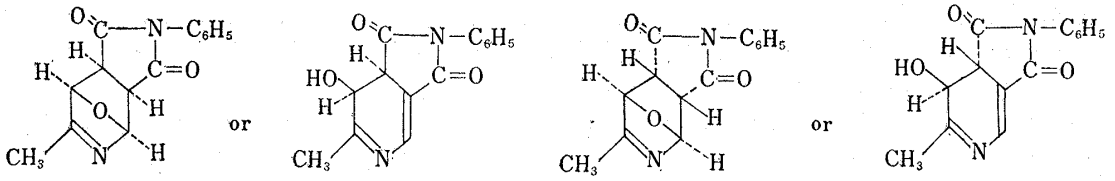
3) E. E. Harris, *et al.* : J. Org. Chem., **27**, 2705 (1962).

4) G. Ya. Kondrat'eva, Ch.-H. Huang : Doklady Akad. Nauk S. S. S. R., **142**, 593 (1962).

5) W. Kimel, W. Leimgruber : Fr. Pat., 1,384,099 (1965), (C. A., **63**, 4263 (1965)).

reaction was capable of producing the compounds of four types (type A, B, C and D) and afforded actually one, two or three products depending on oxazoles and dienophiles; thus, the scope of this reaction is more extensive than described before.

The following experiments refer to isolation of intermediates and aromatisation of them to pyridine derivatives. Ⅶ reacted with Ⅸ in ether solution to give an adduct (XXV), $C_{10}H_{10}ON_4 \cdot H_2O$, m. p. 168°, IR ν_{max}^{KBr} cm^{-1} : 3430, 3340, 3240 (O—H and N—H), 2240 (w.) (aliphatic C≡N), 2150 (s.) (conjugated aliphatic C≡N), 1625, 1605 (C=N and C=C), which was assigned to be 2-amino-5-hydroxy-5,6-dimethyl-4,5-dihydro-3,4-pyridinedicarbonitrile according to its analytical data and infrared spectrum. Treatment of XXV with mixture of acetic anhydride and pyridine produced an aromatized compound (XXVI), $C_9H_8N_4$, m. p. 235°, whose diazotization in aqueous acetic acid yielded an oxo-compound (XXVII), $C_9H_7ON_3$, m. p. 283° (decomp.), IR ν_{max}^{KBr} cm^{-1} : 2220 (C≡N), 1660 (C=O). The properties of XXVII resembled to those of 2-oxo-5-ethyl-6-methyl-1,2-dihydro-3,4-pyridinedicarbonitrile,[6] so XXVI or XXVII was considered to be 2-amino-5,6-dimethyl-3,4-pyridinedicarbonitrile (type A) or 2-oxo-5,6-dimethyl-1,2-dihydro-3,4-pyridinedicarbonitrile, respectively.



XXVIII XXIX

Chart 1.

I was refluxed with XIV in ethyl acetate for 8 hours to yield an adduct (XXVIII) as fine powder, $C_{14}H_{12}O_3N_2 \cdot H_2O$, m. p. 172~174° (decomp.). When the same reaction was carried out at room temperature for 3 days, another adduct (XXIX), $C_{14}H_{12}O_3N_2 \cdot H_2O$, m.p. 170~180° (decomp.), was obtained as hard layer sticked on a wall of vessel. Aromatisation of XXVIII or XXIX was effected by heating both in acetic acid and in nitrobenzene, in any cases, the former compound afforded N-phenyl-6-methyl-3,4-pyridinedicarboximide (XXX), $C_{14}H_{10}O_2N_2$, m. p. 172°, IR ν_{max}^{KBr} cm^{-1}: 1780, 1705 (C=O), (type A), and the latter gave N-phenyl-5-hydroxy-6-methyl-3,4-pyridinedicarboximide (XXXI), $C_{14}H_{10}O_3N_2$, m. p. 229~230°, IR ν_{max}^{KBr} cm^{-1} : 1760, 1685 (C=O), (type C); structures of these products were established by acid hydrolysis to corresponding 3,4-pyridinedicarboxylic acid derivatives. The adducts, XXVIII and XXIX, may be given the structures as shown in Chart 1 on the ground of the results obtained above, and this assumption is also supported by the posturated structures for adducts of furan with dienophiles in literatures[7~9] Moreover, heating of I with XIV in nitrobenzene afforded XXXI accompanied with XXX as a by-product.

On the basis of these observations, we conclude that the reaction involves fundamentally three steps : the first step is Diels-Alder condensation of oxazoles (XXXII) with dienophiles to yield endo-oxo compounds (XXXIII), the second is formation of 3,4-dihydropyridine intermediates (XXXIV) by cleavage of oxygen-bridge, and the last is aromatisation to pyridine derivatives of four types (XXXV-A, -B, -C and -D) under elimination of two substituents attached on C-3 ane C-4 of XXXIV.

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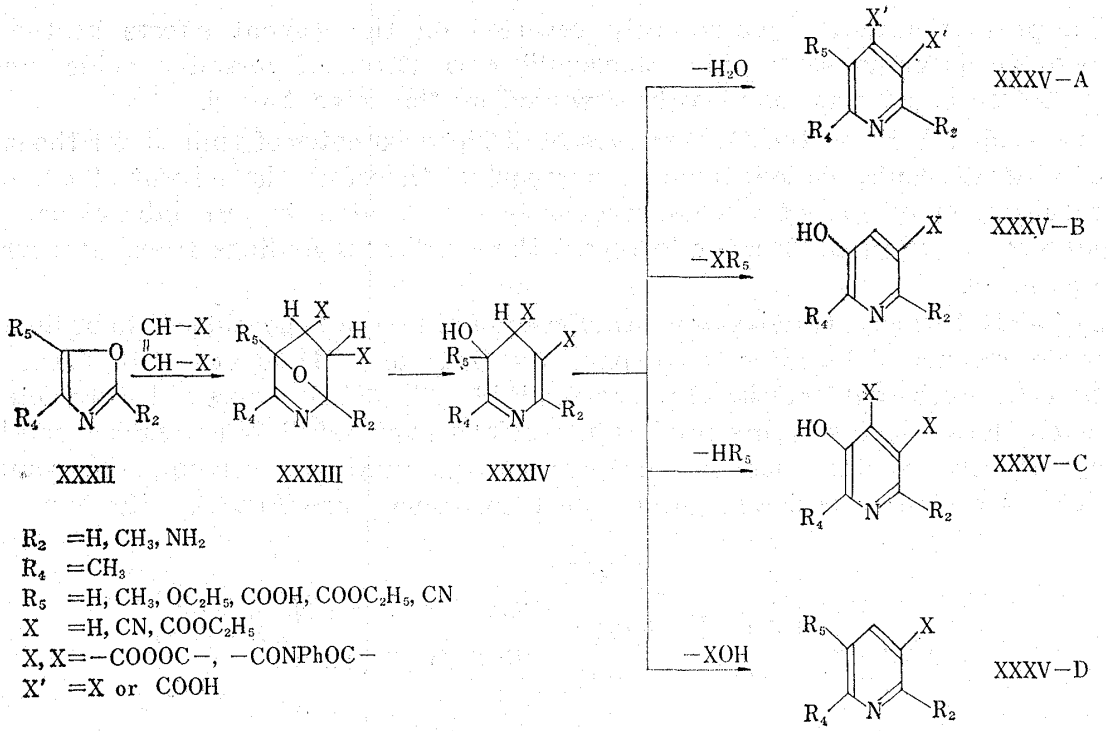

Chart 2.

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The Solvent Effects on the Optical Rotatory Dispersion of Dithiocarbamates of Amines

Various types of solvent effects on the optical rotatory dispersion (ORD) and the circular dichroism (CD) of several compounds have been reported[1~8] and they had also been reviewed by Djerassi, *et al.*[9]

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