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Studies on the Diels-Alder Reaction of 4-Carboxymethyl-5-ethoxyoxazole

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The Diels–Alder reaction of 4-carboxymethyl-5-ethoxyoxazole (I) was investigated. First, the mechanism and the stereochemistry of the adducts in the course of the Diels–Alder reaction were discussed. Second, the reaction of I with asymmetrical dienophiles gave the substance that an electron attracting group was preferentially introduced at γ-position of pyridine nucleus. Finally, the reaction of I with maleic anhydride, fumaric acid, maleic acid and methacrylic acid afforded the decarboxylated compounds. The mechanism of these reaction was discussed.

G.Y. Kondrat'yeva's synthesis[2] of cinchomeronic acid by Diels–Alder reaction of maleic anhydride with oxazole has provided unusually efficient routes[3] to Vitamin B_6. In the previous paper,[4] we described new synthetic route to pyridoxine by the application of the Diels–Alder reaction of 4-carboxymethyl-5-ethoxyoxazole (I) which was obtained from aspartic acid. The present paper deals with the stereochemistry of the adducts in the course of the Diels–Alder reaction.

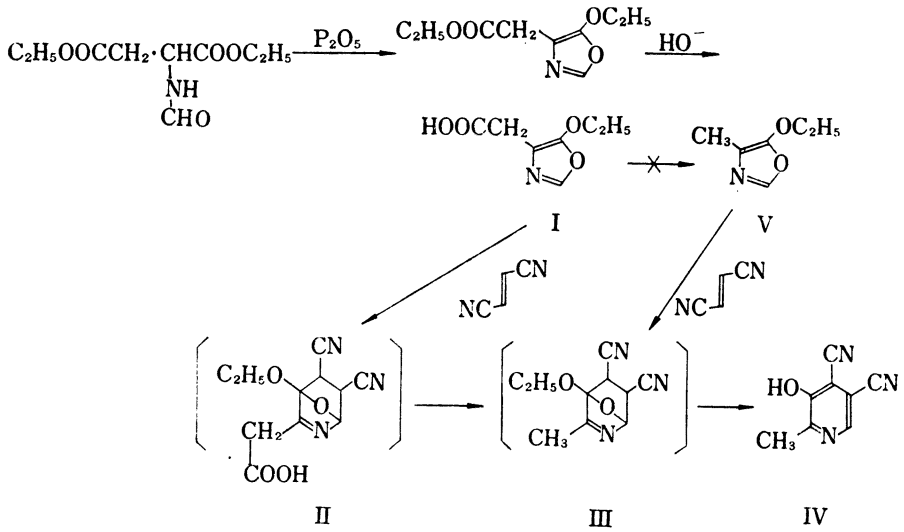


Chart 1

1) Location: *Juso-Nishino-cho, Higashiyodogawa-ku, Osaka.*
2) G. Ya. Kondrat'yeva, *Khim. Nauk i Prom.*, **2**, 666 (1957); *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1959**, 484.
3) *a*) E.E. Harris, E.E. Firestone, K. Pfister, 3rd, R.R. Boettcher, F.J. Cross, R.B. Currie, M. Monaco, E.R. Peterson and W. Reuter, *J. Org. Chem.*, **27**, 2705 (1962); *b*) Takeda Chem. Ind. Ltd., Belg. Patent 648226 (1964); *c*) Hoffmann-La Roche and Co. AG, Belg. Patent, 640507, 645469 (1964), 664497 (1965); *d*) T. Naito and T. Yoshikawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 918 (1966); *e*) T. Yoshikawa, F. Ishikawa, Y. Omura and T. Naito, *Chem. Pharm. Bull.* (Tokyo), **13**, 873 (1965); *f*) T. Naito, K. Ueno, M. Sano, Y. Omura, I. Itoh and F. Ishikawa, *Tetrahedron Letters*, **1968**, 5757; *g*) R.A. Firestone, E.E. Harris and W. Reuter, *Tetrahedron*, **23**, 943 (1967).
4) T. Miki and T. Matsuo, *J. Pharm. Soc. Japan.*, **87**, 323 (1967).

Diethyl N-formylasparate was treated with phosphorous pentoxide to afford 5-ethoxy-4-ethoxycarbonylmethyloxazole, bp_3 84—85°, which was readily hydrolyzed to I, mp 80—81°, in alkaline solution.

The Diels–Alder reaction of I with 1 mole of fumaronitrile or maleonitrile on heating and the subsequent treatment of the products with methanolic hydrochloride gave 4,5-dicyano-3-hydroxy-2-methylpyridine (IV). This was converted to pyridoxine by hydrogenation and subsequent diazotization.[5]

The pathway of the Diels–Alder reaction was followed with the nuclear magnetic resonance (NMR) spectra of the reaction mixture in $CDCl_3$. In proportion to the decreasing signals of I and fumaronitrile, new signals of two compounds [adduct (IIIa); 2.25 (3H, singlet), 2.84 (1H, doublet), 3.57 (1H, quartet), 6.05 ppm (1H, doublet); adduct (IIIb); 2.32 (3H, singlet), 3.04 (1H, doublet), 3.22 (1H, doublet), 5.97 ppm (1H, singlet)] increased, and these signals were in good agreement with that of the reaction mixture obtained from the reaction of oxazole (V) with fumaronitrile. The signals of IV [2.63 (3H, singlet), 8.36 ppm (1H, singlet)] appeared too. During the reaction, no existence of the supposed adduct (II) was observed and the slight signals of V[6] were observed.

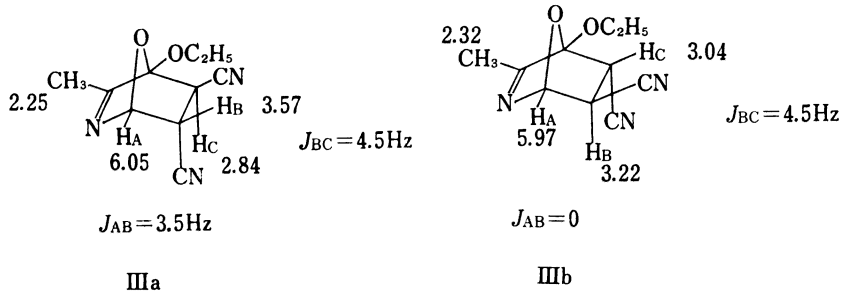


Chart 2. Chemical shifts are indicated by ppm from TMS in $CDCl_3$

The orientation of the cyano groups in IIIa and IIIb was determined based on the value of the coupling constants between the protons H_A and H_B also H_B and H_C. The coupling (3.5 Hz) between H_A and H_B of the adduct IIIa indicate that H_B proton is in the exo-position, whereas singlet H_A of the adduct IIIb indicate that H_B is in the endo-position. Further, the similar coupling constants (4.5 Hz) between H_B and H_C in both of the adducts IIIa and IIIb showed that the vicinal cyano groups take the *trans*-configuration each other.

The oxazole I decomposes on heating above 190°. During the decomposition no formation of 5-ethoxy-4-methyloxazole V was observed by means of a gas chromatographic analysis. Thus, it has been concluded that the decarboxylation occurs simultaneously with the additive reaction between I and fumaronitrile.

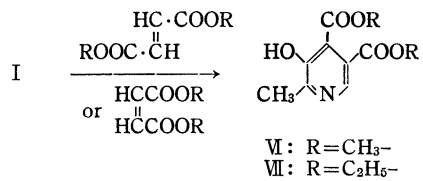


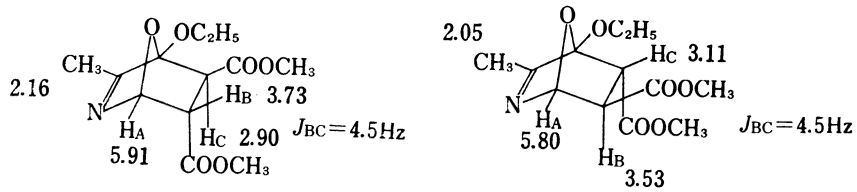
Chart 3

Treatment of I with a fumaric or maleic acid ester at 120° gave 5-hydroxy-6-methylcinchomeronate, (VI) and (VII), which were converted to pyridoxine by the reduction of the ester groups. In these case, VI and VII were formed directly without the treatment of the adduct with alcoholic hydrochloride. When the additive reaction of I with dimethyl fumarate was stopped in a short time, small amounts of two isomeric adducts, (VIIIa) and (VIIIb), were

5) A. Cohen and E.G. Hughes, Brit. Patent 625997 (1949); A. Cohen, J.W. Haworth and E.G. Hughes, *J. Chem. Soc.*, **1952**, 4374.

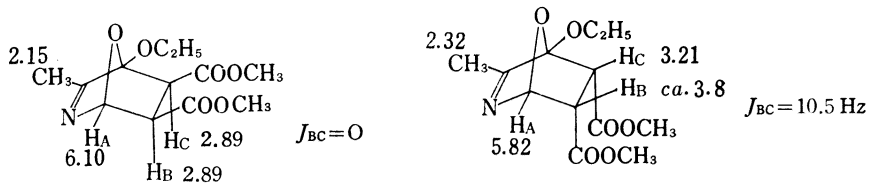
6) The oxazole V should be formed by the reverse Diels–Alder reaction of III.

observed in NMR spectrum. The structures of the adducts were assigned as shown in the following formula.



VIIIa VIIIb

Chart 4. Chemical Shifts are indicated by ppm from TMS in $CDCl_3$



IXa IXb

Chart 5. Chemical Shifts are indicated by ppm from TMS in $CDCl_3$

On the other hand, during the reaction of I and dimethyl maleate the presence of the exo- and endo-adducts, (IXa) and (IXb), was observed. The chemical shift of the H_B proton in IXb could not be determined exactly because of the presence of the neighbouring signals of methylene and methoxycarbonyl groups. The protons H_B and H_C in IXa appeared at the same position as a singlet peak in $CDCl_3$, but appeared as a AB quartet type in benzene-d_6. Consequently, the structures of IXa and IXb were assigned as shown in Chart 5.

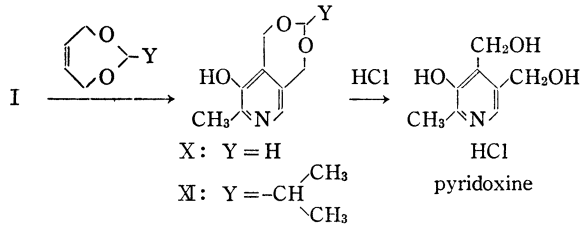


Chart 6

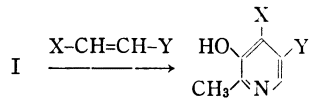


Chart 7

Reaction of I with 15—20 moles of a 4,7-dihydro-1,3-dioxepine compound afforded a 3-hydroxylated pyridine compound (X or XI) in a relatively low yield. The products were converted to pyridoxine by acidic hydrolysis.

The Diels–Alder reaction of I with the other dienophiles proceeded smoothly to give the corresponding pyridines (Table I). Thier structures were confirmed by NMR spectroscopy as shown in Table II. The NMR spectra of (XII), (XIII) and (XIV) indicated the presence of ortho-protons as shown in formula (A). The structure (B) was assigned to XV due to the large chemical shift of the H_α proton and the small J-value (2Hz) in (XV). The chemical shifts of the H_α proton in (XVI), (XVII) and (XVIII) were similar to these in XII, XIII and XIV.

Table I

Compound	X	Y	mp (°C)	Yield (%)	
XII	COOH	H	329 —332	92	A
XIII	CN	H	235 —238 (decomp.)	85	
XIV	$COOCH_3$	H	50.5— 51	64	
XV[a]	H	$COOCH_3$	203 —205	6.4	B
XVI	COOH	CH_3	298 —301 (decomp.)	70	
XVII	CN	CH_3	201 —203 (decomp.)	72	
XVIII	$COOCH_3$	CH_3	65 — 66	50	
XIX[b]	CH_3	$COOCH_3$	142 —143	6.2	C

a) XV was obtained with XIV in the reaction of I with methyl acrylate.
b) XIX was obtained with XVIII in the reaction of I with methyl crotonate.

This fact indicates that methyl groups should be located at the β-position (formula C). On the other hand, the down field shift of the H_α proton in (XIX) shows that the methyl grou is located at the γ-position.

In view of the above results, it may be concluded that in the reaction of I with dienophile an electron attracting group is preferentially introduced at γ-position of pyridine nucleus.

Table II. Chemical Shifts (ppm) and Coupling Constants (Hz) of Aromatic Proton in N-NaOD at 60 MHz

	H_α	H_β	H_γ	$J_{\alpha\beta}$	$J_{\alpha\gamma}$
XII	7.64	7.23	—	5.2	—
XIII	7.45	7.11	—	5.0	—
XIV	7.61	7.20	—	5.2	—
XV	8.09	—	7.33	—	2
XVI	7.54	—	—	—	—
XVII	7.20	—	—	—	—
XVIII	7.30	—	—	—	—
XIX	7.76	—	—	—	—

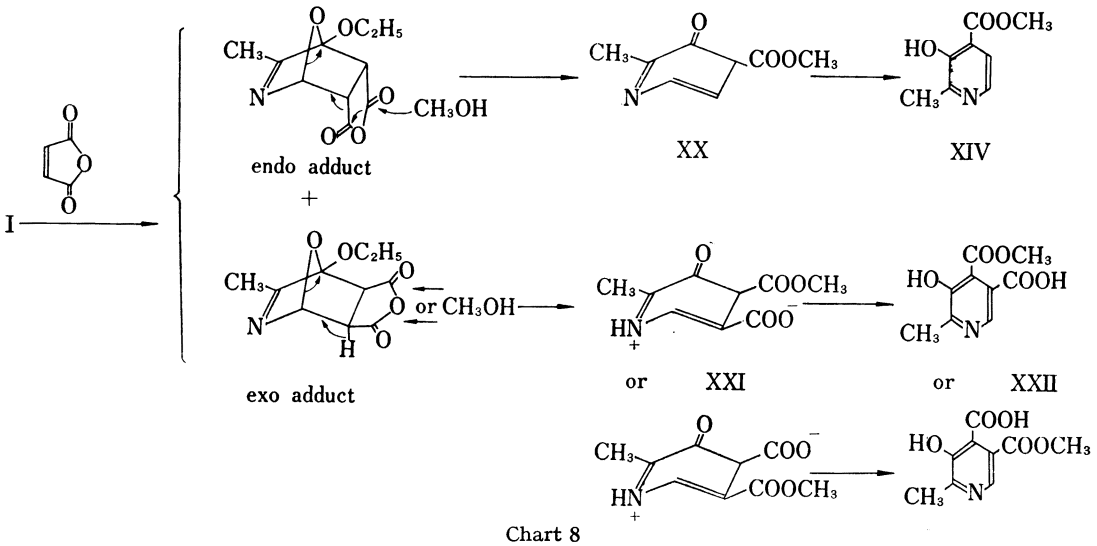


Chart 8

The reaction of I with maleic anhydride gave a mixture of the endo- and exo-adducts, which was treated with methanolic hydrogen chloride to afford two compounds. They were separated by recrystallization and chromatography. The compound of the lower mp was the same with XIV in all respects, and the other compound (mp 336—337°) was deduced to be the monomethylester (XXII) from infrared (IR) and NMR spectra. On the basis of these observation, we concluded that esterification and decarboxylation took place in the endo-adduct (Chart 8) to yield (XX), which was isomerized to XIV, whereas no decarboxylation occurred in the exo-adduct and *via* the intermediate (XXI), the monester XXII was obtained. The higher the reaction temperature, the greater the content of XIV in the product decreased. This may be interpreted that the higher reaction temperature results in the preferential formation of the exo-adduct to the endo-adduct and producing the more yield of XXII.

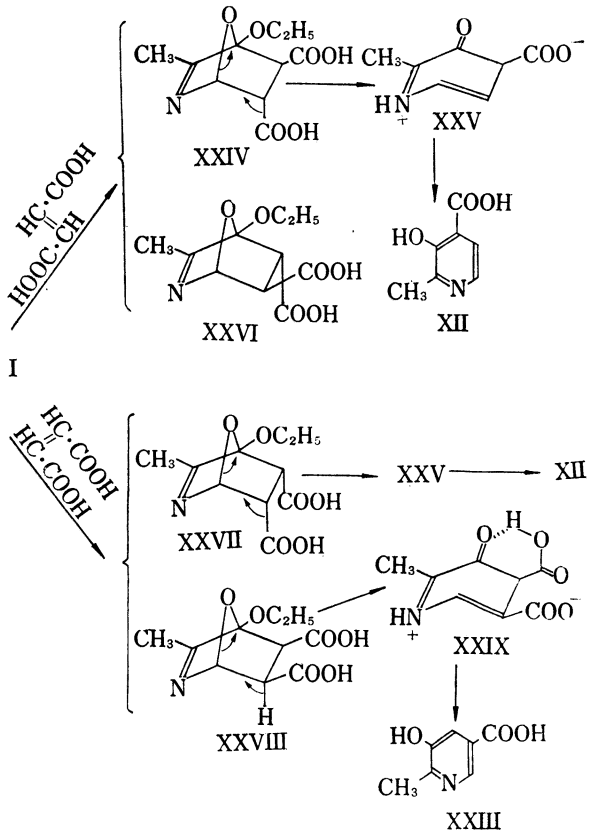


Chart 9

We then turned our experiment to the reaction of I with fumaric and maleic acid. Refluxing of I with fumaric acid in ethanol provided only a single product (yield, 88%), which was identical with the monoacid XII. On the other hand, the reaction of I with maleic acid gave a mixture of the two products (yield, 95%), XII and (XXIII) in a ratio of 1 to 1, which were separated by recrystallization from water. The structure of the latter XXIII, mp 320—322°, was confirmed by the observation of *meta*-protons in NMR spectrum. The reaction pathways may be shown with the figures in Chart 9. Reaction of I with fumaric acid: decarboxylation occurs in the adduct (XXIV) more readily than (XXVI) to yield 3-ketopyridine (XXV), which is immediately isomerized to XII.[7] In the postulated adduct XXVI, the reverse reaction may be preferred to the decarboxylation on the isomerization to 5-hydroxy-6-methylcinchomeronic acid. Reaction of I with maleic acid: decarboxylation of the endo-adduct (XXVII) follwed by the isomerization gave XII. In the exo-adduct (XXVIII) which may be formed in high ratio as in case of the adduct IXa the reaction starts with the cleavage of the C–H bond to give (XXIX), which may be decarboxylated to XXIII since the rate of decarboxylation in XXIX is faster than that of isomerization.[7]

The reaction of I with methacrylic acid afforded an expected compound (XXX), mp 100—102°. Its NMR spectrum showed the existence of the *ortho*-protons in pyridine ring. The reaction mechanism is also deduced as shown in Chart 10.

7) The fact that the anions of β-keto acids are susceptible to decarboxylation, but less readily than the corresponding acids, appears to be entirely general. For example, K.J. Pedersen, *J. Am. Chem. Soc.*, **51**, 2098 (1929); G.A. Hall, *ibid.*, **71**, 2691 (1949).

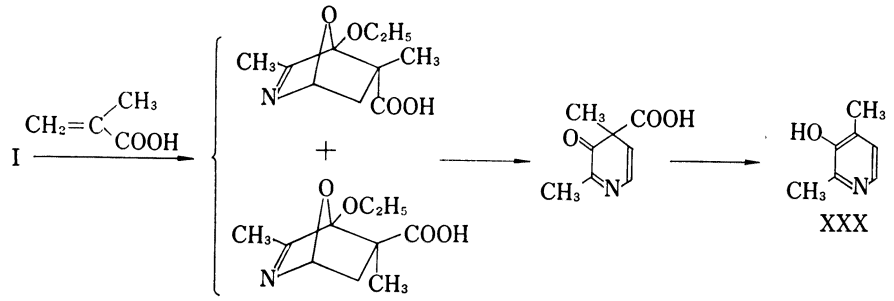


Chart 10

Experimental[8]

5-Ethoxy-4-ethoxycarbonylmethyloxazole——To a suspension of 160 ml of $CHCl_3$, 28 g of P_2O_5 and 16 g of Hyflo Super-Cel (Wako Pure Chem. Ind. Ltd.) was added, over 1 hr at 60°, a solution of 20 g of diethyl N-formylasparate[9] in the same solvent. Vigorous stirring was continued for a further 4 hr at 60°. To the cooled reaction mixture was added water and the aqueous solution was made alkaline to litmus with $NaHCO_3$. After Hyflo Super-Cel was filtered off, the organic layer was separated and dried over anhyd. Na_2SO_4. After evaporation of solvent, the residual oil was distilled. bp 84—85° (3 mmHg). Yield, 14 g (76%). *Anal.* Calcd. for $C_9H_{13}O_4N$: C, 54.26; H, 6.58; N, 7.07. Found: C, 54.22; H, 6.71; N, 7.08. NMR ($CDCl_3$, ppm): 1.26 (3H, triplet), 1.37 (3H, triplet), 3.45 (2H, singlet), 4.17 (2H, quartet), 4.23 (2H, quartet), 7.43 (1H, singlet).

4-Carboxymethyl-5-ethoxyoxazole (I)——To a stirred solution of 10 g of 5-ethoxy-4-ethoxycarbonylmethyloxazole in 5 ml of MeOH was slowly added a solution of 3 g of KOH in 30 ml of 80% MeOH. After stirring for 30 min, the reaction mixture was acidified with 10% H_2SO_4, and condensed under reduced pressure. The resultant solution was extracted with AcOEt. The extract was dried over anhyd. Na_2SO_4 and evaporation of AcOEt gave 6.2 g (73%) of I. Recrystallization from benzene gave colorless prisms, mp 80—81°. *Anal.* Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.30; H, 5.20; N, 8.15. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1681, 1523. NMR ($CDCl_3$, ppm): 1.40 (3H, triplet), 3.56 (2H, singlet), 4.28 (2H, quartet), 7.64 (1H, singlet).

Diels-Alder Reaction with Fumaronitrile——A solution of 0.50 g of oxazole I and 0.23 g of fumaronitrile in 10 ml of $CHCl_3$ was heated under reflux for 5 hr. To the cooled reaction mixture was added 1 ml 10% HCl–MeOH and the solvent was removed rapidly. To the residue was added ether and an insoluble material was filtered off. The filtrate was dried over anhyd. Na_2SO_4 and condensed *in vacuo* to give a crystalline residue, which was purified by recrystallization from benzene to pale yellow needles (IV), mp 189—191°. Yield, 0.28 g (60%). The IR spectrum was identical with that of an authentic sample prepared from 5-ethoxy-4-methyloxazole (V) and fumaronitrile according to the literature.[3a]

The experiment following the reaction by taking the NMR spectrum was carried out in $CDCl_3$ at 50°, and the NMR spectra at different times were measured. The III_A/III_B ratio was kept in *ca.* 3/7 during the reaction.

According the literature,[5] hydrogenation of IV produced 4,5-bisaminomethyl-3-hydroxy-2-methylpyridine trihydrochloride, mp 292° (decomp.), which was treated with nitrous acid to give pyridoxine.

Diels-Alder Reaction with Maleonitrile——A solution of 0.5 g of oxazole I and 0.23 g of maleonitrile in 5 ml of $CHCl_3$ was heated under reflux for 4 hr. After working up in a similar manner as described above, there was obtained 0.24 g (51%) of IV.

Diels-Alder Reaction with Dimethyl Maleate——A mixture of 17.1 g of oxazole I and 20 g of dimethyl maleate was heated at 120° for 2 hr. Ether was added to the cooled reaction mixture giving a precipitate, which was crystallized from benzene–AcOEt to give colorless needles (VI), mp 140—141°. Yield, 21.2 g (90%). IR spectrum was identical with that of an authentic sample prepared from V and dimethyl maleate. NMR ($CDCl_3$, ppm): 2.64 (3H, singlet), 4.0 (3H, singlet), 4.05 (3H, singlet), 8.38 (1H, singlet).

Diels-Alder Reaction with Dimethyl Fumarate——A mixture of 8.5 g of oxazole I and 13 g of dimethyl fumarate was heated at 120° for 2 hr. After working up in a same manner as described above, 8 g (80%) of VI was obtained.

8) All boiling and melting points were uncorrected. UV spectra were measured with a Perkin-Elmer 450 spectrophotometer, IR spectra with a Hitachi EPI-S2 spectrophotometer, and NMR spectra with a Varian HA-100 and A-60 spectrometer using tetramethylsilane as a internal standard.

9) K. Freudenberg, *Chem. Ber.*, **58**, 2407 (1925).

Diels-Alder Reaction with Diethyl Maleate——A mixture of 17.1 g of oxazole I and 25 g of diethyl maleate was heated at 120° for 2 hr. After removal of excess diethyl maleate *in vacuo*, the residue was distilled. 22.8 g (85%) of (VII) was obtained. bp 132—138° (0.2 mmHg).[5] NMR ($CDCl_3$, ppm): 1.28 (3H, triplet), 1.36 (3H, triplet), 2.60 (3H, singlet), 4.18 (2H, quartet), 4.21 (2H, quartet), 8.3 (1H, singlet).

Diels-Alder Reaction with Diethyl Fumarate——A mixture of 8.5 g of oxazole I and 12 g of diethyl fumarate was heated at 115—120° for 2 hr. After working up in a similar manner as described above. 10.8 g (78%) of VII was obtained.

Both of VI and VII were reduced with $LiAlH_4$ to pyridoxine, isolated as its hydrochloride in 68% yield according to the literature.[5] The melting point and IR spectrum were identical with those of an authentic sample.

Diels-Alder Reaction with 4,7-Dihydro-1,3-dioxepine——A mixture of 1.0 g of oxazole I, 11.7 g of 4,7-dihydro-1,3-dioxepine,[10] 0.3 g of copper powder, 0.3 g of glass powder and 0.1 g of N,N-dimethylaniline was heated in a sealed tube for 8 hr at 175°. After the copper and glass powder were filtered off, excess 4,7-dihydro-1,3-dioxepine was distilled off *in vacuo*, and the residual oil was extracted with hot water. The extract was treated with charcoal, and was condensed to give a crystalline solid (X), which was recrystallized from acetone–ether to give colorless needles of mp 178—179°. Yield, 0.25 (24%). *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.37; H, 6.01; N, 7.71. UV λ_{max}^{EtOH} nm (ε): 282.0 (5436), 326.0 (1397). NMR (D_2O, ppm): 2.46 (3H, singlet), 4.91 (2H, singlet), 5.12 (4H, singlet), 7.50 (1H, singlet). The orange oil, obtained from concentration of the mother liquors of X, was dissolved in 10 ml of 15% HCl, and the solution was heated at 70° for 20 min. After removal of water and formed aldehyde *in vacuo*, to the residue was added acetone to gave 0.15 g of pyridoxine hydrochloride, mp 201—203°.

Acidic Hydrolysis of X to Pyridoxine——A solution of 0.20 g of X in 10 ml of 15% HCl was heated at 60° for 30 min, and evaporated to dryness. To the residue was added acetone–EtOH yielding a crystalline solid of pyridoxine hydrochloride, mp 202—203°. Yield, 0.23 g (95%). The IR spectrum was identical with an authentic sample.

Diels-Alder Reaction with 2-Isopropyl-4,7-dihydro-1,3-dioxepine——A mixture of 1.0 g of oxazole I, 18 g of 2-isopropyl-4,7-dihydro-1,3-dioxepine,[10] 0.3 g of copper powder, 0.3 g of glass powder and 0.1 g of N,N-dimethylaniline was heated in a sealed tube for 8 hr at 180°. After working up in a similar manner as described above, there was obtained a crystalline solid (XI), which was recrystallized from EtOH–acetone to give colorless needles of mp 161—163°. Yield, 0.26 g (20%). *Anal.* Calcd. for $C_{12}H_7O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.33; H, 7.74; N, 5.99. UV λ_{max}^{EtOH} nm (ε): 283.1 (5290), 326.0 (1228). NMR ($CDCl_3$, ppm): 0.97 (6H, doublet), 2.40 (3H, singlet), 1.90 (1H, multiplet), 4.49 (1H, doublet), 4.77 (2H, singlet), 4.83 (2H, singlet), 7.81 (1H, singlet). By treating the mother liquors of XI as described above for that of X, 0.11 g of pyridoxine hydrochloride was obtained. mp 201—204°.

Acidic Hydrolysis of XI to Pyridoxine——After working up in a similar manner as described above, from 0.22 g of XI was obtained pyridoxine hydrochloride, mp 202—204°. Yield, 0.18 g (94%).

Diels-Alder Reaction with Acrylic Acid——A solution of 0.20 g of oxazole I and 0.20 g of acrylic acid in 3 ml EtOH was refluxed for 2 hr and cooled to give a crystalline solid (XII). Recrystallization from water gave colorless needles of mp 329—332°. Yield, 0.17 g (92%). *Anal.* Calcd. for $C_7H_7O_3N$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.08; H, 4.69; N, 9.18. NMR (1N NaOD, ppm): 2.30 (3H, singlet), 7.23 (1H, doublet, $J=5.2$ Hz), 7.64 (1H, doublet, $J=5.2$ Hz).

Diels-Alder Reaction with Acrylonitrile——A solution of 0.60 g of oxazole I and 0.93 g of acrylonitrile in 10 ml of EtOH was refluxed for 4 hr and condensed to give a solid (XIII). Recrystallization from MeOH gave colorless prisms of mp 235—238° (decomp.). Yield, 0.40 g (85%). *Anal.* Calcd. for $C_7H_6ON_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.45; H, 4.54; N, 20.75. NMR (1N NaOD, ppm): 2.50 (3H, singlet), 7.11 (1H, doublet, $J=5$ Hz), 7.45 (1H, doublet, $J=5$ Hz).

Diels-Alder Reaction with Methyl Acrylate——A mixture of 3.0 g of oxazole I and 15 g of methyl acrylate was heated at 80° for 6 hr. After removal of excess methyl acrylate, to the residue was added 20 ml ether, and the solution was cooled overnight at 4° to give 0.20 g of a solid (XV), which was recrystallized from EtOH–ether to give colorless needles of mp 203—205°. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.51; H, 5.35; N, 8.27. IR ν_{max}^{Nujol} cm^{-1}: 1732. NMR (1N NaOD, ppm): 2.45 (3H, singlet), 3.43 (3H, singlet), 7.33 (1H, doublet, $J=2$ Hz), 8.08 (1H, doublet, $J=2$ Hz). The mother liquors of XV was chromatographed on silica gel. Elution with benzene afforded colorless needles (XIV) of mp 50.5—51°. Yield, 1.7 g. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.56; H, 5.34; N, 8.29. IR ν_{max}^{Nujol} cm^{-1}: 1691. NMR (1N NaOD, ppm): 2.19 (3H, singlet), 3.20 (3H, singlet), 7.20 (1H, doublet, $J=5.2$ Hz), 7.61 (1H, doublet, $J=5.2$ Hz).

The Conversion Among XII, XIII and XIV——To 1.5 g XIII was added 8 ml of 10% NaOH, and the solution was refluxed for 5 hr. After cooling, the reaction mixture was acidified with 10% HCl to give crystals XII. Yield, 1.26 g (74%).

10) K.C. Brannock and G.R. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).

To a suspension of 0.5 g XII in 50 ml MeOH was introduced dried HCl gas, and the solution was refluxed for 2 hr. After removal of MeOH, to the residue was added water, and the solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extracts was evaporated, and the residue XIV was purified by chromatography on silica gel using benzene. Yield, 0.44 g (81%).

To 0.4 g XIV was added 10 ml of 10% NaOH, and the solution was refluxed for 2 hr. After cooling, the solution was neutralized with 10% HCl to give a solid XII. Yield, 0.33 g (90%).

Diels-Alder Reaction with Crotonic Acid——A solution of 1.0 g of oxazole I and 0.50 g of crotonic acid in 5 ml of xylene was refluxed for 4 hr. After removal of xylene *in vacuo*, to the residue was acetone to give a solid (XVI). Recrystallization from hot water gave colorless needles, mp 298—301° (decomp.). Yield, 0.44 g (45%). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.70; H, 5.38; N, 8.34. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1610. NMR (1NNaOD, ppm): 2.32 (3H, singlet), 2.42 (3H, singlet), 7.54 (1H, singlet).

Diels-Alder Reaction with Crotononitrile——A solution of 1.0 g of oxazole I and 1.2 g of crotononitrile in 10 ml of benzene was refluxed for 5 hr, and cooled to give a solid (XVII). Recrystallization from acetone-ether gave colorless prisms of mp 201—203°. Yield, 0.63 g (72%). *Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.91; H, 5.33; N, 18.80. NMR (1NNaOD, ppm): 2.13 (3H, singlet), 2.28 (3H, singlet), 7.20 (1H, singlet).

Diels-Alder Reaction with Methyl Crotonate——A mixture of 2.0 g of oxazole I and 8 g of methyl crotonate was heated in a sealed tube for 4 hr at 150—160°. After removal of excess methyl crotonate *in vacuo*, the residual oil was chromatographed on silica gel. Elution with benzene-ether afforded 1.47 g (50%) of (XIII) and 0.18 g (6.2%) of (XIX). The former XIII was recrystallized from ether to give colorless plates of mp 65—66°. *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.68; H, 6.16; N, 7.86. IR ν_{max}^{Nujol} cm^{-1}: 1672. NMR ($CDCl_3$, ppm): 2.42 (3H, singlet), 2.48 (3H, singlet), 3.98 (3H, singlet), 7.90 (1H, singlet).[11] The later XIX was recrystallized from benzene gave colorless plates of mp 142—143°. *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.77; H, 6.13; N, 7.67. IR ν_{max}^{Nujol} cm^{-1}: 1721. NMR ($CDCl_3$, ppm): 2.54 (6H, singlet), 3.91 (3H, singlet), 8.50 (1H, singlet).[12]

The Conversion Among XVI, XVII and XVIII——By treating XVI, XVII and XVIII as described in the conversion among XII, XIII and XIV, XVI (78%) was obtained from XVII and XVIII (76%) from XVI.

Diels-Alder Reaction with Maleic Anhydride——A solution of 1.0 g of oxazole I and 0.58 g of maleic anhydride in 8 ml of MeOH was refluxed for 1 hr, and condensed to give a yellow, unstable oil. To this oil was added 10 ml of 10% HCl–MeOH, and the solution was allowed to stand for 30 min. After removal of MeOH, to the residual oil was added ether. The ether solution was treated with aq. $NaHCO_3$ and condensed to give 0.43 g of a crystalline solid (XXII), which was recrystallized from EtOH to give colorless prisms of mp 336—337°. *Anal.* Calcd. for $C_9H_9O_5N$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.20; H, 4.81; N, 6.91. IR ν_{max}^{Nujol} cm^{-1}: 1732. NMR (1NNaOD, ppm): 2.44 (3H, singlet), 3.47 (3H, singlet), 7.90 (1H, singlet). The mother liquors of XXII was chromatographed on silica gel. Elution with benzene afforded 0.19 g of colorless needles XIV, mp 50—51°. Further, the same reactions at different temperature were carried in MeOH, and the XIV/XXII ratios were shown in Table III. The esterification of maleic anhydride in these conditions were not observed in the NMR spectra.

Table III

Reaction temp. (°C)	Reaction time (hr)	XIV/XXII ratio
21	1	2.2
35	1	1.2
53	1	0.50
Reflux	1	0.56

Diels-Alder Reaction with Fumaric Acid——A solution of 1.7 g of oxazole I and 1.3 g of fumaric acid in 60 ml EtOH was refluxed for 4 hr. The separated crystals at 45—50° was filtered off and washed with EtOH. Yield, 1.35 g (88%). mp 330—332°. The IR and NMR spectra were identical with that of XII obtained above.

Diels-Alder Reaction with Maleic Acid——A solution of 1.7 g of oxazole I and 1.3 g of maleic acid in 60 ml EtOH was refluxed for 4 hr, and condensed to give a crystalline solid, whose NMR spectrum indicated it to be a mixture of XII and (XXIII) (1: 1). Yield, 1.45 g (95%). Repeated recrystallizations from hot water gave colorless needles XXIII of mp 320—322° and XII of mp 329—330°. *Anal.* Calcd. for C_7-

11) This signal appeared at 7.30 ppm in 1NNaOD.
12) This signal appeared at 7.76 ppm in 1NNaOD.

H_7O_3N XXIII: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.71; H, 4.61; N, 9.05. NMR (1NNaOD, ppm): 2.42 (3H, singlet), 7.37 (1H, doublet, $J=2$ Hz), 8.10 (1H, doublet, $J=2$ Hz).

Diels-Alder Reaction with Methacrylic Acid——A solution of 5.0 g of oxazole I and 3.5 g of methacrylic acid in 20 ml of toluene was refluxed for 6 hr. After removal of toluene and excess methacrylic acid *in vacuo*, to the residue was added benzene to give a crystalline solid (XXX). Recrystallization from benzene–ether gave colorless needles of mp 100—102°. Yield, 2.0 g (56%). *Anal.* Calcd. for C_7H_9ON: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.47; H, 7.43; N, 11.39. NMR ($CDCl_3$, ppm): 2.27 (3H, singlet), 2.43 (3H, singlet), 6.94 (1H, doublet, $J=5$ Hz), 7.74 (1H, doublet, $J=5$ Hz).

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