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Studies on the Diels-Alder Reaction of 5-Ethoxy-4-ethoxycarbonylmethyloxazole

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The Diels–Alder reaction of 5-ethoxy-4-ethoxycarbonylmethyloxazole (I) with dienophiles was investigated. The stereochemistry of the addition products that had an exocyclic double bond was confirmed by the spectroscopic data. The reaction of I with maleic anhydride gave *endo*- (II) and *exo*-adduct (III), and the isomerization of II to III proceeded easily. The reaction of I with eight symmetrical dienophiles afforded the isomeric adducts. Similar treatment of asymmetrical dienophiles afforded the corresponding adducts, respectively. The stereochemistry of these adducts was discussed.

Kondraty'eva[2] found that the Diels–Alder reaction of oxazole with maleic anhydride afforded cinchomeronic acid. This reaction was applied by Harris, *et al.*[3] to the synthesis of pyridoxine. After that, the Diels–Alder reaction of oxazoles with dienophiles has been the subject of intensive study[4] for the synthesis of pyridoxine and its derivatives. Previously,[5] we described several synthetic routes to pyridoxine by the Diels–Alder reaction of 5-ethoxy-4-ethoxycarbonylmethyloxazole and 4-carboxymethyl-5-ethoxyoxazole.

In this paper are reported some of the features of the Diels–Alder reaction of 5-ethoxy-4-ethoxycarbonylmethyloxazole (I) with dienophiles along with the stereochemistry of the addition products.

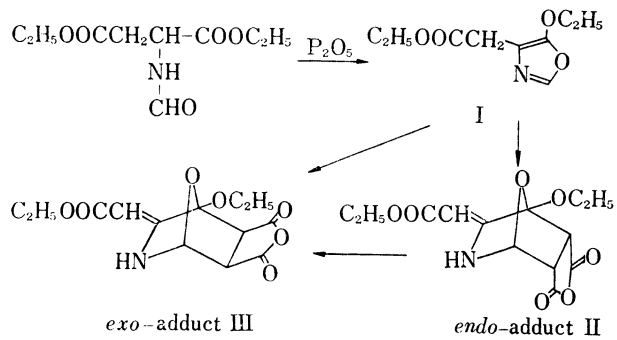


Chart 1

The oxazole I was prepared by heating diethyl N-formylaspartate with phosphorous pentoxide in 76% yield.

First, we investigated the reaction of the oxazole I with maleic anhydride. The reaction was effected by heating I with maleic anhydride in ethanol to give colorless prisms (III) of mp 150.5°. On the other hand, the same reaction at 10° gave colorless needles (II)

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

of mp 118°. The two substances were identical on elemental analysis and their empirical formula established as adducts of I and maleic anhydride. The infrared (IR) spectra of these compounds show the existence of an α,β-unsaturated ester (1683 cm^{-1} for II and 1680 cm^{-1} for III). The ultraviolet (UV) absorption maxima appear at 298 and 274 nm, respectively. The nuclear magnetic resonance (NMR) spectra show the signals of a NH proton and a methine proton, but no methylene protons. These spectral data indicate the structure having an exocyclic double bond for II and III.

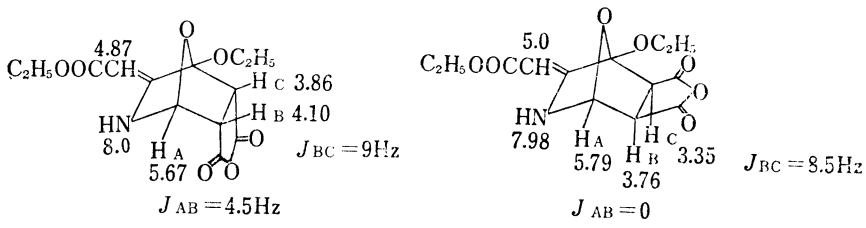


Chart 2[a)]

a)Chemical shifts are indicated by ppm from TMS in $CDCl_3$.

The stereochemistry of the compounds II and III was confirmed by NMR spectroscopy. The coupling constant (4.5 cps) between the protons H_A and H_B of II suggests that II is an *endo*-adduct, whereas the fact that no splitting was observed at the signal of the H_A proton of III suggests that III is an *exo*-adduct. The signal of the H_C proton of II appears at 3.86 ppm (doublet), while that of H_B appears at 4.10 (quartet), which changes into doublet (J= 9 Hz) by irradiating at the H_A proton freuency (5.67 ppm). The two signals at 3.35 and 3.76 ppm in the spectrum of III have been assigned to the vicinal protons H_C and H_B in accordance with the assignment in II, although the reverse assignment is not excluded. The coupling constants (8.5—9 Hz) between H_B and H_C in both of II and III indicate the *cis* configuration. Thus the structures of II and III have been determined to be as shown in Chart 2.

We found that the isomerization of II to III proceeded in an appropriate solvent even at room temperature and the progress was easily observed by means of NMR and UV spectroscopy.[6)]

Second, we investigated the reactions of I with symmetrical dienophiles. As the dienophiles were employed the following eight compounds, *i.e.*, dimethyl fumarate, dimethyl maleate, diethyl fumarate, diethyl maleate, fumaronitrile, maleonitrile, *trans*- and *cis*-dibenzoylethylene. The reactions smoothly proceeded on heating and the corresponding adducts were given. The spectral data (Table I) of them also showed the presence of an exocyclic double bond.

The stereochemistry of the adducts was established by NMR spectroscopy in a manner similar to those of II and III. The orientation of the X groups was determined based on the observation whether the coupling was present between the protons H_A and H_B and the J-value found for H_B and H_C. The coupling constants (3—3.7 Hz) between the protons H_A and H_B of (IV), (VI), (VIII) and (X) show that the H_B proton is in the *exo*-position, whereas no splitting was observed at the signal of the H_A proton of (V), (VII), (IX) and (XI), thus indicating the H_B proton to be in the *endo*-position. Furthermore, the appearance of coupling (4.5—5 Hz) between the vicinal protons H_B and H_C of IV, V, VI, VII, VIII, IX, X and XI shows

6) After this work had been finished a synthesis of II was reported N.D. Doktorova, L.V. Ionova, M. Ya. Karpeisky, N. Sh. Padyukova, K.F. Turchin and V.L. Florentiev, *Tetrahedron*, **25**, 3527 (1969). However, the melting point (137—138°) reported in the paper was lower than ours and the NMR spectrum agreeded very closely with that of the mixture of II and III (*ca.* 1: 1) obtained in our hands.

that the X groups of these compounds are in the *trans*-configuration. In the same manner, it has been established that the H_B proton in (XII), (XIII) and (XVI) is in the *endo*-position. The coupling constant (9—9.5 Hz) between the vicinal protons H_B and H_C indicates that the X groups are in the *cis*-configuration. In the reaction of I with *cis*-dienophiles the formation of the *endo*-adduct was observed only in the reaction with maleonitrile. The signal of the H_A proton in (XV) appeared as doublet (J=3 Hz), whereas unsplitting of the signal of the H_A proton shows that (XIV) is an *exo*-adduct. The coupling cosntant (9.5 Hz) between

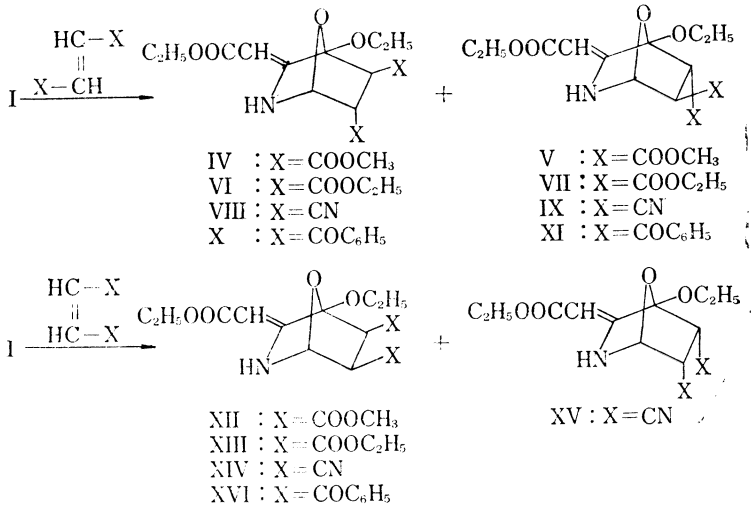
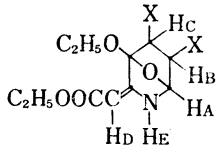


Chart 3

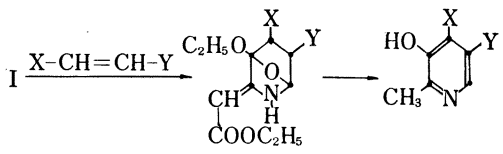
TABLE I.



Compound	UV: λ_{max}^{EtOH} nm (ε)	IR: ν_{max}^{Nujol} cm^{-1}		NMR ($CDCl_3$, ppm)						
		COOEt	>CH-	H_A	H_B	H_C	H_D	H_E	J_{AB}(Hz)	J_{BC}(Hz)
IV[a]	—	—	—	5.63	3.8	3.19	4.86	7.87	3.5	4.5
V	271.5 (19920)	1680	1642	5.61	3.68	3.57	4.71	7.72	0	4.5
VI	272.0 (18910)	1679	1641	5.53	3.82	3.09	4.80	7.77	3.7	4.5
VII	271.2 (19860)	1671	1640	5.60	3.67	3.53	4.72	7.71	0	4.5
XIII	268.5 (16630)	1688	1650	5.70	3.64	3.24	4.97	8.23	3	4.5
IX	267.0 (15950)	1670	1638	5.66	3.33	3.33	5.02	7.90	0	0[b]
X[c]	251.5 (39500)	1690	1651	5.96	4.97	4.32	4.74	8.68	3	5
XI[c]	251.0 (33600)	1671	1631	5.58	4.73	4.62	4.00	8.79	0	4.5
XII	272.5 (20410)	1670	1635	5.88	3.26	3.26	4.87	7.80	0	0[d]
XIII	273.5 (20350)	1683	1635	5.84	3.22	3.22	4.86	7.74	0	0[d]
XIV	268.0 (21620)	1696	1658	5.76	3.77	3.47	4.87	8.43	0	9.5
XV	291.0 (18620)	1689	1653	5.62	3.92	3.20	5.02	7.88	3	9.5
XVI	253.5 (32820)	1690	1650	6.20	4.58	3.80	4.97	7.87	0	9.5

a) The isolation of this substance was unsuccessful.
b) The J-value was 0 Hz in $CDCl_3$, but 4.5 Hz in benzene-d_6.
c) The NMR spectrum was obtained in DMSO-d_6.
d) The J-value was 0 Hz in $CDCl_3$, but 9 Hz in benzene-d_6.

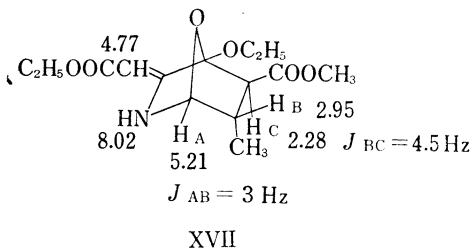
the vicinal protons H_B and H_C of XIV and XV indicates *cis*-configuration. Consequently the structures of all the adducts have been determined to be as shown in Chart 3.



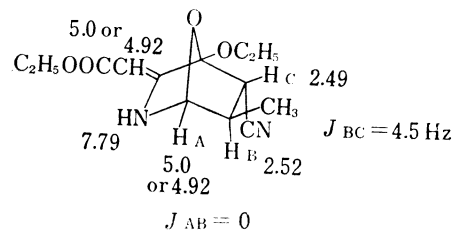
	X	Y		X	Y
XVII :	$COOCH_3$	CH_3	XX :	COOH	CH_3
XVIII :	CN	CH_3	XXI :	COOH	H
XIX :	CN	H			

Chart 4

Lastly, we investigated the reactions of I with asymmetrical dienophiles. Methyl crotonate and crotononitrile were used as the asymmetrical dienophiles and gave the adducts (XVII) and (XVIII), respectively. It is apparent from their NMR spectra that they have an exocyclic double bond. The signal of the H_A proton in XVII appeared as a doublet (J=3 Hz), whereas no splitting was observed at the signal of the H_A proton of XVIII. The coupling constant (4.5 Hz) between the vicinal protons H_B and H_C indicates that they are in *trans*. Accordingly the structures of these adducts have been determined to be as shown by the following formulae.



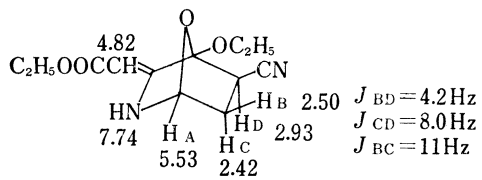
XVII



XVIII

Chart 5[a)]

a) Chemical shifts are indicated by ppm from TMS in $CDCl_3$.



XIX

Chart 6[a)]

a) Chemical shifts are indicated by ppm from TMS in $CDCl_3$.

XVII and XVIII were converted on heating in 10% hydrochloric acid to the pyridine compound (XX), whose IR spectrum was identical with that of the authentic sample prepared by another route.[7)]

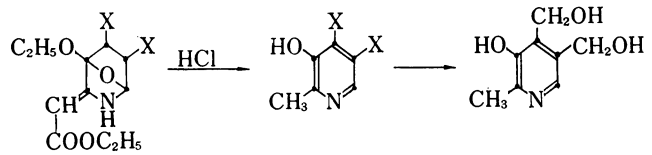
Similarly, the structure of the adduct (XIX) of I and acrylonitrile was determined to be as shown in Chart 6. Treatment of XIX with 10% hydrochloric acid produced 4-carboxypyridine derivative (XXI).

These results indicate that the formation of the adduct furnishing, on acid treatment, the pyridine compound substituted with an electron attracting group at γ position occurs preferentially in the Diels–Alder reaction of I.

The compounds, IV, V, VI, VII XII and XIII, were treated with hydrochloric acid to give the corresponding pyridine compounds, (XXII) and (XXIII), which were converted to pyridoxine by hydrogenation.[8)]

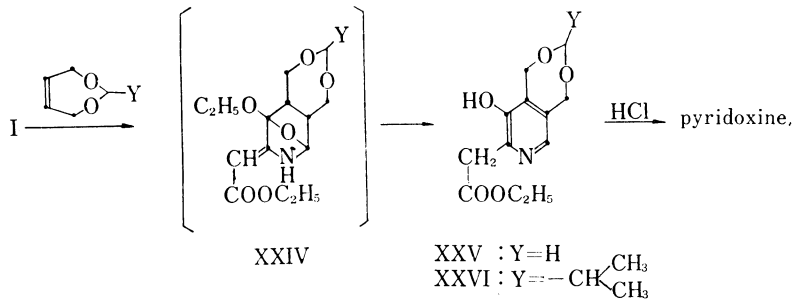
The reaction of I with 4,7-dihydro-1,3-dioxepine derivatives provided also a route to pyridoxine, thus I and 4,7-dihydro-1,3-dioxepine derivatives were heated at 180—190° to

7) T. Matsuo and T. Miki, *Chem. Pharm. Bull.* (Tokyo), in press.
8) A. Cohen, J.W. Haworth and E.C. Hughes, *J. Chem. Soc.*, **1952**, 4374.



IV,V, XII : X= $COOCH_3$ XXII : X= $COOCH_3$ pyridoxine
VI,VII,XIII : X= $COOC_2H_5$ XXIII : X= $COOC_2H_5$

Chart 7



XXIV XXV : Y=H
XXVI : Y= $-CH(CH_3)_2$

Chart 8

afford the 3-hydroxylated pyridines, (XXV) and (XXVI). In order to reveal the process of these reactions, we attempted to follow the reaction by taking the UV spectrum. Consequently, it was observed that the absorption appearing at 270 nm (absorption of an α,β-unsaturated ester) in the early stage changed gradually into 280 nm (absorption of pyridine ring). On the basis of this observation, we conclude that the reaction involves two step: the first step is the Diels-Alder reaction of the oxazole I with the dienophiles to afford the adduct (XXIV), and the second is the formation of pyridine compounds by cleavage of the oxygen bridge. It is considered that the cleavage of oxygen bridge in the reaction occurs by heat. XXVI and XXVII were readily converted to pyridoxine by acidic hydrolysis.

Experimental[9]

5-Ethoxy-4-ethoxycarbonylmethyloxazole (I)——To a suspension of 320 ml of 1,2-dichloroethane, 56 g of P_2O_5 and 32 g of Hyflo Super-Cel (Wako Pure Chem. Ind. Ltd.) was added, over 1 hr at 55—60°, a solution of 40 g of diethyl N-formylaspartate in the same solvent. Vigorous stirring was continued for 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 the solvent, the residual oil was distilled. bp 84—85° (3 mmHg). Yield, 28 g. *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. IR ν_{max}^{liquid} cm^{-1}: 1735, 1665, 1511. NMR ($CDCl_3$, ppm): 1.26 (3H, triplet), 1.37 (3H, triplet), 3.45 (3H, singlet), 4.17 (2H, quartet), 4.23 (2H, quartet), 7.43 (1H, singlet).

2-Carbethoxymethylidene-3-ethoxy-3,6-epoxypiperidine-*endo*-4,5-dicarboxylic Anhydride (II)——1.0 g of oxazole I was allowed to stand with 0.49 g of maleic anhydride at 5—10° in 30 ml of EtOH. After 6 hr, the solution was concentrated to one third of its original volume. The separated crystalline solid was recrystallized from ether to give colorless needles II, mp 118°. Yield, 0.45 g (30%). *Anal.* Calcd. for $C_{13}H_{15}O_7N$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.53; H, 5.21; N, 4.60. IR ν_{max}^{Nujol} cm^{-1}: 1870, 1790, 1683, 1645. UV λ_{max}^{EtOH} nm (ε): 298 (7730), 231 (6620). NMR ($CDCl_3$, ppm): 1.25 (3H, triplet), 1.32 (3H, triplet), 3.86 (1H, doublet, J=9 Hz), 4.0 (2H, quartet), 4.10 (1H, quartet, J=9 and 4.5 Hz), 4.20 (2H, quartet), 4.87 (1H, singlet), 5.67 (1H, doublet, J=4.5 Hz), 8.0 (1H, broad).

9) 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.

***Exo* Compound (III) of II**——A solution of 0.5 g of oxazole I and 0.25 g of maleic anhydride in 30 ml of benzene was heated under reflux for 3 hr. After cooling, a crystalline substance was separated. Recrystallization from EtOH gave colorless prisms III, mp 150.5°. Yield, 0.55 g (74%). *Anal.* Calcd. for $C_{13}H_{15}O_7N$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.81; H, 5.36; N, 4.52. IR ν_{max}^{Nujol} cm^{-1}: 1870, 1790, 1680, 1640. UV λ_{max}^{EtOH} nm (ε): 273.8 (19820). NMR ($CDCl_3$, ppm): 1.32 (3H, triplet), 1.35 (3H, triplet), 3.35 (1H, doublet, J=8.5 Hz), 3.76 (1H, doublet, J=8.5 Hz), 3.97 (2H, quartet), 4.20 (2H, quartet), 5.0 (1H, singlet), 5.79 (1H, singlet), 7.98 (1H, broad).

Isomerization of II to III——A solution of 0.5 g of *endo*-adduct II in 10 ml of $CHCl_3$ was heated at 50° for 3 hr, and was condensed *in vacuo* to give 0.5 g of *exo*-adduct III, mp 117°, which was identical with the sample obtained in the above run.

Diels-Alder Reaction with Dimethyl Fumarate——A mixture of 1.0 g of oxazole I and 1.1 g (1.5 mole) of dimethyl fumarate was heated at 110° for 5 hr. Removal of excess dimethyl fumarate *in vacuo* gave a mixture of (IV) and (V) (3: 7), which was recrystallized from benzene–*n*-hexane to give colorless prisms V, mp 122—123.5°. *Anal.* Calcd. for $C_{15}H_{21}O_8N$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.62; H, 6.16; N, 4.18. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1733, 1680, 1642. UV λ_{max}^{EtOH} nm (ε): 271.5 (19920). NMR ($CDCl_3$, ppm): 1.25 (3H, triplet), 1.33 (3H, triplet), 3.57 (1H, doublet, J=4.5 Hz), 3.68 (1H, doublet, J=4.5 Hz), 3.72 (3H, singlet), 3.78 (3H, singlet), 3.93 (2H, quartet), 4.13 (2H, quartet), 4.71 (1H, singlet), 5.61 (1H, singlet), 7.72 (1H, broad). An attempt to isolate IV was unsuccessful, but the signals of IV in NMR spectrum were assigned as described below. NMR ($CDCl_3$, ppm): 1.28 (3H, triplet), 1.36 (3H, triplet), 3.19 (1H, doublet, J=4.5 Hz), 3.74 (3H, singlet), 3.80 (3H, singlet), *ca.* 3.8 (1H), *ca.* 4.0 (4H), 4.86 (1H, singlet), 5.63 (1H, doublet, J=3.5 Hz), 7.87 (1H, broad).

Diels-Alder Reaction with Diethyl Fumarate——A mixture of 1.0 g of oxazole I and 1.3 g (1.5 mole) of diethyl furmarate was heated at 110° for 4 hr. After removal of excess diethyl fumarate *in vacuo*, to the residue was added ether (30 ml) yielding crystals of (VI). Yield, 1.05 g (56%). Recrystallization from benzene–petroleum ether gave colorless prisms, mp 133—133.5°. *Anal.* Calcd. for $C_{17}H_{25}O_8N$: C, 54.98; H, 6.79; N, 3.79. Found: C, 55.17; H, 6.78; N, 3.46. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1679, 1641. UV λ_{max}^{EtOH} nm (ε): 272.0 (18910). NMR ($CDCl_3$, ppm): 1.2—1.3 (12H), 3.09 (1H, doublet, J=4.5 Hz), 3.82 (1H, quartet, J=4.5 and 3.7 Hz), *ca.* 4.1 (8H), 4.80 (1H, singlet), 5.53 (1H, J=3.7 Hz), 7.77 (1H, broad). Cooling of the mother liquors yielded 0.45 g of (VII). Recrystallization from *n*-hexane gave colorless plates, mp 78.5—79°. *Anal.* Calcd. for $C_{17}H_{25}O_8N$: C, 54.98; H, 6.79; N, 3.77. Found: C, 54.98; H, 6.86; N, 3.80. IR ν_{max}^{Nujol} cm^{-1}: 1736, 1671, 1640. UV λ_{max}^{EtOH} nm (ε): 271.2 (19860). NMR ($CDCl_3$, ppm); 1.25—1.34 (12H), 3.53 (1H, doublet, J=4.5 Hz), 3.67 (1H, doublet, J=4.5 Hz), 3.95—4.23 (8H), 4.72 (1H, singlet), 5.60 (1H, singlet), 7.71 (1H, broad). The NMR spectrum of the reaction mixture showed that the VI/VII ratio was 3/7.

Diels-Alder Reaction with Fumaronitrile——A solution of 3.0 g of oxazole I and 1.2 g of fumaronitrile in 40 ml of EtOH was heated under reflux for 6 hr. The mixture was condensed *in vacuo* to give a crystalline substance, which was a mixture of (VIII) and (IX) (1: 1). Yield, 4.0 g (96%). Repeated recrystallizations from MeOH–ether gave colorless needles VIII of mp 145° and colorless needles IX of mp 170—171°. *Anal.* Calcd. for $C_{13}H_{15}O_4N_3$ VIII: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.36; H, 5.48; N, 14.94. IR ν_{max}^{Nujol} cm^{-1}: 1688, 1650. UV λ_{max}^{EtOH} nm (ε): 268.5 (16630). NMR ($CDCl_3$, ppm): 1.30 (3H, triplet), 1.38 (3H, triplet), 3.24 (1H, doublet, J=4.5 Hz), 3.64 (1H, quartet, J=3 and 4.5 Hz), 4.0 (2H, quartet), 4.22 (2H, quartet), 4.97 (1H, singlet), 5.70 (1H, doublet, J=3 Hz), 8.23 (1H, broad). *Anal.* Calcd. for $C_{13}H_{15}O_4N_3$: IX: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.06; H, 5.56; N, 15.18. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1638. UV λ_{max}^{EtOH} nm (ε): 267.0 (15950). NMR ($CDCl_3$, ppm): 1.29 (3H, quartet), 1.33 (3H, quartet), 3.33 (2H, singlet),[10] 3.95 (2H, quartet), 4.15 (2H, quartet), 5.02 (1H, singlet), 5.66 (1H, singlet), 7.90 (1H, broad).

Diels-Alder Reaction with *trans*-Dibenzoylethylene[11]——A solution of 2.0 g of oxazole I and 2.4 g of *trans*-dibenzoylethylene in 15 ml of EtOH was heated under reflux for 2 hr, and condensed *in vacuo* to give a crystalline solid, which was a mixture of (X) and (XI) (3: 7). Yield, 3.5 g (80%). Repeated recrystallizations from EtOH gave colorless needles X of mp 147—148° and colorless prisms XI of mp 154—155°. *Anal.* Calcd. for $C_{25}H_{25}O_6N$ X: C, 68.95; H, 5.79; N, 3.22. Found: C, 69.12; H, 5.88; N, 3.33. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1651. UV λ_{max}^{EtOH} nm (ε): 251.5 (39500). NMR (DMSO-d_6, ppm): 0.92 (3H, triplet), 1.20 (3H, triplet), 3.60 (2H, quartet), 4.05 (2H, quartet), 4.32 (1H, doublet, J=5 Hz), 4.74 (1H, singlet), 4.97 (1H, quartet, J=3 and 5 Hz) 5.96 (1H, doublet, J=3 Hz), 7.5—8.0 (10H, multiplet), 8.68 (1H, singlet). *Anal.* Calcd. for $C_{25}H_{25}O_6N$ XI: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.66; H, 5.75; N, 3.48. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1671, 1631. UV λ_{max}^{EtOH} nm (ε): 251.0 (33600). NMR (DMSO-d_6, ppm): 1.09 (3H, triplet), 1.12 (3H, triplet), 3.72 (2H, quartet), 4.00 (1H, singlet), 4.02 (2H, quartet), 4.62 (1H, doublet, J=4.5 Hz), 4.73 (1H, doublet, J=4.5 Hz), 5.58 (1H, singlet), 7.5—8.0 (10H, multiplet), 8.79 (1H, singlet).

Diels-Alder Reaction with Dimethyl Maleate——A mixture of 2.0 g of oxazole I and 3.2 g of diemthyl maleate was heated at 110° for 3 hr, and cooled to give a crystalline solid (XII). Yield, 2.24 g (65%). Re-

10) This signal splitted into doublet (J=4.5 Hz) in benzene-d_6.

11) J.B. Conant and R.E. Lutz, *J. Am. Chem. Soc.*, **45**, 1303 (1923).

crystallization from benzene–petroleum ether gave colorless plates of mp 113—113.5°. *Anal.* Calcd. for $C_{15}H_{21}O_8N$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.21; H, 5.96; N, 4.12. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1670, 1635. UV λ_{max}^{EtOH} nm (ε): 272.5 (20410). NMR ($CDCl_3$, ppm): 1.23 (3H, triplet), 1.28 (3H, triplet), 3.26 (2H, singlet),[12] 3.70 (3H, singlet), 3.73 (3H, singlet), 3.88 (2H, quartet), 4.15 (2H, quartet), 4.87 (1H, singlet), 5.88 (1H, singlet), 7.80 (1H, broad).

Diels-Alder Reaction with Diethyl Maleate——As above, 0.5 g of oxazole I was treated with 0.7 g of diethyl maleate to give colorless needles (XIII) (benzene–petroleum ether), mp 98.5—99.5°. *Anal.* Calcd. for $C_{17}H_{25}O_8N$: C, 54.98; H, 6.79; N, 3.77. Found: C, 54.95; H, 6.61; N, 3.91. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1683, 1635. UV λ_{max}^{EtOH} nm (ε): 273.5 (20350). NMR ($CDCl_3$, ppm): 1.25 (6H, triplet), 1.30 (6H, triplet), 3.22 (2H, singlet),[12] 3.9—4.2 (8H, multiplet), 4.86 (1H, singlet), 5.84 (1H, singlet), 7.74 (1H, broad).

Diels-Alder Reaction with Maleonitrile——A solution of 0.2 g of oxazole I and 0.08 g of maleonitrile in 5 ml of dioxane was heated at 70° for 5 hr, and was condensed *in vacuo* to give a crystalline solid, which was a mixture of (XIV) and (XV) (*ca.* 1 : 1). Yield, 0.24 g (86%). Repeated recrystallizations from benzene gave colorless plates XIV of mp 169—170° and colorless prisms XV of mp 139—140°. *Anal.* Calcd. for $C_{13}H_{15}O_4N_3$ XIV: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.29; H, 5.60; N, 15.14. IR ν_{max}^{Nujol} cm^{-1}: 1696, 1658. UV λ_{max}^{EtOH} nm (ε): 268.0 (21620). NMR ($CDCl_3$, ppm): 1.27 (3H, triplet), 1.37 (3H, triplet), 3.47 (1H, doublet, J=9.5 Hz), 3.77 (1H, doublet, J=9.5 Hz), 3.98 (2H, quartet), 4.17 (2H, quartet), 4.87 (1H, singlet), 5.76 (1H, singlet), 8.43 (1H, broad). *Anal.* Calcd. for $C_{13}H_{15}O_4N_3$ XV: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.59; H, 5.42; N, 15.35. IR ν_{max}^{Nujol} cm^{-1}: 1689, 1653. UV λ_{max}^{EtOH} nm (ε): 291.0 (18620). NMR ($CDCl_3$, ppm): 1.29 (3H, triplet), 1.33 (3H, triplet), 3.20 (1H, doublet, J=9.5 Hz), 3.92 (1H, quartet, J=3 and 9.5 Hz), 3.94 (2H, quartet), 5.02 (1H, singlet), 5.62 (1H, dobulet, J=3 Hz), 7.88 (1H, broad).

Diels-Alder Reaction with *cis*-Dibenzoylethylene[11]——A solution of 0.5 g of oxazole I and 0.59 g of *cis*-dibenzoylethylene in 5 ml of EtOH was heated under reflux for 2 hr, and was condensed to give a crystalline solid (XVI). Yield, 0.93 g (85%). Recrystallization from EtOH gave colorless needles of mp 159—160°. *Anal.* Calcd. for $C_{25}H_{25}O_6N$: C, 68.95; H, 5.79; N, 3.22. Found: C, 69.01; H, 5.66; N, 3.40. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1650. UV ν_{max}^{EtOH} nm (ε): 253.5 (32820). NMR ($CDCl_3$, ppm): 0.97 (3H, triplet), 1.28 (3H, triplet), 3.72 (2H, quartet), 3.80 (1H, doublet, J=9 Hz), 4.13 (2H, quartet), 4.58 (1H, doublet, J=9 Hz), 4.97 (1H, singlet), 6.20 (1H, singlet), 7.2—7.6 (10H, multiplet), 7.87 (1H, broad).

Diels-Alder Reaction with Methyl Crotonate——A mixture of 2.0 g of oxazole I and 2.2 g of methyl crotonate was heated at 130° for 8 hr. After removal of excess methyl crotonate *in vacuo*, to the residue was added ether (20 ml) yielding a solid. Recrystallization from MeOH gave colorless prisms (XVII), mp 125—126°. Yield, 0.8 g (27%). *Anal.* Calcd. for $C_{14}H_{21}O_6N$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.24; H, 7.08; N, 4.75. IR ν_{max}^{Nujol} cm^{-1}: 1739, 1678, 1634. UV λ_{max}^{EtOH} nm (ε): 274.5 (19910). NMR ($CDCl_3$, ppm): 0.98 (3H, doublet, J=7 Hz), 1.22 (3H, triplet), 1.26 (3H, triplet), 2.28 (1H, doublet, J=4.5 Hz), 2.95 (1H, multiplet), 3.72 (3H, singlet), 3.80 (2H, quartet), 4.13 (2H, quartet), 4.77 (1H, singlet), 5.21 (1H, doublet, J=3 Hz), 8.02 (1H, broad).

Diels-Alder Reaction with Crotononitrile——A mixture of 2.0 g of oxazole I and 2.1 g of crotononitrile was heated at 90° for 8 hr. After removal of excess crotononitrile *in vacuo*, to the residue was added ether (30 ml) yielding a solid. Recrystallization from MeOH gave colorless plates (XVIII), mp 162—163°. Yield, 1.4 g (52%). *Anal.* Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.41; H, 6.82; N, 10.42. IR ν_{max}^{Nujol} cm^{-1}: 1670, 1636. UV λ_{max}^{EtOH} nm (ε): 272.5 (18270). NMR ($CDCl_3$, ppm): 1.27 (3H, triplet), 1.30 (3H, triplet), 2.49 (1H, doublet, J=4.5 Hz), 2.52 (1H, multiplet), 3.94 (2H, quartet), 4.13 (2H, quartet), 4.92 (1H, singlet), 5.0 (1H, singlet), 7.79 (1H, broad).

Diels-Alder Reaction with Acrylonitrile——A solution of 0.5 g of oxazole I and 0.28 g of acrylonitrile in 2 ml of EtOH was heated under reflux for 4 hr, and condensed to give a crystalline solid (XIX). Yield, 0.56 (88%). Recrystallization from benzene gave colorless plates of mp 135—136°. *Anal.* Calcd. for $C_{12}H_{16}O_4N$: C, 57.13; H, 6.39; N, 11.11. Found: C, 56.98; H, 6.34; N, 11.02. IR ν_{max}^{Nujol} cm^{-1}: 1682, 1642. UV λ_{max}^{EtOH} nm (ε): 273 (18500). NMR ($CDCl_3$, ppm): 1.28 (3H, triplet), 1.36 (3H, triplet), 2.42 (1H, quartet, J=8 and 11 Hz), 2.50 (1H, multiplet), 2.93 (1H, quartet, J=4.2 and 11 Hz), 3.94 (2H, quartet), 4.14 (2H, quartet), 4.82 (1H, singlet), 5.53 (1H, doublet, J=2.5 Hz), 7.74 (1H, broad).

Hydrolysis of XVII with 10% HCl to give (XX)——A suspension of 0.3 g of XVII in 20 ml of 10% HCl and 2 ml of acetic acid was heated at 80° for 5 hr. The mixture was evaporated under reduced pressure to dryness. The residue was neutralized with 10% Na_2CO_3 yielding a solid. Recrystallization from hot water gave colorless needles XX, mp 298—300° (decomp.), whose IR spectrum was identical with that of the authentic sample prepared by another route.[7] Yield, 0.12 g (68%).

Hydrolysis of XVIII with 10% HCl to give XX——A suspension of 0.27 g of XVIII in 20 ml of 10% HCl and 2 ml of acetic acid was heated at 80° for 6 hr. After working up in a similar manner as described above, there was obtained 0.12 g (66%) of XX as a solid.

Hydrolysis of XIX with 10% HCl to give (XXI)——A suspension of 0.24 g of XIX in 20 ml of 10% HCl and 2 ml of acetic acid was heated under reflux for 5 hr. The mixture was evaporated under reduced pres-

12) This signal splitted into doublet (J=9 Hz) in benzene-d_6.

sure to dryness. The residue was neutralized with 3% $NaHCO_3$ yielding a solid. Recrystallization from hot water gave colorless needles XXI, mp 329—330°, whose IR spectrum was identical with that of the authentic sample prepared by another route.[7] Yield, 0.11 g (71%).

Acidic Hydrolysis of IV to (XXII)——To a solution of 0.34 g of IV in 20 ml of MeOH was added 5 ml of 15% HCl. The mixture was heated at 50° for 30 min, and condensed. The residue was neutralized with 3% $NaHCO_3$, yielding a solid. Recrystallization from benzene–AcOEt gave colorless plates XXII, mp 140—141°, whose IR spectrum was identical with that of the authentic sample prepared by another route.[7] Yield, 0.15 g (67%). As above, V and XII were also converted to XXII.

Acidic Hydrolysis of VII to (XXIII)——To a solution of 0.37 g of VII in 30 ml of EtOH was added 7 ml of 15% HCl. The mixture was heated at 60° for 30 min, and condensed to give a crystalline solid XXIII as a hydrochloride, mp 139—140°, whose IR spectrum was identical with that of the authentic sample prepared by another route.[7] Yield, 0.15 g (51%). VI and XIII were also converted to XXIII hydrochloride.

Diels–Alder Reaction of I with 4,7-Dihydro-1,3-dioxepine[13]——A mixture of 1.5 g of oxazole I, 15 g of 4,7-dihydro-1,3-dioxepine and 50 mg of hydroquinone was heated in a sealed tube for 6 hr at 180°. After removal of excess 4,7-dihydro-1,3-dioxepine, the residue was extracted with hot water. The extract was evaporated to give an orange oil, which was chromatographed on silica gel. Elution with benzene afforded colorless crystals, which were recrystallized from benzene–ether to give colorless needles (XXV), mp 128—129°. Yield, 0.22 g (11.5%). *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.91; N, 5.53. Found: C, 56.85; H, 5.85; N, 5.33. UV λ_{max}^{EtOH} nm (ε): 282.5 (5170). IR ν_{max}^{Nujol} cm^{-1}: 1725. NMR ($CDCl_3$, ppm): 1.31 (3H, triplet), 3.95 (2H, singlet), 4.23 (2H, quartet), 4.82 (2H, singlet), 4.98 (2H, singlet), 5.02 (2H, singlet), 7.90 (1H, singlet).

Acidic Hydrolysis of XXV to Pyridoxine——A solution of 0.20 g of XXV in 15 ml of 15% HCl was heated at 60° for 40 min, and evaporated to dryness. To the residue was added acetone–EtOH yielding a crystalline solid of pyridoxine hydrochloride, mp 202—204°, which was proved to be identical with the authentic sample by mixture melting point determination and IR spectrum. Yield, 0.155 g (95%).

Diels–Alder Reaction of I with 2-Isopropyl-4,7-dihydro-1,3-dioxepine[13]——A mixture of 1.0 g of oxazole I, 14.3 g of 2-isopropyl-4,7-dihydro-1,3-dioxepine and 30 mg of hydroquinone was heated in a sealed tube at 190° for 6 hr. After working up in a similar manner as described above, there was obtained a red oil, which was chromatographed on silica gel. Elution with ether afforded colorless crystals, which were recrystallized from benzene to give colorless plates (XXVI), mp 134—134.5°. Yield, 0.2 g (13.5%). *Anal.* Calcd. for $C_{15}H_{21}O_5N$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.15; H, 7.03; N, 4.74. UV λ_{max}^{EtOH} nm (ε): 283 (5250). IR ν_{max}^{Nujol} cm^{-1}: 1727. NMR ($CDCl_3$, ppm): 0.98 (6H, doublet), 1.30 (3H, triplet), 1.90 (1H, multiplet), 3.97 (2H, singlet), 4.22 (2H, quartet), 4.52 (1H, doublet), 4.80 (2H, singlet), 4.85 (2H, singlet), 7.90 (1H, singlet).

Acidic Hydrolysis of XXVI to Pyridoxine——According to the method described for the hydrolysis of XXV, 0.20 g of XXVI was hydrolyzed to give 0.13 g (93%).

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