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A NEW 1,3-DIPOLAR CYCLOADDITION REACTION

SYNTHESIS OF SOME ISOXAZOLIDINE DERIVATIVES*[1]

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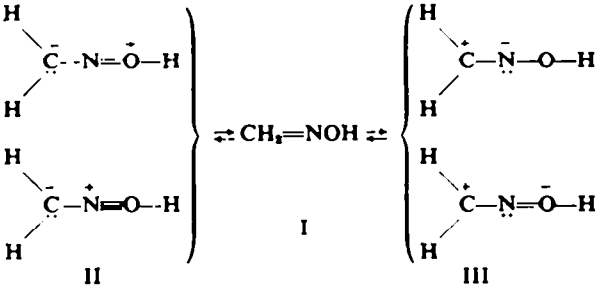
Abstract—A new 1,3-dipolar cycloaddition reaction with formaldoxime as a 1,3-dipole compound has been discovered. Stereospecificity of the reaction and mass spectral data are discussed. With ethyl propiolate, 3,5-diethoxycarbonylpyridine, formed *via* a 1,4-dipolar cycloaddition reaction, was obtained.

THE 1,3-dipolar cycloaddition reaction[1] has received considerable attention in recent years; for one reason, the method provides a novel and facile method for the synthesis of certain heterocyclic compounds. The reaction, according to Huisgen,[1] has been defined as the reaction between dipolarophiles and 1,3-dipole compounds to yield heterocyclic compounds.

To date, a number of 1,3-dipole compounds fall into this category and give rise to various heterocyclic compounds by the reaction with dipolarophiles. No 1,3-dipolar cycloaddition reaction has been recorded, however, with formaldoxime (I)[2] which is prepared by the reaction of formaldehyde and hydroxylamine and is supposed to be equilibrated among the following resonance formulae:

Chart 1



The present paper reports a novel 1,3-dipolar cycloaddition reaction between formaldoxime (I) and some α,β-unsaturated nitriles and esters, which provides a new synthesis of isoxazolidine compounds.

The reaction of acrylonitrile with formaldoxime proceeded in a refluxing aqueous methanol to give an oily substance which was proved to be a mixture of two compounds by TLC. Chromatography of this oily material on silica gel furnished two oily substances, which showed the IR absorption bands attributable to an unconjugated C≡N and C—O bonds (2250, 1035 cm^{-1}) and the elemental analyses were consistent with the formulae IV and V, respectively. The NMR spectra clearly

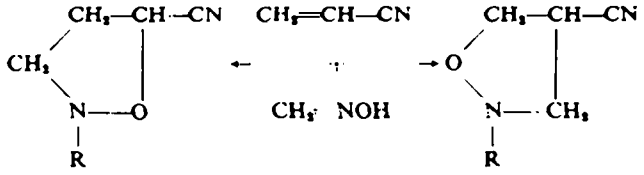
*[1] This paper was presented at the *86th Annual Meeting of the Pharmaceutical Society of Japan*, Sendai, 23 October (1966).

[1] R. Huisgen, *Angew. Chem.* 75, 604 (1963).

[2] W. R. Dunstan and A. L. Bossi, *J. Chem. Soc.* 73, 353 (1898).

demonstrated that the products should have the structures IV and V rather than VI and VII, the latters also being one possibility from a point of view of the classical theory of organic chemistry.

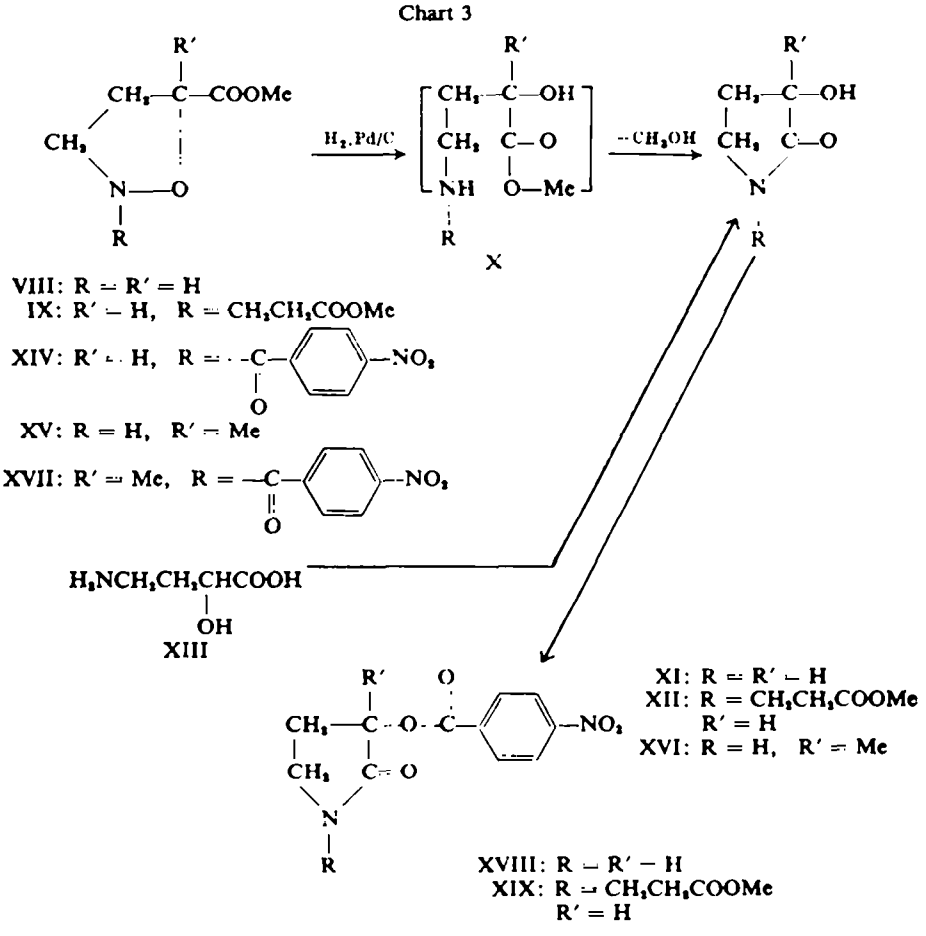
Chart 2



IV: R = H
V: R = CH_2CH_2CN
VI: R = H
VII: R = CH_2CH_2CN

Similarly, an investigation was carried out with methyl acrylate and formaldoxime. The chromatography of the reaction product on silica gel gave two oily substances, which were assigned the structures VIII and IX from the elemental analyses, the mol. wt and NMR measurements [VIII; 4·59 ppm (couple of doublets, J 8 and 5 c/s, 1H), IX; 4·58 ppm (couple of doublets, J 8 and 6 c/s)].

Chart 3



VIII: R = R′ = H
IX: R′ = H, R = CH_2CH_2COOMe
XIV: R′ = H, R = $-C(=O)-C_6H_4-NO_2$
XV: R = H, R′ = Me
XVII: R′ = Me, R = $-C(=O)-C_6H_4-NO_2$
$H_2NCH_2CH_2CHCOOH$ (OH) XIII
XI: R = R′ = H
XII: R = CH_2CH_2COOMe, R′ = H
XVI: R = H, R′ = Me
XVIII: R = R′ = H
XIX: R = CH_2CH_2COOMe, R′ = H

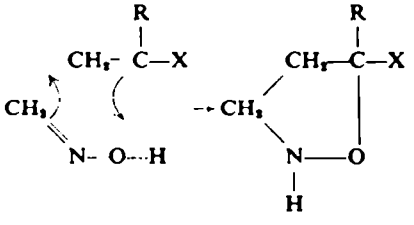
The hydrogenolysis of these compounds over Pd-C at room temperature afforded lactams (XI and XII) in quantitative yields [IR: 1690, 1680 cm^{-1}, respectively, NMR (D_2O) XI; 4·45 ppm (triplet, J 7 c/s, 1H), XII; 4·45 ppm (triplet, J 7 c/s 1H)]. The lactam thus obtained from VIII was identical with an authentic sample prepared from XIII[3] and by comparison of the IR spectra.

As these lactams apparently should be formed *via* an intermediate aminoester X, this provides unambiguous chemical evidence for the structures of the isoxazolidines obtained by the present 1,3-dipolar cycloaddition reaction.

When the reaction was carried out with methyl methacrylate a single product was obtained, of which the elemental analysis, IR spectrum (3200 cm^{-1}) and NMR spectrum [D_2O, 1·52 ppm (singlet, 3H), 2·0–2·7 ppm (multiplet, 2H), 3·0–3·4 ppm (multiplet, 2H), 3·75 ppm (singlet, 3H), 5·71 ppm (broad singlet, 1H)] showed good agreement with the structure XV. Again, the hydrogenolysis of XV yielded 3-hydroxy-3-methyl-2-pyrrolidone (XVI) quantitatively [NMR (D_2O): 1·38 ppm (singlet, 3H), 2·27 ppm (split triplet, J 7 c/s 2H), 3·37 ppm (split triplet, J 7 c/s 2H)].

All these results suggested that the 1,3-dipolar cycloaddition reaction had occurred between α,β-unsaturated nitriles or esters and the resonance form II[3,4] of formaldoxime, which bears a negative charge on the methylene carbon and the positive one at the oxygen. The mechanism of the reaction would then be expressed as follows:

Chart 4



R = H, Me
X = CN, COOMe

In general, it has often been observed[1] that 1,3-dipolar cycloaddition reactions proceed stereospecifically. In order to examine the stereochemical aspects of the cycloaddition with formaldoxime, the reactions with dimethyl fumarate and maleate were studied in detail.

Under similar conditions as aforementioned oily substances were obtained from the fumarate in 88% yield and from the maleate in 73% yield. TLC examination and NMR spectra demonstrated that the crude reaction product from the fumarate did not contain any appreciable quantity of the product obtained from the maleate.

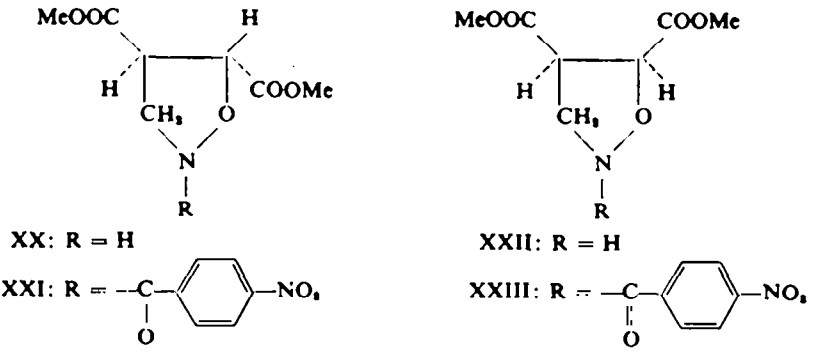
In the NMR spectrum of the purified product from the fumarate the coupling constant between the 4- and 5-protons was 3 c/s; while, the product from the maleate showed a coupling constant of 8 c/s. This, therefore, almost certainly establishes that

[3,4] Similar direction of cycloaddition *via* the back polarization has been observed in the reaction of ethyl acrylate with some nitrones.[4]

[3] E. Fischer and A. Göddertz, *Ber. Dtsch. Chem. Ges.* **43**, 3277 (1910).

[4] R. Huisgen, *Angew. Chem.* 75, 627 (1963); G. R. Delpierre and M. Lamchem, *Proc. Chem. Soc.* 386 (1960).

Chart 5



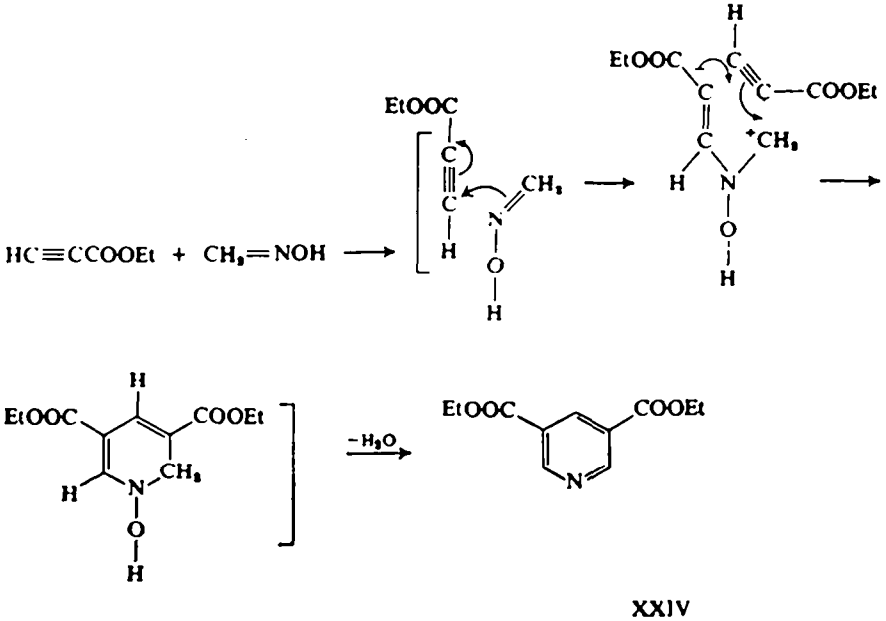
the former should be assigned the structure XX (dihedral angle between the 4- and 5-protons is 120°) and the latter the structure XXII (dihedral angle is 0°).

From these results it is evident that stereospecific *cis*-addition had occurred in the present 1,3-dipolar cycloaddition reaction.

As the isoxazolidine derivatives described were mostly oily at room temperature, solid derivatives and some *p*-nitrobenzoyl derivatives (XIV, XVII, XXI, XXIII and XXVIII) have been synthesized.

As an extention of the present 1,3-dipolar cycloaddition reaction, an acetylenic compound having strongly electron-attracting group was investigated. Thus formaldoxime and ethyl propiolate gave an oily product from which the main product was isolated by chromatography on silica gel as a crystalline substance (m.p. 51°). The mass spectrum (M^+ 223) and elemental analysis established the molecular formula $C_{11}H_{13}O_4N$. From the IR spectrum [nujol, 1725 (C—O), 1600 (C N)cm^{-1}] and the

Chart 6



XXIV

NMR spectrum [1·44 ppm (triplet, J 7 c/s, 6H), 4·48 ppm (quartet, J 7 c/s, 4H), 8·35 ppm (triplet, J 1·5 c/s, 1H), 8·90 ppm (doublet, J 1·5 c/s, 2H)], this compound was established as 3,5-diethoxycarbonylpyridine (XXIV).[5] In this case a 1,4-dipolar cycloaddition mechanism[6] would be operative.

Mass spectra of some isoxazolidine derivatives. The mass spectra of several isoxazolidine derivatives were also studied. Though it lacks detailed data necessary for correct mechanistic interpretation of fragments, we tried to present a possible interpretation of principal fragments and those which seem to support the structures described above.

The mass spectra of isoxazolidine (XXV[7]; Fig. 1), 5-methyl-5-methoxycarbonyl-isoxazolidine (XV; Fig. 2), 2-ethoxycarbonyl-isoxazolidine (XXVI[7]; Fig. 3) and 2-ethoxycarbonyl-5-methoxycarbonylisoxazolidine (XXVII; Fig. 4) exhibit the molecular-ion peaks ranging from 8·5 to 65% of the base peak in the spectra.

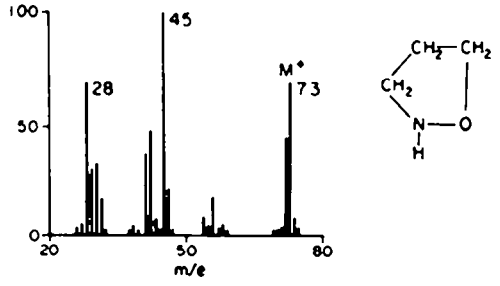


FIG. 1

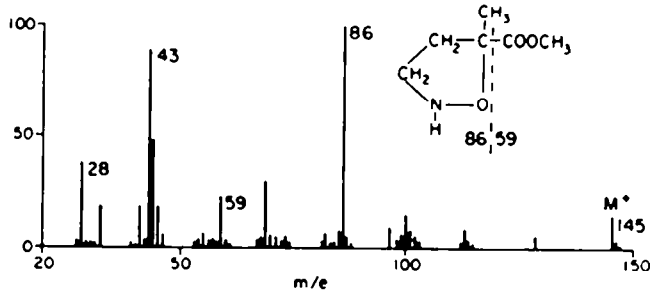


FIG. 2

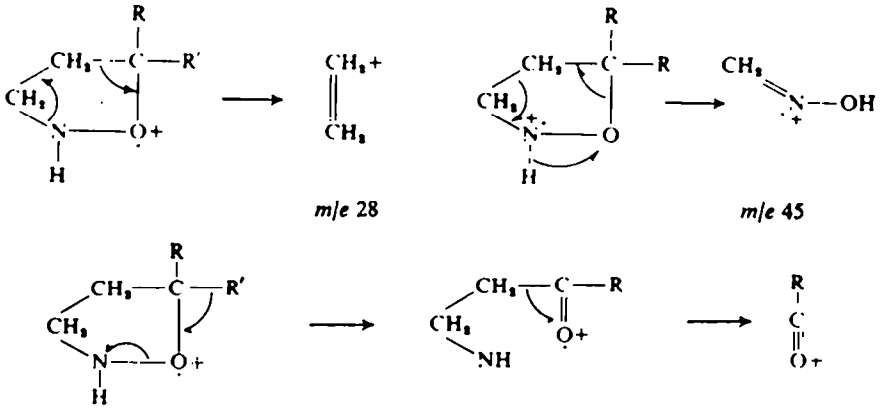
In the mass spectra of XXV and XV, intense fragments at *m/e* 28 and 45 may arise from ethylene- and formaldoxime ion radicals, respectively.

The most remarkable difference in the fragmentation of these two compounds was seen in the abundances at *m/e* 29 and 43 which may be formed as shown below. The compound XV exhibits an intense peak at *m/e* 43 but in almost negligible extent a peak at *m/e* 29.

In the mass spectra of 2-ethoxycarbonylisoxazolidine (XXVI) and 2-ethoxy-carbonyl-5-methoxycarbonylisoxazolidine (XXVII), the base peaks are both at *m/e* 29; the mechanism of the fragmentation would be very much similar to the one described

[5] H. Stetter and H. Hennig, *Chem. Ber.* **88**, 789 (1955).
[6] R. Huisgen and K. Herbig, *Liebigs Ann.* **688**, 98 (1965).
[7] H. King, *J. Chem. Soc.* 432 (1942).

Chart 7



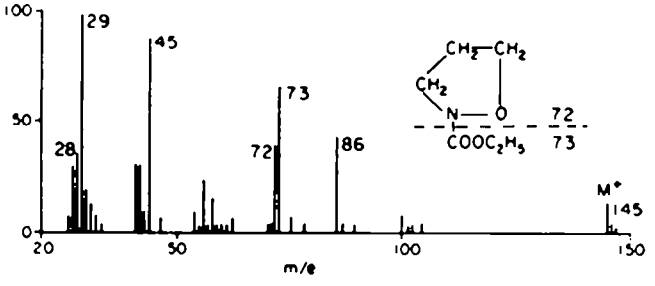


FIG. 3

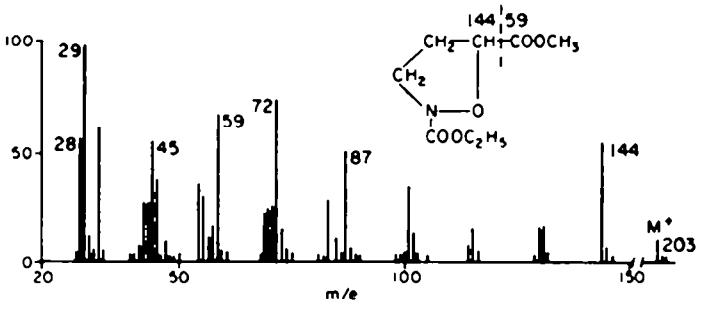


FIG. 4

above. The intense fragment at *m/e* 28 in both compounds (37 and 58%, respectively) implies the presence of an ethylene moiety in the molecule.

EXPERIMENTAL

NMR spectra were measured with a Varian A-60 instrument unless otherwise noted in $CDCl_3$ with TMS as internal standard. All m.ps are uncorrected. Mass spectra were measured with a Hitachi RMU-6D double focusing mass spectrometer; ion source temp 200°, chamber voltage 80 V and evaporation temp 25° (XXV), 150° (XV), 120° (XXVI), 130° (XXVII).

5-Methoxycarbonylisoxazolidine (VIII) *and 2-(β-methoxycarbonylethyl)5-methoxycarbonylisoxazolidine* (IX). To a soln of hydroxylamine hydrochloride (20 g) and NaOH (11·5 g) in 30% MeOHaq (60 ml) was added formaldehyde (37%, 23·5 g) below 35°. To the soln of formaldoxime[9] thus obtained was added methyl acrylate (24·8 g) at 22°. The mixture was heated at 70° for 2 hr and after cooling extracted with $CHCl_3$ to yield an oily substance (28·4 g). Chromatography of this oily substance (720 mg) on silica gel using $CHCl_3$–Me_2CO–EtOH (90:10:2) as solvent yielded VIII (98 mg) and IX (510 mg) as yellowish oil respectively. (VIII, Found: C, 46·05; H, 6·89; N, 10·70. $C_5H_9NO_3$ requires: C, 45·79; H, 6·92; N, 10·67%. IX, Found: C, 49·60; H, 7·08; N, 6·97. $C_9H_{15}NO_5$ requires: C, 49·76; H, 6·96; N, 6·45%.)

2-(p-Nitrobenzoyl)5-methoxycarbonylisoxazolidine (XI). To a soln of VIII (131 mg) in pyridine (0·3 ml) was added *p*-nitrobenzoyl chloride (197 mg). The mixture was heated at 90° for 10 min. After cooling, 3N HCl (5 ml) was added and the separated solid collected and washed with $NaHCO_3$aq and then with H_2O. The pure product crystallized from EtOH as colorless needles, m.p. 75–76°. (Found: C, 51·18; H, 4·09; N, 9·76. $C_{12}H_{12}N_2O_6$ requires: C, 51·43; H, 4·32; N, 9·98%.)

2-Ethoxycarbonyl-5-methoxycarbonylisoxazolidine (XXVII). A soln of VIII (70 mg) and ethyl chloroformate (70 mg) in pyridine (0·1 ml) was heated at 80° for 10 min. After adding 3N HCl (0·1 ml), the reaction mixture was extracted with $CHCl_3$ to give an oily product (71 mg). Chromatography of this oily product on silica gel using $CHCl_3$–Me_2CO–EtOH (90:10:2) as solvent yielded XXVII (60 mg). (Found: 48·05; H, 6·48; N, 6·93. $C_8H_{11}NO_5$ requires: C, 47·29; H, 6·45; N, 6·89%.)

5-Cyanoisoxazolldine (IV), *2-(β-cyanoethyl)5-cyanoisoxazolidine* (V). Using acrylonitrile (15·4 g) in place of methyl acrylate in the firstly described procedure, an oily product (15·6 g) was obtained. Chromatography of this oily product (600 mg) on silica gel using $CHCl_3$–Me_2CO–EtOH (100:3:1) as solvent yielded IV (43 mg) and V (460 mg) as oily matter respectively. IV was converted to XXVIII as yellowish crystals, m.p. 114–116°. [V, Found: C, 55·08; H, 6·24; N, 27·75. $C_7H_8N_2O$ requires: C, 55·61; H, 6·00; N, 27·80%. XXVIII, Found: C, 53·76; H, 3·57; N, 17·18. $C_{11}H_8N_2O_4$ requires: C, 53·44; H, 3·67; N, 17·00%). NMR, IV: 4·80 ppm (triplet, J 7 c/s, 1H), V: 4·85 ppm (triplet, J 7 c/s, 1H).]

5-Methoxycarbonyl-5-methylisoxazolidine (XV). Using methyl methacrylate (29 g) in place of methyl acrylate in the firstly described procedure an oily product (9·5 g) was obtained. Vacuum distillation gave colorless oil, b.p. 63° (0·3 mm Hg). (Found: C, 49·88; H, 7·34; N, 9·81. $C_6H_{11}NO_3$ requires: C, 49·64; H, 7·64; N, 9·65%.)

2-(p-Nitrobenzoyl)5-methoxycarbonyl-5-methylisoxazolidine (XVII). XV and *p*-nitrobenzoyl chloride in pyridine gave yellowish prisms, m.p. 89–91°. (Found: C, 52·85; H, 5·02; N, 9·46. $C_{13}H_{14}N_2O_6$ requires: C, 53·06; H, 4·80; N, 9·52%.)

3-Hydroxy-2-pyrrolidone (XI). Hydrogenation of VIII (131 mg) in EtOH (15 ml) with a Pd catalyst (10% on charcoal, 100 mg) resulted in smooth absorption of 1 mole equivalent H_2 in a period of about 30 min. Filtration, evaporation of solvent gave a solid matter (100 mg). The pure product crystallized from $CHCl_3$–hexane as colorless prisms, m.p. 85° (sinters at 75°). (Found: C, 47·30; H, 6·77; N, 13·78. Calc. for $C_4H_7NO_2$: C, 47·52; H, 6·98; N, 13·86%.)

1-(β-Methoxycarbonylethyl)3-hydroxy-2-pyrrolidone (XII). Hydrogenation of IX (217 mg) in EtOH (20 ml) with a Pd catalyst (10% on charcoal, 200 mg) and purification of the product by the chromatography on silica gel using $CHCl_3$–Me_2CO–EtOH (80:20:3) as solvent yielded XII as an oil (167 mg). (Found: C, 51·61; H, 6·83; N, 7·39. $C_8H_{13}NO_4$ requires: C, 51·33; H, 7·00; N, 7·48%.)

3-Hydroxy-3-methyl-2-pyrrolidone (XVI). Hydrogenation of XV (145 mg) in EtOH (15 ml) with a Pd catalyst (10% on charcoal, 150 mg) and recrystallization of the crude product from EtOH–hexane afforded XVI as colorless needles, m.p. 163° (115 mg). (Found: C, 51·94; H, 7·75; N, 12·26. $C_5H_9NO_2$ requires: C, 52·16; H, 7·88; N, 12·17%.)

3-(p-Nitrobenzoyloxy)2-pyrrolidone (XVIII). Treatment of XI with *p*-nitrobenzoyl chloride in pyridine gave yellowish prisms, m.p. 161·5–163°. (Found: C, 52·74; H, 4·14; N, 10·87. $C_{11}H_{10}N_2O_5$ requires: C, 52·88; H, 4·03; N, 11·20%.)

1-(β-Methoxycarbonylethyl)3-(p-nitrobenzoyloxy)2-pyrrolidone (XIX). Yellowish prisms, m.p. 102–104°. (Found: C, 53·43; H, 4·75; N, 8·40. $C_{15}H_{16}N_2O_7$ requires: C, 53·57; H, 4·80; N, 8·33%.)

4,5-trans-Bis(methoxycarbonyl)isoxazolidine (XX). Using methyl fumarate (10 g) in place of methyl acrylate in the firstly described procedure, the mixture was refluxed for 2 hr. After evaporation

of MeOH the residue was taken up with $CHCl_3$ to give an oily product (11·5 g). Chromatography of this oily product (800 mg) on silica gel using $CHCl_3$–Me_2CO–EtOH (90:10:2) as solvent yielded XX (620 mg) as an oil which solidified on standing, m.p. 57–58°. (Found: C, 44·55; H, 5·97; N, 7·19. $C_7H_{11}NO_5$ requires: C, 44·44; H, 5·86; N, 7·41%.)

2-(p-*Nitrobenzoyl*)4,5-trans-*bis*(*methoxycarbonyl*)*isoxazolidine* (XXI). Reaction of *p*-nitrobenzoyl chloride with XX in pyridine afforded XXI as colorless crystals, m.p. 84–85°. (Found: C, 49·50; H, 4·43; N, 8·31. $C_{14}H_{14}N_2O_8$ requires: C, 49·71; H, 4·17; N, 8·28%.)

4,5-cis-*Bis*(*methoxycarbonyl*)*isoxazolidine* (XXII). In a similar procedure to obtain XX, methyl maleate (10 g) gave an oily product (9·6 g). Purification by chromatography on silica gel afforded yellowish oil. (Found: C, 44·36; H, 5·88; N, 7·16. $C_7H_{11}NO_5$ requires: C, 44·44; H, 5·86; N, 7·41%.)

2-(p-*Nitrobenzoyl*)4,5-cis-*bis*(*methoxycarbonyl*)*isoxazolidine* (XXIII). Treatment of XXII with *p*-nitrobenzoyl chloride in pyridine gave XXIII as colorless crystals, m.p. 82·5–83·5°. Admixture with XXI caused depression of the m.p. (Found: C, 49·44; H, 4·22; N, 8·29. $C_{14}H_{14}N_2O_8$ requires: C, 49·71; H, 4·17; N, 8·28%.)

3,5-*Diethoxycarbonylpyridine* (XXIV). To a soln of ethyl propiolate (3·8 g) in 50% MeOHaq (40 ml) was added trimeric formaldoxime[9] (1·0 g). The mixture was refluxed for 4 hr. After evaporation of MeOH the residue was extracted with $CHCl_3$ to give reddish yellow oil (4·3 g). Chromatography of this oily product on silica gel using $CHCl_3$–Me_2CO–EtOH (93:7:1) as solvent gave XXIV as an oil which solidified on standing, m.p. 51°.[8] (Found: C, 59·22; H, 5·84. Calc. for $C_{11}H_{13}NO_4$: C, 59·18; H, 5·87%. Mass: M^+ 223.)

Acknowledgment—The authors are grateful to Dr. S. Tatsuoka, Head of the Division, and Dr. Y. Abe, Head of the Chemical Laboratories, for the encouragement throughout this work. Thanks are also due to Mr. M. Kan for elemental analysis, to Mr. T. Shima for the measurement of mass spectra and to Miss F. Kasahara for the measurement of NMR spectra.