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The Addition Reaction of Diethyl Acetamidomalonate Anion to Ethyl *α,β*-Dibromoacrylate, and the Base-catalyzed Reactions of the Adduct

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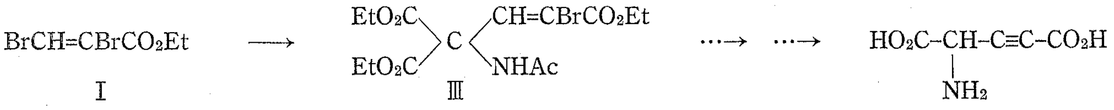
The addition reaction of diethyl acetamidomalonate anion to ethyl *α,β*-dibromoacrylate (I) and base catalyzed reactions of the adduct, diethyl 4-acetamido-2-bromo-4-carbethoxy-*trans*-glutaconate (IIIb), were described. Addition of bromine to ethyl propiolate in carbon tetrachloride or acetic acid gave exclusively ethyl *cis-α,β*-dibromoacrylate (Ia). The reaction of both Ia and ethyl *trans-α,β*-dibromoacrylate (Ib) with diethyl acetamidomalonate anion gave the same product IIIb. Treatment of IIIb with sodium amide or potassium *t*-butoxide gave ethyl 2-bromo-3-(5-ethoxy-2-methyl-4-oxazolyl)acrylate (VIII). The reaction of IIIb with sodium ethoxide afforded diethyl 4-acetamido-4-ethoxy-*trans*-glutaconate (XVIII). The structures of VIII and XVIII were proved.

In the preceding paper, we reported the Michael reaction of ethyl *β*-chloroacrylate with acylaminomalonic esters.[2] A similar reaction was carried out with ethyl *α,β*-dibromoacrylate (I) and diethyl acetamidomalonate anion to obtain diethyl 2-bromo-4-acetamido-4-carbethoxy-glutaconate (III), which could be used as the starting material for the synthesis of yet unknown *α*-acetylenic-*α*-aminoacids.



The glutaconate III, however, resisted dehydrobromination by strong bases and underwent unexpected reactions. In this paper, we will describe the stereochemistry of the Michael reaction and the base-catalyzed reactions of the product III.

The starting ethyl *α,β*-dibromoacrylate was prepared by addition of bromine to ethyl propiolate. Bromine was absorbed quickly at room temperature in carbon tetrachloride under ultraviolet irradiation or in glacial acetic acid, but a higher temperature (60—65°) and a longer reaction time (3 hr) were required when the addition was carried out in carbon tetrachloride without illumination. Under these reaction conditions exclusively one isomer (Ia) of ethyl *α,β*-dibromoacrylate was obtained, in contrast with the addition of chlorine to methyl propiolate which yielded a 41:39 mixture of methyl *cis*-[3] and *trans-α,β*-dichloroacrylate.[4] The nuclear magnetic resonance (NMR) spectrum of Ia showed a singlet peak at 8.23 ppm due to the *β*-hydrogen in addition to the carbethoxy signals at 4.30 (2H, quartet, $J=7$ cps) and 1.35 ppm (3H, triplet, $J=7$ cps). The spectrum of the crude sample before distillation showed no peaks due to the other isomer. Based on the chemical shifts for the *β*-hydrogens of methyl *α,β*-dichloroacrylates[4] (7.71 and 7.01 ppm for the *cis*- and the *trans*-

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[1] Location, *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*

[2] Y. Kishida and A. Terada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2417 (1969).

[3] In the *α,β*-dihalogenoacrylic acid derivatives, the terms, *cis*- and *trans*- are related to the two halogen atoms.

[4] A.N. Kurtz, E. Billups, R.B. Greenlee, H.F. Hamil and W.T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

[5] The NMR spectra were taken on Varian A-60 spectrometer in carbon tetrachloride if other solvents were not indicated. Tetramethylsilane was used as the internal standard.

ester, respectively), we assigned the *cis*-structure (*cis*-addition product) to Ia. This was supported by the fact that the alkaline hydrolysis of Ia afforded the known[6] *cis*-α,β-dibromoacrylic acid (IIa) of mp 86.5—88°, whose NMR spectrum showed two singlets at 8.48 (1H, vinyl proton) and 11.80 ppm (1H, carboxylic hydrogen).

To establish the *cis*-configuration for Ia, the synthesis of the *trans*-isomer (Ib) was attempted. Rappe and Andersson have reported[6a] that addition of bromine to propiolic acid in water afforded *trans*-α,β-dibromoacrylic acid (IIb) of mp 73—74° in addition to the previously reported[6b] *cis*-dibromo acid (IIa) of mp 85—86°. We repeated this addition reaction and found that when the temperature was kept at 20° throughout the reaction, *trans*-addition occurred exclusively to yield only the *trans*-isomer (IIb). Evaporation of water without heating under reduced pressure left a crude sample of IIa, mp 67—71° whose NMR spectrum showed only singlet peaks at 7.40 and 12.00 ppm,[6a] assigned to the β-hydrogen and the carboxylic proton, respectively. Careful recrystallization under 25° from petroleum ether gave pure *trans*-α,β-dibromoacrylic acid (IIb) of mp 73—74°. This acid (IIb) was so labile in a solution at elevated temperatures that recrystallization from boiling petroleum ether gave a 2:1 mixture[7] of the *trans*- (IIb) and the *cis*- acid (IIa). Moreover, when the bromine addition to propiolic acid was carried out without cooling, the temperature rose to 35° and a 8:3 mixture[7] of IIb and IIa was produced. In these mixtures, the presence of IIa was noticed by the appearance of a new singlet peak at 8.48 ppm in NMR spectrum, in addition to the peak at 7.40 ppm due to IIb. The formation of IIa reported in the literature[6] should be the result of isomerization of the firstly formed *trans*-addition product (IIb).

It has been observed for many geometrical pairs of α,β-unsaturated acids and esters that the β-hydrogen situated *cis* to the carboxyl or ester group shows an absorption peak at a lower field than that *trans* to the carboxylic substituent, because of the deshielding effect of these substituents.[8]

The esterification of the *trans*-acid (IIb) afforded a 1:3 mixture[7] of Ia and Ib, whose NMR spectrum showed the peaks assigned to Ib at 7.08 (1H, singlet), 4.33 (2H, quartet, $J=7$ cps) and 1.38 ppm (3H, triplet, $J=7$ cps), besides the peaks due to Ia. The higher field chemical shift of the vinyl proton of Ib (7.08 ppm) than that of Ia (8.23 ppm) indicates that Ia is the *cis*-isomer and Ib the *trans*.

These results confirm the stereospecific *cis*-addition of bromine to ethyl propiolate under the conditions employed. It should be noted that this is the first example of an exclusive *cis*-addition of halogen to a carbon–carbon triple bond.

Diethyl acetamidomalonate reacted smoothly at 25° with Ia in the presence of potassium *t*-butoxide to afford diethyl 2-bromo-4-acetamido-4-carbethoxyglutaconate (IIIb) of mp 140—141° in 87% yield. The NMR spectrum in deuteriochloroform showed an olefinic proton at 8.38 (1H, singlet), a broad singlet due to the amide proton at 7.35, a quartet due to methylene protons of the three carbethoxy groups at 4.50 (6H, $J=7$ cps), an acetyl signal at 2.03 (3H, singlet), two methyl triplets at 1.50 (3H, $J=7$ cps) and 1.33 ppm (6H, $J=7$ cps). The low field chemical shift of 8.38 ppm suggests that the vinyl hydrogen is situated *cis* to the carbethoxy group, *i.e.* IIIb is diethyl 2-bromo-4-acetamido-4-carbethoxy-*trans*-glutaconate.

Catalytic hydrogenation of IIIb using platinum oxide gave diethyl N-acetyl-2-carbethoxyglutamate (IV) of mp 64—65°, whose NMR spectrum showed an A_2B_2 type multiplet centered at 2.38 ppm, besides other peaks due to an amide, an acetyl and three carbethoxy groups. Hydrolysis of IV followed by decarboxylation and esterification with diazomethane afforded

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[6] *a*) C. Rappe and K. Andersson, *Arkiv. Kemi*, **24**, 303 (1965) [*C.A.*, **63.** 4156*e* (1966)]; *b*) E. Baudrowski, *Chem. Ber.*, **15**, 2698 (1882).

[7] The ratio was measured by the integration of the NMR absorptions due to the β-hydrogens of the isomeric pair.

[8] L.M. Jackmann and R.H. Wiley, *Proc. Chem. Soc.*, **1958** 196; *idem*, *J. Chem. Soc.*, **1960**, 2886; L.A. Singer and N.P. Kong, *J. Am. Chem. Soc.*, **89**, 5251 (1967); *idem*, *Tetrahedron Letters*, **1967**, 643.

dimethyl N-acetylglutamate (V) of bp 128—132° (0.001 mmHg), whose infrared (IR) spectrum was identical with that of an authentic sample.[9] These results proved the carbon skeleton of IIIb.

The *trans*-structure of IIIb was established by photo-isomerization of IIIb. After 18 hr ultraviolet irradiation of a chloroform solution of IIIb in the presence of iodine at 35—40°, the formation of a 1:4 mixture of IIIa and IIIb was observed by NMR spectroscopy in deuteriochloroform. In the 7.5—8.5 ppm region, a sharp singlet appeared at 7.67 ppm, in addition to the peak at 8.38 ppm due to the vinyl proton of IIIb, and was assigned to the olefinic proton of IIIa situated *trans* to the carbethoxy group. A pure sample of the *cis*-isomer (IIIa), mp 95—96°, was isolated by fractional recrystallization and showed the following NMR

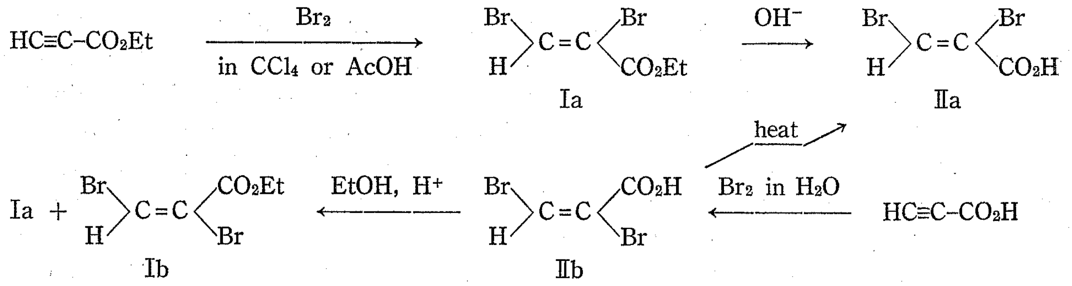


Chart 1

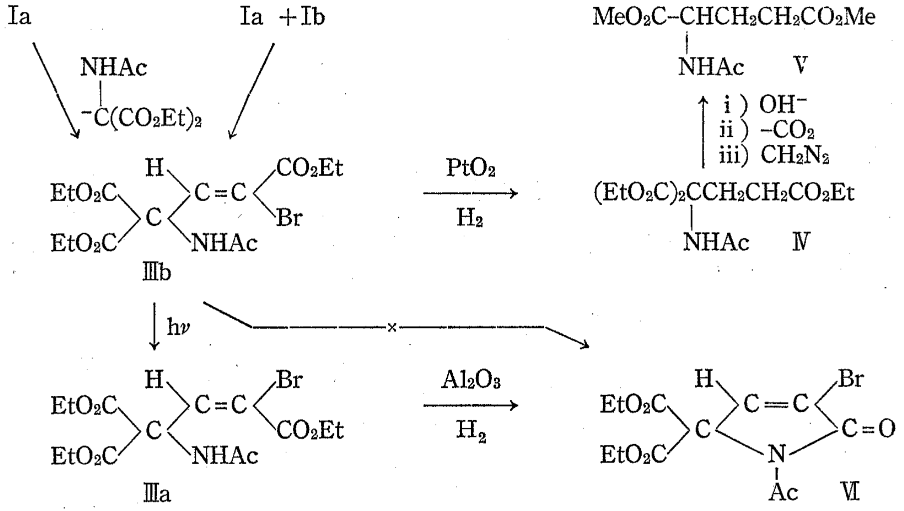
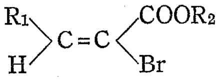
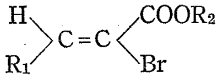


Chart 2

Table I. Chemical Shifts for the Vinyl Proton of α-Bromoacrylates

R_1	R_2	 No.	ppm	 No.	ppm
Br	H	IIb	7.40	IIa	8.48
Br	Et	Ib	7.08	Ia	8.23
Br	Me			X	8.25
adm-	Et	IIIa	7.67[a]	IIIb	8.38[a]
adm-	Me			IX	8.40[a]

adm-=acetamidodicarbethoxymethyl
a) in $CDCl_3$, others in CCl_4

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[9] E. Abdelhalden and G. Pitschalk, *Z. Physiol. Chem.*, **265** 31 (1940) [*C.A.*, **35** 1383⁶ (1941)].

spectrum in deuteriochloroform: 7.67 (1H, singlet, vinyl proton), 7.22 (1H, broad singlet, –NH–CO–), 4.28 (4H, quartet, $J=7$ cps, –O–CH_2–Me), 4.26 (2H, quartet, $J=7$ cps, –O–CH_2–Me), 1.98 (3H, singlet, –CO–CH_3), 1.33 (3H, triplet, $J=7$ cps, –CH_3), and 1.25 ppm (6H, triplet, $J=7$ cps, –CH_3). The lower chemical shift of the vinyl proton of IIIb (8.38 ppm) than that of the other isomer (IIIa) (7.67 ppm) shows that IIIb has the *trans* structure and IIIa *cis*. The NMR data for the geometrical pairs of acrylic acid derivatives are listed in Table I.

The configurations of IIIa and IIIb were further proved by the following chemical evidence. When treated with a column of alumina (Woelm, Grade II), IIIa was converted with a loss of ethanol to 1-acetyl-3-bromo-5,5-dicarbethoxy-2-oxo-3-pyrroline (VI) of mp 107—108°, while the *trans*-isomer (IIIb) did not change under the same conditions. When a 5:4 mixture[7) of IIIa and IIIb was chromatographed on an alumina column, VI and unchanged IIIb were obtained.

The substitution reactions of various activated vinyl halides with thiols and amines have been shown to proceed with retention of configuration.[10) In the reaction of Ia with acetamidomalonate anion, a similar displacement seemed to occur with complete retention of configuration, yielding IIIb. The reaction of a 1:3 mixture[7) of Ia and Ib with acetamidomalonate anion, however, afforded only the same product IIIb. The crude product before recrystallization was examined by NMR spectroscopy, but any peak that might be due to the *cis*-isomer (IIIa) was not observed. This shows that a thermodynamically controlled addition–elimination mechanism would be operative as illustrated in Chart 3. Addition of acetamidomalonate anion to Ia or Ib yields a common intermediate anion (VII), and the elimination of the bromine atom from VII occurs preferentially in a manner to give the thermodynamically stable isomer (IIIb). Such an addition–elimination mechanism has been depicted for the reaction of β-chlorocrotonic esters with thiols.[10c)

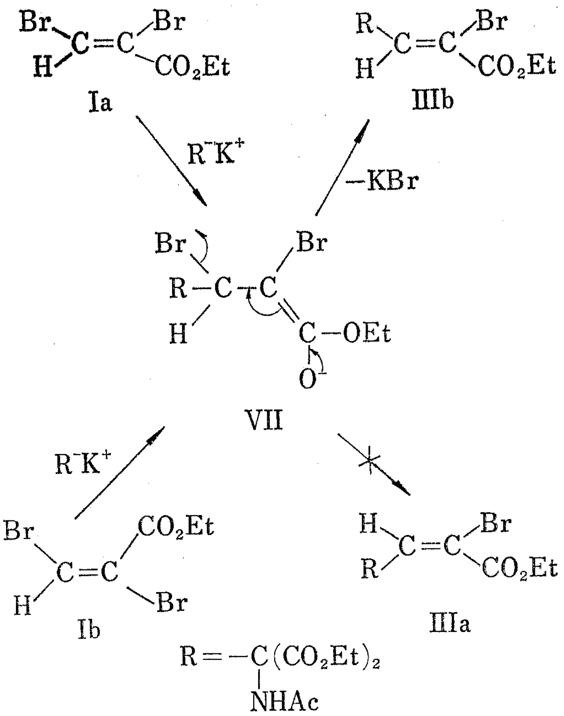

Chart 3

The attempts to obtain an acetylenic compound by treating IIIb with various bases were unsuccessful, but other interesting reactions occurred. Heating of IIIb in a refluxing potassium *t*-butoxide solution for 2 hr gave a crystalline compound (VIII), $C_{11}H_{14}O_4NBr$, of mp 83—84° in 30% yield. The reaction of IIIb with sodium amide in boilding tetrahydrofuran or toluene afforded the same product in better yields (53 and 69%, respectively). The NMR spectrum of VIII showed absorption peaks at 7.70 (1H, singlet), 4.31 (2H, quartet, $J=7$ cps), 4.22 (2H, quartet, $J=7$ cps), 2.35 (3H, singlet), 1.43 (3H, triplet, $J=7$ cps) and 1.33 ppm (3H, triplet, $J=7$ cps), indicating that one of the three carbethoxy groups of IIIb was lost. The low field signal at 7.70 ppm suggested the presence of a *trans* α,β-unsaturated

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10) *a)* W.E. Truce, J.E. Parr and M.L. Gobarty, *Chem. Ind.* (London), **1967**, 660 and the references cited therein; *b)* F. Montanari and A. Negrini, *Gazz. Chim. Ital.*, **87**, 1102 (1957); *c)* D.E. Jones, R.O. Morris, C.A. Vernon and R.F.M. White, *J. Chem. Soc.*, **1960** 2349; *d)* A.E. Pohland and W.R. Benson, *Chem. Rev.*, **66**, 161 (1966).

ester system and that one of the geminal carbethoxy groups was lost. To ascertain this presumption, a similar reaction with methyl 4-acetamido-2-bromo-4,4-dicarbethoxy-*trans*-2-butenoate (IX) was carried out. Addition of bromine to methyl propiolate in acetic acid also gave exclusively methyl *cis*-α,β-dibromoacrylate (X), which showed NMR absorption peaks at 8.25 (1H, singlet, olefinic proton) and 3.85 ppm (3H, singlet,-CO_2CH_3). The reaction of X with acetamidomalonate anion afforded IX of mp 127—128°, the *trans*-structure of which was assigned by the low field NMR absorption peak at 8.40 ppm, as in the case of IIIb. Treatment of IX with sodium amide in boiling tetrahydrofuran gave a solid compound of mp 97—98°, $C_{10}H_{12}O_4NBr$, whose NMR spectrum showed peaks at 7.75 (1H, singlet), 4.35 (2H, quartet, $J=7$ cps, -O-CH_2Me), 3.80 (3H, singlet, -CO_2CH_3), 2.37 (3H, singlet, -$COCH_3$) and 1.45 (3H, triplet, $J=7$ cps, -CH_3). The peak at 3.80 ppm due to the carbomethoxy group indicated that a carbethoxy group eliminated form IX. Alkaline hydrolysis of VIII and XI gave the same acid (XII) of mp 167°. These results suggest that a cyclization reaction between the acetamido and one of the geminal carbethoxy groups of III and IX occurred, giving ethyl and methyl *trans*-2-bromo-3-(2-methyl-5-ethoxy-4-oxazolyl)acrylate, VIII and IX, respectively. The NMR spectra described above and the IR data listed in Table II were reasonable for the proposed structure of VIII and XI. A similar oxazole derivative, ethyl *trans*-3-(5-ethoxy-2-phenyl-4-oxazolyl)acrylate (XIII) of mp 83—84°, was obtained from diethyl 4-benzamido-4-carbethoxyglutaconate.[2] The NMR spectrum of XIII showed peaks at 8.0—7.2 (5H, aromatic multiplet), 7.40 (1H, doublet, $J=16$ cps), 6.38 (1H, doublet, $J=16$ cps), 4.42 (2H, quartet, $J=7$ cps), 4.19 (2H, quartet, $J=7$ cps), 1.47 (3H, triplet, $J=7$ cps) and 1.30 ppm (3H, triplet, $J=7$ cps). The *trans*-structure with respect to the side chain double bond was evidenced by the large spin-spin coupling constant (16 cps) between the two olefinic protons. In addition a low field chemical shift (7.40 ppm) of the vinyl hydrogen β to the carbethoxy group was noticed. Hydrolysis of XIII gave the corresponding acid, *trans*-3-(5-ethoxy-2-phenyl-4-oxazolyl)acrylic acid (XIV) of mp 198—201°, which was in turn hydrogenated catalytically to 3-(5-ethoxy-2-phenyl-4-oxazolyl)propionic acid (XV) of mp 91—92.° To confirm the structure of these oxazole derivatives, XV was synthesized in-

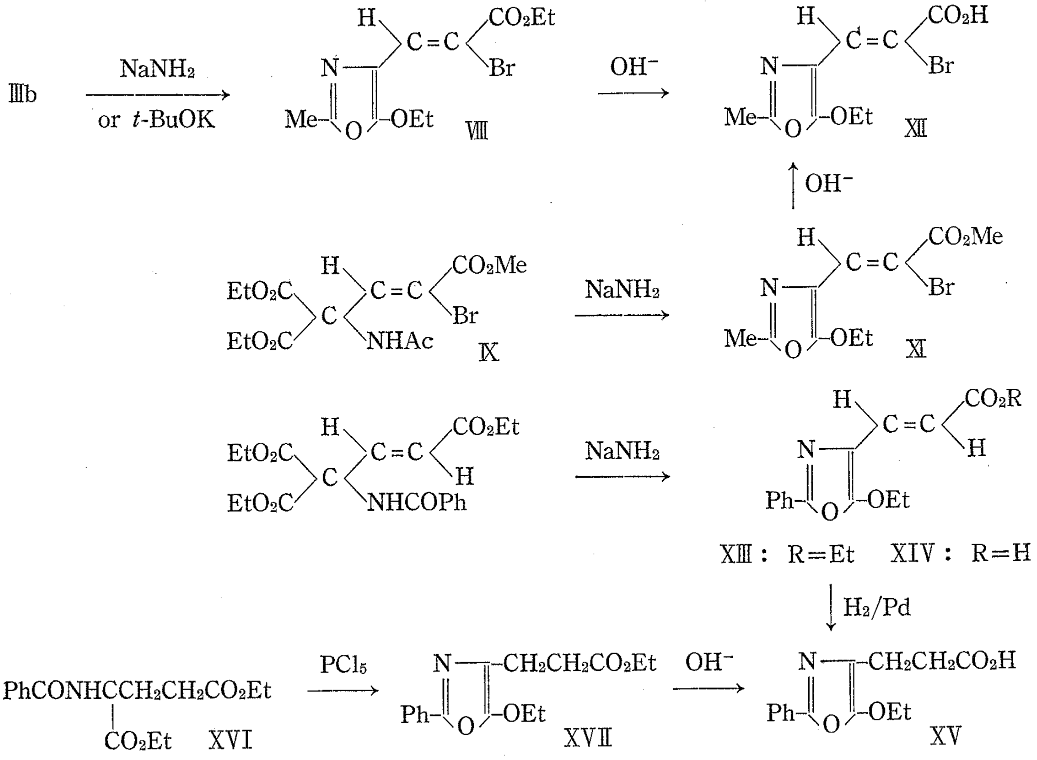
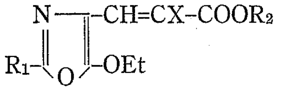


Chart 4

dependently. According to the general method for the synthesis of 5-ethoxyoxazoles,[11] ethyl 3-(5-ethoxy-2-phenyl-4-oxazolyl)propionate (XVII) was prepared by heating diethyl N-benzoylglutamate (XVI) with phosphorous pentachloride in chloroform. Alkaline hydrolysis of XVII afforded the corresponding acid (XV), which was identical in all respects with the sample obtained from XIV.

Table II. IR and UV Spectra of 3-(4-Oxazolyl)acrylic Acids and Esters



No.	R$_1$	R$_2$	X	Solvent	IR$^{a)}$ cm^{-1}				UV$^{b)}$ $^{\mathrm{EtOH}}_{\mathrm{max}}$ mμ(e)
					Oxazole ring[12]		Side chain $\nu_{C=O}$	Side chain $\nu_{C=C}$	
VIII	Me	Et	Br	CCl_4	1590 s	1479 w	1724 s	1634 s	229 (6010)
					1366 m	901 m	1706 s		312 (20600)
XI	Me	Me	Br	CCl_4	1592 s	1481 w	1730 m	1636 s	
					1355 m	901 m	1712 s		
XIII	Ph	Et	H	CCl_4	1613 s	1481 w	1712 s	1644 s	222 (20050)
					1343 m	898 w			316 (26770)
XIV	Ph	H	H	$CDCl_3$	1602s$^{c)}$	1484 w	1689 s	1629 s	223 (18190)
					1343 m	894 m			311.5(24530)

a) Perkin–Elmer model 221 *b)* Beckman DK–2 *c)* shoulder

When IIIb was heated in a sodium ethoxide solution, a bromine–free product (XVIII) or mp 76—77° with a formula of $C_{13}H_{21}O_6N$ was obtained in 76.6% yield. In another run, a small amount of XII (2.9%) was isolated by silica gel column chromatography together with the main product (XVIII). The NMR spectrum of XVIII showed a broad singlet at 7.42, two doublets at 6.82, 6.13 ($J=16$ cps), two almost overlapping quartets at 4.20, 4.17 (4H in total, $J=7$ cps), a multiplet centered at 3.55 (2H), a singlet at 1.97 (3H) and two triplets at 1.27 (6H, $J=7$ cps) and 1.18 ppm (3H, $J=7$ cps). The multiplet at 3.55 ppm, which approximated a double quartet, and the methyl signal at 1.18 ppm were interpreted as due to an ethoxy group attached to an asymmetric carbon atom. Such non–equivalence of methylene protons linked by an oxygen atom to an asymmetric center has been recognized.[13]

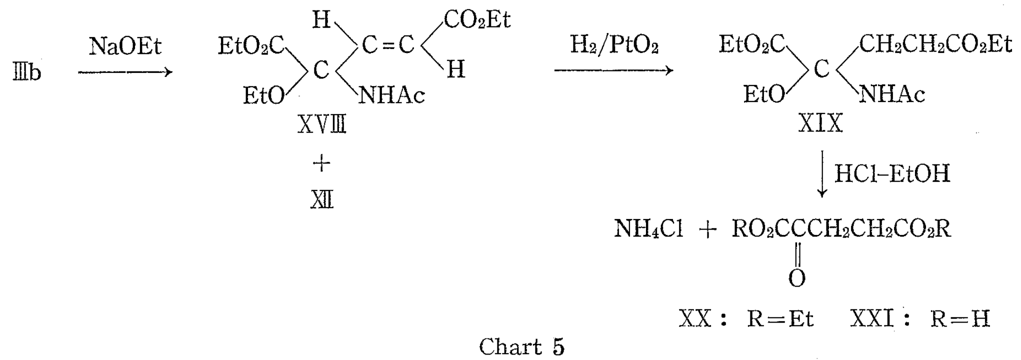


Chart 5

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[11] J.W. Cornforth, "The Chemistry of Penicillin," ed. by H.T. Clarke, J.R. Hohnson and Sir Robert Robinson, Princeton Univ. Press, 1949, p. 688.

[12] G. Sbrana, E. Castellucci and M. Ginanneschi, *Spectrochim. Acta*, 23 A 751 (1967); E. Borello, A. Zecchina and A. Appiano, *ibid.*, **22**, 977 (1966).

[13] J.A. Elvidge and R.G. Forster, *J. Chem. Soc.*, **1964**, 981; J.D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964).

From other signals, the presence of an acetamido group, two vinyl hydrogens attached to a *trans* double bond and two carbethoxy groups was evidenced. The IR spectrum of XVIII in carbon tetrachloride supported this evidence, showing two ester bands at 1761, 1724, amide bands at 3333, 1701, 1484 and a band due to a *trans* double bond at 973 cm^{-1}. On the basis of these spectral data, XVIII was assumed to be diethyl 4-acetamido-4-ethoxy-*trans*-glutaconate. The structure of XVIII was further confirmed by the following chemical degradation. Catalytic hydrogenation of XVIII gave diethyl N-acetyl-2-ethoxyglutamate (XIX) of mp 64—65°, whose NMR spectrum in deuteriochloroform showed an A_2B_2 type multiplet (4H) at 2.38 ppm together with the peaks reasonably assignable to other groups in the molecule. When XIX was hydrolyzed in a mixture of hydrochloric acid and ethanol, diethyl α-ketoglutarate (XX), α-ketoglutaric acid (XXI) (as its 2,4-dinitrophenylhydrazone) and ammonium chloride were isolated and identified with corresponding authentic samples by comparisons of their IR spectra.

Tentative mechanisms of these unusual reactions of IIIb leading to VIII and XVIII are depicted as follows:

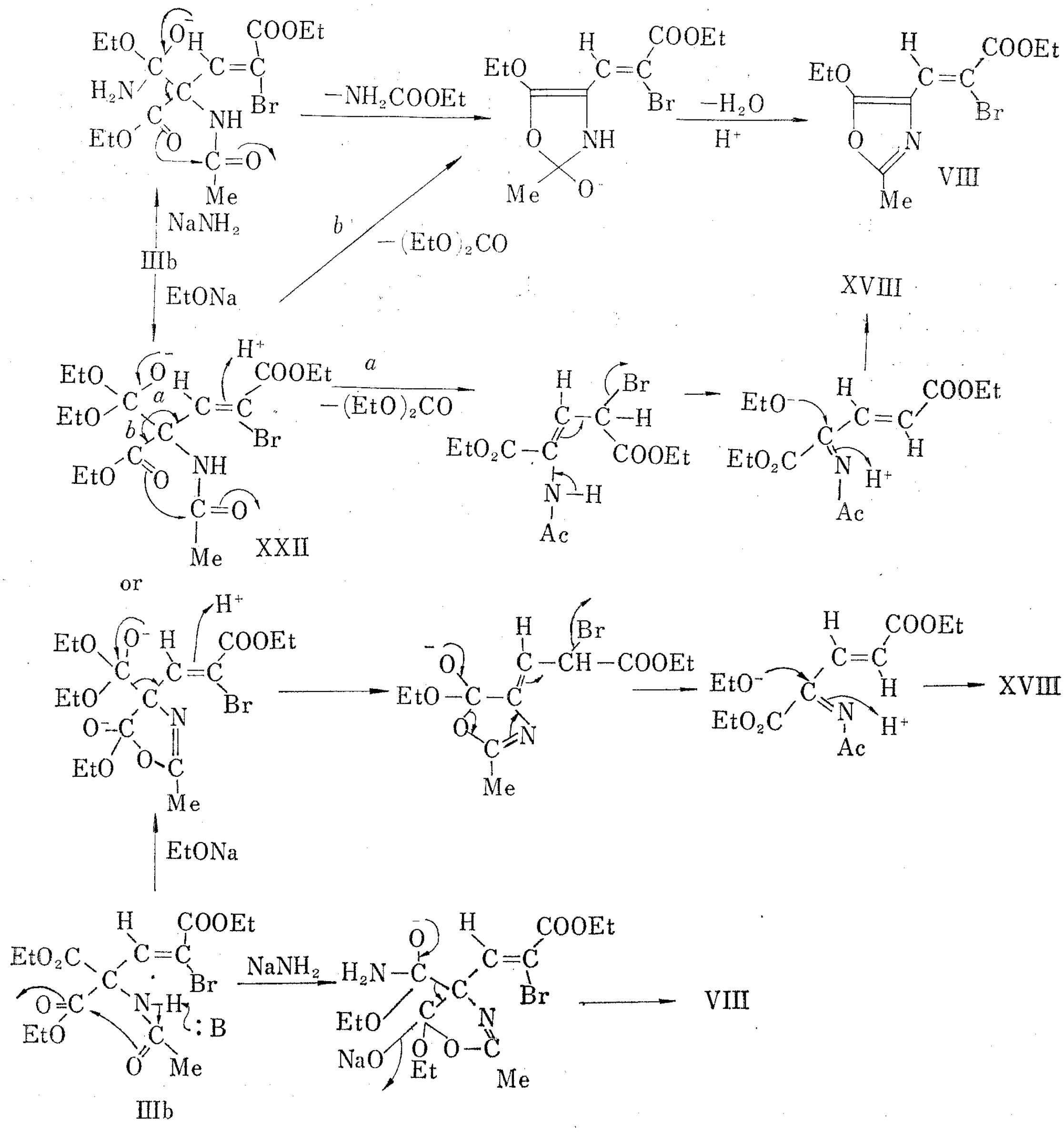

Chart 6

The isolation of VIII in addition to XVIII in the reaction of IIIb with sodium ethoxide suggests the two different paths (*a* and *b* in Chart 6) from the common intermediate XXII. Since diethyl acetamidomethylmalonate did not change under the same conditions, the electron withdrawing effect of the acrylic ester system in IIIb seems to be necessary for the cleavage of the carbon–carbon bond between the tertiary carbon and one of the geminal carbethoxy groups.

Experimental[14]

Ethyl *cis*-2,3-Dibromoacrylate (Ia)——a) To a solution of ethyl propiolate (4.9 g, 0.05 mole) in CCl_4 (30 ml) was added a solution of bromine (8.0 g, 0.05 mole) in CCl_4 (20 ml) at 60—70° during the period of 3 hr. After refluxed for additional 1 hr, the solvent was evaporated. Distillation of the residue afforded ethyl *cis*-2,3-dibromoacrylate of bp 69—71° (2 mmHg). Yield, 8.5 g (64%). IR cm^{-1} (film): $\nu_{C=O}$ 1760, $\nu_{C=C}$ 1580. NMR (CCl_4) δ: 8.23 (1H, singlet, vinyl H), 4.30 (2H, quartet, J=7 cps, $O-CH_2-Me$), 1.35 (3H, triplet, J=7 cps, CH_3). *Anal.* Calcd. for $C_5H_6O_2Br_2$: C, 23.28; H, 2.34; Br, 60.03. Found: C, 23.11; H, 2.35; Br, 60.07.

b) To a solution of ethyl propiolate (2.94 g, 0.03 mole) in CCl_4 (30 ml) was added dropwise a solution of bromine (4.80 g, 0.03 mole) in CCl_4 (10 ml) during 8 min under the irradiation of an UV lamp (Ishii). Bromine was absorbed quickly and the reaction mixture became colorless after the addition was completed. After stirred for additional 30 min, the solvent was evaporated under reduced pressure. The residue was proved to be almost pure Ia containing no *trans* isomer by NMR spectroscopy. Yield, 7.33 g, (94.7%).

c) To a solution of ethyl propiolate (1.96 g, 0.02 mole) in AcOH (10 ml) was added a solution of bromine (3.20 g, 0.02 mole) in AcOH (5 ml) during the period of 1 hr, protected from light. The inner temperature was kept at 26—27°. After allowed to stand for a night, the mixture was poured into 100 ml of water. Colorless oil separated and was taken up in $CHCl_3$. The organic layer was washed twice with 5% $NaHCO_3$, once with water and dried over Na_2SO_4. Evaporation of the solvent afforded 4.41 g of crude Ia (85.5%), whose NMR spectrum showed the absence of the *trans* isomer.

***cis*-2,3-Dibromoacrylic Acid (IIa)**——A mixture of Ia (1.00 g, 3.87 mmoles) and 2% NaOH (10 ml) was stirred for 4 hr at 26—27°. The homogeneous solution was washed with $CHCl_3$, acidified with conc. HCl to pH 2 and extracted twice with $CHCl_3$. The combined extract was washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crystalline residue (0.540 g, 60.7%) was recrystallized from hexane to afford white needles of IIa, mp 86.5—88°.[6] IR cm^{-1} (film): $\nu_{C=O}$ 1706, $\nu_{C=C}$ 1563. NMR (CCl_4) δ: 11.80 (1H, singlet, COOH), 8.48 (1H, singlet, vinyl H). *Anal.* Calcd. for $C_3H_2O_2Br_2$: C, 15.67; H, 0.88; Br, 69.53. Found: C, 15.90; H, 0.82; Br, 69.33.

Bromination of Propiolic Acid——a) To a solution of propiolic acid (1.40 g, 0.02 mole) in water (20 ml) was added a mixture of bromine (3.20 g, 0.02 mole) and water (20 ml) in 2 hr. The inner temperature was kept at 20° under water-cooling. After stirred for additional 2 hr, the mixture was evaporated under reduced pressure without heating. The residue was dissolved in benzene, washed with small amount of water to remove hydrogen bromide and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure without heating gave 2.61 g (54.6%) of crude *trans*-2,3-dibromoacrylic acid (IIb), mp 69—72°, whose NMR spectrum showed no peak due to the *cis* acid (IIa). The crude acid was dissolved in petroleum ether at 25° and cooled in an ice-bath to give colorless needles of pure IIb, mp 73—74°. NMR (CCl_4) δ: 12.00 (1H, singlet, COOH), 7.40 (1H, singlet, vinyl H). *Anal.* Calcd. for $C_3H_2O_2Br_2$: C, 15.67; H, 0.88; Br, 69.53. Found: C, 15.43; H, 0.91; Br, 69.42.

b) To a solution of propiolic acid (3.50 g, 0.05 mole) in water (20 ml) was added dropwise a mixture of bromine (8.00 g, 0.05 mole) and water (10 ml) in 2 hr, at 26°. The inner temperature rose to 35° at the end of the reaction. After allowed to stand for additional 2 hr, the mixture was evaporated under reduced pressure. The residue was found to be a 3:8 mixture of IIa and IIb on the basis of the NMR spectrum.

Esterification of IIb——A mixture of IIb (2.50 g, 10.8 mmoles), dried benzene (100 ml), abs. EtOH (50 ml) and a few drops of conc. H_2SO_4 was refluxed for 14 hr. Sixty ml of the azeotrope was removed. After cooling, the mixture was poured into water (140 ml). The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic solution was washed with 5% $NaHCO_3$, water and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled to give 1.27 g (45.7%) of a 3:1 mixture of ethyl *trans*-2,3-dibromoacrylate (Ib) and Ia, boiling at 81—85° (11 mmHg) (bath temperature). NMR (CCl_4) δ: 8.21 (singlet, vinyl H of Ia), 7.08 (singlet, vinyl H of Ib), 4.33 (quartet, J=7 cps, $O-CH_2-Me$ of Ia), 4.29 (quartet, J=7 cps, OCH_2-Me of Ia), 1.38 (triplet, J=7 cps, CH_3 of Ib), 1.37 (triplet, J=7 cps, CH_3 of Ia), relative ratio: 1:3:6:2:9:3. *Anal.* Calcd. for $C_5H_6O_2Br_2$: C, 23.28; H, 2.34; Br, 60.03. Found: C, 23.45; H, 2.35; Br, 60.18.

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14) Melting points are uncorrected.

Diethyl 4-Acetamido-2-bromo-4-carbethoxy-*trans*-glutaconate (IIIb)——Diethyl acetamidomalonate (17.4 g, 0.08 mole) was added at once to a solution of potassium (3.12 g, 0.08 atom) in *t*-BuOH (120 ml). To the mixture was added a solution of Ia (20.6 g, 0.08 mole) in *t*-BuOH(20 ml) over 2 hr under water-cooling. The reaction mixture was stirred for a night at room temperature, and the solvent was evaporated. The residue was washed with water, dried and recrystallized from EtOH to give white prisms of diethyl 4-acetamido-2-bromo-4-carbethoxy-*trans*-glutaconate (IIIb), mp 140—141°. Yield, 27.4 g (87.2%). IR cm^{-1} ($CHCl_3$): ν_{N-H} 3425, $\nu_{C=O}$ 1745, 1727, 1678, $\nu_{C=C}$ 1623. NMR ($CDCl_3$) δ: 8.38 (1H, singlet, vinyl H), 7.35 (1H, singlet, –NH–), 4.50 (6H, quartet, $J=7$ cps, $-O-CH_2-Me$), 2.03 (3H, singlet, $J=7$ cps, $-CO-CH_3$), 1.50 (3H, triplet, $J=7$ cps, CH_3), 1.33 (6H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{14}H_{20}O_7NBr$: C, 42.65; H, 5.11; N, 3.55; Br, 20.27. Found: C, 42.88; H, 5.10; N, 3.58; Br, 20.18.

Diethyl N-Acetyl-2-carbethoxyglutamate (IV)——Platinum oxide (0.063 g) was suspended in 10 ml of EtOH and reduced with hydrogen gas. After 11 ml of the gas was absorbed, a solution of IIIb (0.985 g, 2.5 mmoles) in EtOH (10 ml) was added. Hydrogen gas was again introduced and 114 ml of the gas was absorbed after 81 min. The catalyst was filtered off and the solvent was evaporated. The residue was extracted three times with boiling hexane. Condensation of the combined extract afforded 0.332 g (87.8%) of diethyl N-acetyl-2-carbethoxyglutamate (IV). Recrystallization from hexane gave white needles of mp 64—65°. Hexane insoluble starting material (0.519 g) was recovered and the yield was based on the amount of the changed IIIb. IR cm^{-1} (CCl_4): ν_{N-H} 3425, $\nu_{C=O}$ 1760, 1739, 1692. NMR (CCl_4) δ: 6.73 (1H, broad singlet, –NH–), 4.23 (4H, quartet, $J=7$ cps, $-O-CH_2Me$), 4.10 (2H, quartet, $J=7$ cps, $-O-CH_2Me$), 2.75—2.00 (4H, A_2B_2 multiplet centered at 2.38, $-CH_2CH_2-$), 1.98 (3H, triplet, $J=7$ cps, CH_3), 1.25 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{14}H_{23}O_7N$: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.78; H, 7.20; N, 4.48.

Dimethyl N-Acetylglutamate (V)——A mixture of IV (0.208 g, 0.656 mmoles) and 1N NaOH (2 ml) was stirred for 24 hr at room temperature. The reaction mixture was acidified with conc. HCl and extracted twice with ether. The aqueous layer was evaporated to dryness. The residue was extracted three times with abs. EtOH. Evaporation of the extract afforded brown oil (0.096 g), which was heated on an oil bath at 195° for 15 min under reduced pressure (0.1 mmHg). After cooling, the residual oily substance (0.052 g) was dissolved in 2 ml of MeOH and mixed with a solution of diazomethane (0.0115 g, 0.275 mmoles) in 1.95 ml of ether. The mixture was stirred for 3 hr under ice cooling and the solvent was evaproated. Distillation of the residue gave 0.035 g(23.2%) of dimethyl N-acetylglutamate (V), bp 128—132° (0.001 mmHg, bath temperature), whose IR spectrum was identical with that of an authentic sample.[9] *Anal.* Calcd. for $C_9H_{15}O_5N$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.99; H, 7.12; N, 6.65.

Diethyl 4-Acetamido-2-bromo-4-carbethoxy-*cis*-glutaconate (IIIa)——A solution of IIIb (36.1 g) in $CHCl_3$ (700 ml) containing a pinch of iodine was stirred at 35—40° for 18 hr under the irradiation of an UV lamp (Ishii). After filtration of the insoluble matter the solvent was evaporated. To the ethanolic solution of the residue a pure sample of IIIb was seeded to separate IIIb (25.9 g) of mp 137—139°. The ethanolic solution was filtered and concentrated. The same crystallization of IIIb was repeated three times and finally the mother liquor was evaporated. The residue (1.623 g) of mp 85—100° was recrystallized from benzene to give colorless plates of mp 93—95° (0.250 g). Further recrystallization from benzene afforded a pure sample of diethyl 4-acetamido-2-bromo-4-carbethoxy-*cis*-glutaconate (IIIa), mp 95—96°. IR cm^{-1} ($CHCl_3$): ν_{N-H} 3425, $\nu_{C=O}$ 1731, 1748, 1681, $\nu_{C=C}$ 1613. NMR ($CDCl_3$) δ: 7.67 (1H, singlet, vinyl H), 7.22 (1H, broad singlet, –NH–), 4.28 (4H, quartet, $J=7$ cps, $-O-CH_2Me$), 4.26 (2H, quartet, $J=7$ cps, $-O-CH_2Me$), 1.98 (3H, singlet, $-COCH_3$), 1.33 (3H, triplet, $J=7$ cps, CH_3), 1.25 (6H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{14}H_{20}O_7NBr$: C, 42.65; H, 5.11; N, 3.55; Br, 20.27. Found: C, 42.81; H, 5.11; N, 3.46; Br, 20.29.

N-Acetyl-3-bromo-5-dicarbethoxy-2-oxo-3-pyrroline (VI)——a) Diethyl 4-acetamido-2-bromo-4-carbethoxy-*cis*-glutaconate (IIIa) (0.050 g, 0.1269 mmole) was chromatographed on Al_2O_3 (Woelm, Grade III, 1.00 g). Elution with 10 ml of benzene gave 0.038 g of N-acetyl-3-bromo-5,5-dicarbethoxy-2-oxo-3-pyrroline (VI) (86.4% yield). Recrystallization from hexane gave white prisms of mp 107—108°. IR cm^{-1} (CCl_4): $\nu_{C=O}$ 1764, 1760, 1727, $\nu_{C=C}$ 1607. NMR ($CDCl_3$) δ: 7.39 (1H, singlet, vinyl H), 4.30 (4H, quartet, $J=7$ cps, $-O-CH_2Me$), 2.60 (3H, singlet, $COCH_3$), 1.29 (6H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{12}H_{14}O_6NBr$: C, 41.40; H, 4.06; N, 4.02; Br, 22.95. Found: C, 41.70; H, 4.11; N, 3.95; Br, 23.27.

b) A 5:4 mixture of IIIa and IIIb (1.774 g) was chromatographed on Al_2O_3 (Woelm, Grade III, 24 g). Elution with 400 ml of hexane afforded 0.604 g of VI. The next 300 ml of the same eluant gave 0.388 g of unchanged IIIb, mp 137—139°.

The Reaction of a Mixture of Ia and Ib with Acetamidomalonate Anion——To a solution of potassium (1.61 mg-atom) in *t*-BuOH (2 ml), was added 0.350 g (1.61 mmoles) of diethyl acetamidomalonate at once. After a few minutes the mixture became clear and then a solution of the 3:1 mixture of Ib and Ia (0.415 g, 1.61 mmoles), obtained by the esterification of IIb, in *t*-BuOH (1 ml) was added dropwise in 5 min. The reaction mixture was stirred at 26° for 2 hr and the solvent was evaporated under reduced pressure. The NMR spectrum of the residue showed only the peaks due to IIIb and trace of starting diethyl acetamidomalonate. The crude product of mp 120—132° (0.581 g, 91.6%) was recrystallized from EtOH to white prisms of IIIb, mp 140—141°.

Ethyl 2-Bromo-3-(5-ethoxy-2-methyl-4-oxazolyl)acrylate (VIII)——a) To a solution of potassium (0.40 g, 0.01 mole) in *t*-BuOH (40 ml) was added 3.94 g (0.01 mole) of IIIb at once. The mixture was refluxed for 2 hr and the solvent was evaporated. The black oily residue was extracted several times with hot hexane. Evaporation of the combined extract afforded 1.012 g (30.0%) of ethyl 2-bromo-3-(5-ethoxy-2-methyl-4-oxazolyl)acrylate (VIII). Recrystllization from hexane gave white needles of mp 81—82°. The analytical sample of mp 82—83° was obtained by further recrystallization. NMR (CCl_4) δ: 7.70 (1H, singlet, vinyl H), 4.31 (2H, quartet, $J=7$ cps, $-O-CH_2Me$), 4.22 (2H quartet, $J=7$ cps, $-O-CH_2Me$), 2.35 (3H, singlet, 2′-CH_3), 1.43 (3H, triplet, $J=7$ cps, CH_3), 1.33 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Cacld. for $C_{11}H_{14}O_4NBr$: C, 43.44; H, 4.64; N, 4.61; Br, 26.27. Found: C, 43.46; H, 4.84; N, 4.64; Br, 26.02.

b) A mixture of IIIb (3.94 g, 0.01 mole), sodium amide (0.38 g, 0.01 mole) and tetrahydrofuran (20 ml) was refluxed for 2 hr. After cooling, AcOH (0.6 g, 0.01 mole) was added and the solvent was evaporated under reduced pressure. Water was added to the residue and the mixture was extracted twice with ether. The ethereal layer was washed three times with 10% $NaHCO_3$, twice with water and dried over Na_2SO_4. Evaporation of the solvent afforded 1.62 g (53.3%) of crystalline VIII. Recrystallization from hexane gave needles of mp 82—83°.

c) A mixture of IIIb (3.9 g, 0.01 mole), sodium amide (0.6 g, 0.015 mole) and anhydrous xylene (50 ml) was refluxed for 1 hr on an oil bath. After cooling, the reaction mixture was poured into water containing 0.9 g of AcOH. The organic layer was washed twice with 10% $NaHCO_3$, three times with water and dried over Na_2SO_4. Evaporation of the solvent gave 2.1 g of crude crystalline VIII (69.1% yield).

Methyl *cis*-2,3-Dibromoacrylate (X)——To a boiling solution of methyl propiolate (30.2 g, 0.36 mole) in CCl_4 (180 ml) was added a solution of bromine (58 g, 0.36 mole) in CCl_4 (50 ml) during the period of 3 hr. After refluxing for additional 3 hr, the solvent was evaporated. Distillation of the residue afforded 48.7 g (55.5%) of methyl *cis*-2,3-dibromoacrylate (X), bp 73—76° (7 mmHg). NMR (CCl_4) δ: 8.25 (1H, singlet, vinyl H), 3.85 (3H, singlet, CH_3). *Anal.* Calcd. for $C_4H_4O_2Br_2$: C, 19.69; H, 1.65; Br, 65.33. Found: C, 19.89; H, 1.61; Br, 65.59.

Methyl 4-Acetamido-2-bromo-4,4-dicarbethoxy-*trans*-2-butenoate (IX)——To a solution of potassium *t*-butoxide prepared from potassium (6.5 g, 0.166 g-atom) and *t*-BuOH (240 ml) was added at once diethyl acetamidomalonate (33.70 g, 0.166 mole). After 5 min stirring, the mixture became clear. To this solution was added dropwise a solution of X (40.50 g, 0.166 mole) in *t*-BuOH (40 ml) in 2 hr. The inner temperature was kept at 25—28° during the reaction. After stirring for additional 2 hr at that temperature, the solvent was evaporated. The residue was collected on a glass filter, washed with plenty of water and dried under reduced pressure. The crude product (54.6 g, 86.6%) was recrystallized from CCl_4 to afford white leaflets of IX, mp 127—128°. IR cm^{-1} ($CHCl_3$): $\nu_{\text{N-H}}$ 3425, $\nu_{\text{C=O}}$ 1751, 1677, $\nu_{\text{C=C}}$ 1623. NMR ($CDCl_3$) δ: 8.40 (1H, singlet, vinyl H), 7.35 (1H, singlet, $-NH-$), 4.31 (4H, quartet, $J=7$ cps, $-O-CH_2Me$), 3.87 (3H, singlet, $-O-CH_3$), 2.05 (3H, singlet, $-CO-CH_3$), 1.27 (6H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{13}H_{18}O_7NBr$: C, 41.07; H, 4.77; N, 3.68; Br, 21.02. Found: C, 41.11; H, 4.89; N, 3.65; Br, 20.94.

Methyl 2-Bromo-3-(5-ethoxy-2-methyl-4-oxazolyl)acrylate (XI)——A mixture of IX (7.60 g, 0.02 mole), sodium amide (1.56 g, 0.04 mole) and tetarhydrofuran (30 ml) was refluxed for 2 hr. After cooling AcOH (2.40 g, 0.04 mole) was added and the solvent evaporated under reduced pressure. To the residue water was added and the mixture extracted three times with ether. The combined extract was washed twice with 5% $NaHCO_3$, three times with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was extracted three times with boiling hexane. The extract was treated with charcoal and concentrated, leaving 2.45 g (42%) of crude XI, mp 92—96°. Recrystallization from hexane afforded white needles of mp 97—98°. NMR (CCl_4) δ: 7.75 (1H, singlet, vinyl H), 4.35 (2H, quartet, $J=7$ cps, $-O-CH_2Me$), 3.80 (3H, singlet, $-O-CH_3$), 2.37 (3H, singlet, 2′-oxazolyl-CH_3), 1.45 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{10}H_{12}O_4NBr$: C, 41.40; H, 4.16; N, 4.82; Br, 27.54. Found: C, 41.76; H, 4.09; N, 4.74; Br, 27.72.

2-Bromo-3-(5-ethoxy-2-methyl-4-oxazolyl)acrylic Acid (XII)——a) A mixture of VIII (0.862 g), 20% NaOH (10 ml) and EtOH (4 ml) was stirred for 18 hr at 25—26°. The reaction mixture was acidified with conc. HCl. White precipitate was collected, washed with water, dried under reduced pressure and weighed 0.606 g (77.4%). Recrystallization from $CHCl_3$ afforded white prisms of XII, mp 157—167° (decomp.). NMR ($(CD_3)_2SO$) δ: 7.80 (1H, singlet, vinyl H), 4.40 (2H, quartet, $J=7$ cps, $-O-CH_2Me$), 2.37 (3H, singlet, 2′-oxazolyl-CH_3), 1.37 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_9H_{10}O_4NBr$: C, 39.14; H, 3.64; N, 5.07; Br, 28.98. Found: C, 38.95; H, 3.66; N, 5.01; Br, 28.73.

b) A mixture of XI (1.259 g), 10% NaOH and EtOH (8 ml) was stirred for 24 hr at 25—27°. The same procedure as described in a) gave 0.838 g (70%) of XII.

Ethyl *trans*-3-(2-Phenyl-5-ethoxy-4-oxazolyl)acrylate (XIII)——A mixture of diethyl 4-benzamido-4-carbethoxyglutaconate[2] (5.738 g, 0.0153 mole), sodium amide (0.72 g, 0.018 mole) and tetrahydrofuran (40 ml) was refluxed for 1 hr. After cooling, AcOH (1.08 g, 0.018 mole) was added and the solvent was evaporated under reduced pressure. To the residue water was added and the mixture was extracted with ether. The extract was washed three times with water, dried over Na_2SO_4 and the solvent evaporated. The residue was extracted three times with boiling hexane. Evaporation of the solvent afforded 1.838 g (42.1%) of XII. Recrystallization from hexane gave white needles of mp 83—84°. NMR (CCl_4) δ: 7.25—

8.00 (5H, aromatic multiplet), 7.40 (1H, doublet, $J=16$ cps, vinyl H), 6.38 (1H, doublet, $J=16$ cps, vinyl H), 4.42 (2H, quartet, $J=7$ cps, –O–CH_2Me), 4.19 (2H, quartet, $J=7$ cps, –O–CH_2Me), 1.47 (3H, triplet, $J=7$ cps, CH_3), 1.30 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.71; H, 6.01; N, 4.91.

***trans*-3-(5-Ethoxy-2-phenyl-4-oxazolyl)acrylic Acid (XIV)**——A mixture of XIII (0.203 g), 10% NaOH (2 ml) and EtOH (2 ml) was allowed to stand for 2 days at room temperature. The mixture was acidified with conc. HCl to pH 3. Crude 3-(5-ethoxy-2-phenyl-4-oxazolyl)-*trans*-acrylic acid (XIV) (0.181 g, 99%) precipitated, was collected, washed with water and recrystallized from EtOH to afford white needles of mp 198—201°. NMR ($(CD_3)_2SO$) δ: 7.4—8.1 (5H, aromatic multiplet), 7.38, 6.27 (AB type doublets, $J=16$ cps, vinyl protons), 4.53 (2H, quartet, $J=7$ cps, –O–CH_2Me), 1.43 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.02; H, 4.91; N, 5.32.

3-(5-Ethoxy-2-phenyl-4-oxazolyl)propionic Acid (XV)——a) A solution of XIV (0.136 g) in AcOEt (25 ml) was added to a mixture of 5% Pd–C (0.100 g) and AcOEt (3 ml) which had been reduced by hydrogen gas (3.6 ml uptake). Hydrogen gas was introduced under stirring till the reaction mixture absorbed 13.20 ml of the gas. The insoluble material was filtered off and washed with AcOEt and EtOH. The filtrate and washings were combined and evaporated under reduced pressure, leaving 0.120 g of solid substance. Recrystallization from benzene yielded small prisms of the starting material (XIV) (0.034 g). The mother liquor was evaporated to dryness and the residue was again recrystallized from benzene to give further amount of XIV. Evaporation of the mother liquor left an oil, which was extracted with boiling hexane. The extract was evaporated to afford an oil. The procedure was repeated three times and finally a crystalline substance (0.013 g) was obtained. Recrystallization from hexane gave fine needles of XV, mp 83—85° (yield, 0.008 g). Analytical sample of mp 91—92° was obtained by further recrystallizations. NMR ($CDCl_3$) δ: 11.40 (1H, singlet, COOH), 7.3—8.1 (5H, aromatic multiplet), 4.28 (2H, quartet, $J=7$ cps, –O–CH_2Me), 2.82 (4H, A_2B_2 multiplet, center, –CH_2CH_2–), 1.42 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.34; H, 5.81; N, 5.68.

b) A mixture of diethyl N-benzoylglutamate (12.28 g, 0.04 mole), PCl_5 (8.40 g, 0.04 mole) and $CHCl_3$ (30 ml) was refluxed for 1 hr. After cooling, the solvent was evaporated. The residue was dissolved again in $CHCl_3$ and the solution was made neutral to litmus by adding 5% solution of NaOEt in EtOH. The mixture was washed twice with water, dried over $MgSO_4$ and the solvent was evaporated. The oily residue (9.95 g) containing ethyl 3-(5-ethoxy-2-phenyl-4-oxazolyl)propionate (XVII) and the starting diethyl N-benzoylglutamate was hydrolyzed without purification. A mixture of the residue (2.89 g) and 10% KOH (8 ml) was refluxed with stirring for 30 min. After cooling the mixture was washed with ether to remove unchanged XVII, acidified with 10% H_2SO_4 and extracted twice with ether. The ethereal solution was extracted with 5% $NaHCO_3$. The aqueous layer was washed with ether and acidified with 10% H_2SO_4. The precipitated crystalline material (0.103 g) was filtered, washed with water, dried and recrystallized from hexane to afford small needles of XV, mp 91—92°, which was identical with the sample obtained in a) in all respects. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.47; H, 5.57; N, 5.68.

Diethyl 4-Acetamido-4-ethoxy-*trans*-glutaconate (XVIII)——a) To a solution of NaOEt prepared from sodium (0.3 g, 0.013 g-atom) and abs. EtOH (20 ml) was added IIIb (5.10 g, 0.013 mole) at once. After 2 hr reflux the solvent was evaporated. Water was added and the mixture extracted three times with ether. The extract was dried over Na_2SO_4 and the solvent evaporated. The residue (2.859 g, 76.6%) was recrystallized from hexane to long needles of XVIII, mp 76—78°. IR cm^{-1} (CCl_4): ν_{N-H} 3333, $\nu_{C=O}$ 1761, 1724, 1701, δ_{C-H} 973. NMR (CCl_4) δ: 7.42 (1H, broad singlet, –NH–), 6.82, 6.13 (a pair of AB type 1H doublets, $J=16$ cps, vinyl hydrogens), 4.20 (2H, quartet, $J=7$ cps, –CO_2CH_2Me), 4.17 (2H, quartet, $J=7$ cps, –CO_2-CH_2Me), 3.55 (2H, multiplet, center, –O–CH_2Me), 1.97 (3H, singlet, $COCH_3$), 1.27 (6H, triplet, $J=7$ cps, CH_3), 1.18 (3H, triplet, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{13}H_{21}O_6N$: C, 54.34; H, 7.37; N, 4.88. Found: C, 54.52; H, 7.32; N, 4.83.

b) A semi-crystallized substance (3.423 g) obtained by the procedure described in a) from IIIb (7.86 g, 0.02 mole), sodium (0.466 g, 0.02 g-atom) and EtOH (30 ml) was chromatographed on 70 g of silica gel (Kanto Kagaku). Elution with $CHCl_3$ afforded VIII (0.160 g, 2.9%) of mp 76—78°. Recrystallization from hexane yielded colorless needles of mp 81—82°. Further elution with the same solvent gave 2.244 g (39.0%) of XVIII, which was recrystallized from hexane to white needles of mp 76—77°.

Diethyl N-Acetyl-2-ethoxyglutamate (XIX)——To a mixture of XVIII (0.153 g, 0.56 mmole), platinum oxide (0.040 g) and EtOH (5 ml) was introduced hydrogen gas. After 50 min stirring, 16.0 ml of the gas was absorbed. The catalyst was filtered off and the solvent evaporated under reduced pressure. Distillation of the residue gave 0.145 g (94%) of XIX, bp 128—130° (0.001 mmHg) (bath temperature). IR cm^{-1} (film): ν_{N-H} 3311, $\nu_{C=O}$ 1736, 1692, 1672. NMR ($CDCl_3$) δ: 7.20 (1H, broad singlet, –NH–), 4.26 (2H, quartet, $J=7$ cps, CO_2CH_2Me), 4.16 (2H, quartet, $J=7$ cps, –CO_2CH_2Me), 3.55 (2H, multiplet, –O–CH_2Me), 2.38 (4H, center, A_2B_2 type multiplet), 2.02 (3H, singlet, $COCH_3$) 1.30, 1.25, 1.17 (3H, triplets, $J=7$ cps, CH_3). *Anal.* Calcd. for $C_{13}H_{23}O_6N$: C, 53.96; H, 8.01; N, 4.84. Found: C, 53.80; H, 8.15; N, 4.90.

Acid Degradation of XIX——A mixture of XIX (0.103 g, 0.36 mmole), EtOH (4 ml) and conc. HCl (2 ml) was heated on a water–bath at 80° for 8 hr. After cooling, the mixture was evaporated under reduced pressure. The residue was washed with anhydrous acetone and insoluble ammonium chloride (0.017 g, 89%) was filtered. The acetone solution was evaporated under reduced pressure and the oily residue was washed with CCl_4. The insoluble solid substance was filtered, dissolved in water and treated with an ethanolic solution of 2,4-dinitrophenylhydrazine. α-Ketoglutaric acid 2,4-dinitrophenylhydrazone (0.011 g, 10%) of mp 202—204° precipitated and was recrystallized from aqueous EtOH to yellow needles of mp 215—217° (0.006 g), which was identical in all respects with an authentic sample. *Anal.* Calcd. for $C_{11}H_{10}O_8N_4$: C, 40.50; H, 3.09; N, 17.18. Found: C, 40.27; H, 3.21; N, 17.15. The carbon tetrachloride solution was concentrated under reduced pressure, leaving 0.044 g (61%) of ethyl α-ketoglutarate, whose IR and NMR spectrum were identical with those of an authentic specimen. NMR (CCl_4) δ: 4.29 (2H, quartet, $J=7$ cps, $-OCH_2Me$), 4.13 (2H, quartet, $J=7$ cps, $-OCH_2Me$), 2.4—3.3 (4H, A_2B_2 type multiplet, CH_2CH_2), 1.37 (3H, triplet, $J=7$ cps, CH_3), 1.23 (3H, triplet, $J=7$ cps, CH_3).