Chem. Pharm. Bull. 25(10)2692—2696(1977)

UDC 547.473.1.04 : 547.442.04

Studies on Ketene and Its Derivatives. LXXXV.[1] Reactions of 4-Bromo-3-hydroxybutanoate and Its Acyl Derivatives

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(Received February 23, 1977)

Acylation of ethyl 4-bromo-3-hydroxybutanoate (I) with acetic anhydride, benzoyl chloride, diketene, and phenyl isocyanate gave rise to ethyl 3-acetoxy-4-bromobutanoate (IIa), ethyl 3-benzoyloxy-4-bromobutanoate (IIb), ethyl 3-acetoacetoxy-4-bromobutanoate (IIc), and ethyl 4-bromo-3-(N-phenylcarbamoyloxy)butanoate (IId), respectively.

Reaction of IIa with sodium ethoxide in abs. ethanol gave ethyl 4-hydroxycrotonate (III) and ethyl 4-bromocrotonate (IV). The similar reaction of IIb afforded IV and 4-benzoyloxycrotonate (Vb). Similarly, IIc was converted to III, 4-acetoacetoxycrotonate (Vc), and 3-acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one (VI). On the other hand, reaction of IId under the same condition did not give the acyl migrated product such as ethyl 4-N-phenylcarbamoyloxycrotonate (Vd) but afforded ethyl 4-anilinocrotonate (VIII).

Keywords——ethyl 4-bromo-3-hydroxybutanoate; acyl migration; diketene; ethyl 4-acyloxycrotonate; 3-acetonyltetrahydrofuran-2-one; ethyl 4-anilinocrotonate

4-Halo-3-hydroxybutanoic acid ester was first synthesized by the hydrolysis of 4-chloro-3-hydroxybutylonitrile.[3] Although the literatures contain several references,[4] the investigation of its chemical behaviours has not been extended so much. Recently, the facile synthesis of I using diketene was reported.[5] The present paper describes the acylation of compound I and the acyl migration of the products.

When ethyl 4-bromo-3-hydroxybutanoate (I) was allowed to react with acetic anhydride, ethyl 3-acetoxy-4-bromobutanoate (IIa: R=CH_3) was obtained in 80% yield. Compound IIa was also obtained by the acetylation of I with acetyl chloride or ketene in 71% or 88% yield, respectively.

I

IIa—d
a: R=CH_3
b: R=C_6H_5
c: R=CH_2Ac
d: R=NHC_6H_5

Chart 1

Similarly, acylation of I with benzoyl chloride, diketene, and phenyl isocyanate gave rise to ethyl 3-benzoyloxy-4-bromobutanoate (IIb: R=C_6H_5), ethyl 3-acetoacetoxy-4-bromobutanoate (IIc: R=CH_2Ac), and ethyl 4-bromo-3-(N-phenylcarbamoyloxy)butanoate (IId: R=$NH\cdot C_6H_5$), respectively. Structural assignment of these products were made on the basis of elemental analyses and spectral data detailed in the experimental section.

When ethyl 3-acetoxy-4-bromobutanoate (IIa) was allowed to react with sodium ethoxide in absoluted ethanol, ethyl 4-hydroxycrotonate (III) and ethyl 4-bromocrotonate (IV) were

1) No. LXXXIV: T. Kato, T. Chiba, M. Daneshtalab, *Chem. Pharm. Bull.* (Tokyo), **24**, 2549 (1976).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) M.R. Lespieau, *C. R. Acad. Sci.*, **127**, 966 (1899).
4) *Cf. a*) René Rambaud, *C. R. Acad. Sci..*, **220**, 742 (1945); *b*) R. Rambaud, and S. Ducher, *Bull. Soc. Chim. Fr.*, **1956**, 466; *c*) R. Rambaud and A. Broche, *Bull. Soc. Chim. Fr.*, **1959**, 33; *d*) F. Binon, P. Bruckner and G. Deltour, *Bull. Soc. Chim. Belg.*, **72**, 166 (1963).
5) *a*) A. Stocker and K.J. Boosen, Brit. Patent 1200158 (1970); *b*) F. DAlo and A. Masserini, *Farmaco.* (Pavia), *Ed. Sci.*, **19**, 30 (1964).

obtained. Compounds III and IV were identified by comparisons of spectral data with those of authentic sample prepared according to the methods reported in the literature.[4a] Reaction of IIb under the same condition gave rise to compound IV and ethyl 4-benzoyloxycrotonate (Vb) in 34% and 21% yield, respectively. As described in the experimental section, IR and NMR spectral data of compound Vb were well consistent with the structure, and it was unequivocally assigned by comparison with an authentic sample prepared by the method described below.

Similar treatment of IIc afforded ethyl 4-acetoacetoxycrotonate (Vc) (45%) and compound III (19%), besides a small amount of 3-acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one (VI) (2%). Compound Vc was identified by comparison with an authentic sample. Compound VI was characterized on the basis of elemental analysis and spectral data, and it was also obtained by the reaction of compound Vc with sodium ethoxide in absolute ethanol in 68% yield. Hydrolysis of compound VI with 10% hydrochloric acid gave rise to 4-acetonyltetrahydrofuran-2-one (VII) in 81% yield.

Reaction of compound IId under the same condition did not give the acyl migrated product such as ethyl 4-N-phenylcarbamoyloxycrotonate (Vd) but afforded ethyl 4-anilinocrotonate (VIII)[6] in 20% yield.

Authentic samples of 4-acyloxycrotonate (Va—d) were obtained by the reaction of compound III with acylating agents, such as acetic anhydride, benzoyl chloride, diketene, and phenyl isocyanate.

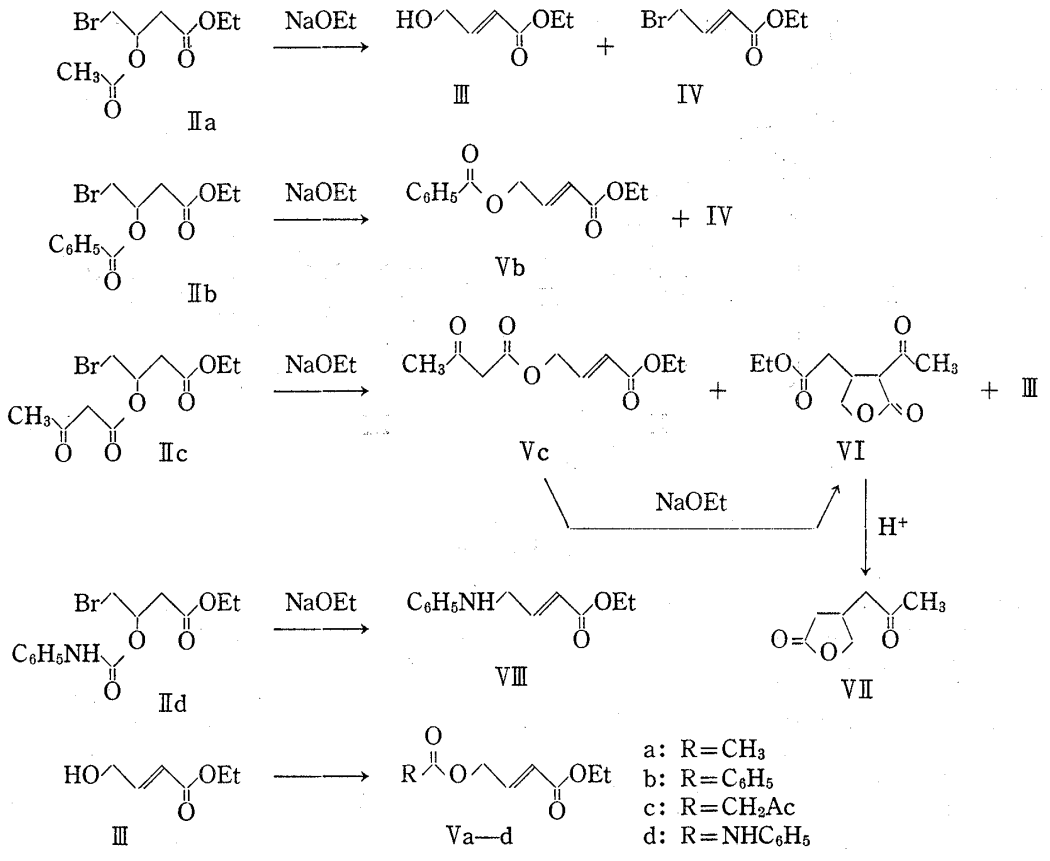

Chart 2

The mechanism of the formation of compound V may require acyl rearrangement of compound II. For example, the elimination of hydrogen bromide from compound IIc results in the migration of the acetoacetoxy group to afford compound Vc.

6) M. Julia and G. Tchernoff, *Bull. Soc. Chim. Fr.*, **1953**, 812.

The formation of the furanone derivatives (VI and VII) can be reasonably elucidated as following: cyclization of Vc gives rise to compound VI, acidic hydrolysis of which would result in the ring cleavage to give the intermediate IX, which was decarboxylated, accompanied with renewed ring closure by elimination of ethanol giving compound VII.

Though in the reaction of compound IIa with sodium ethoxide the acyl migrated compound, ethyl 4-acetoxycrotonate (Va), was not detected, it seemed to be resonable to assume the similar pathway to form compound (Va) as an intermediate, which was hydrolyzed to convert into III. In fact, it was found that compound Va was unstable toward base converting readily to compound III.

On the other hand, in the reaction of compound IId, elimination of hydrogen bromide results in the cyclization to give the oxazolidone intermediate (X), which, on base-catalized ring cleavage, is transformed to the intermediate XI. Decarboxylation of XI gives rise to the compound VIII.

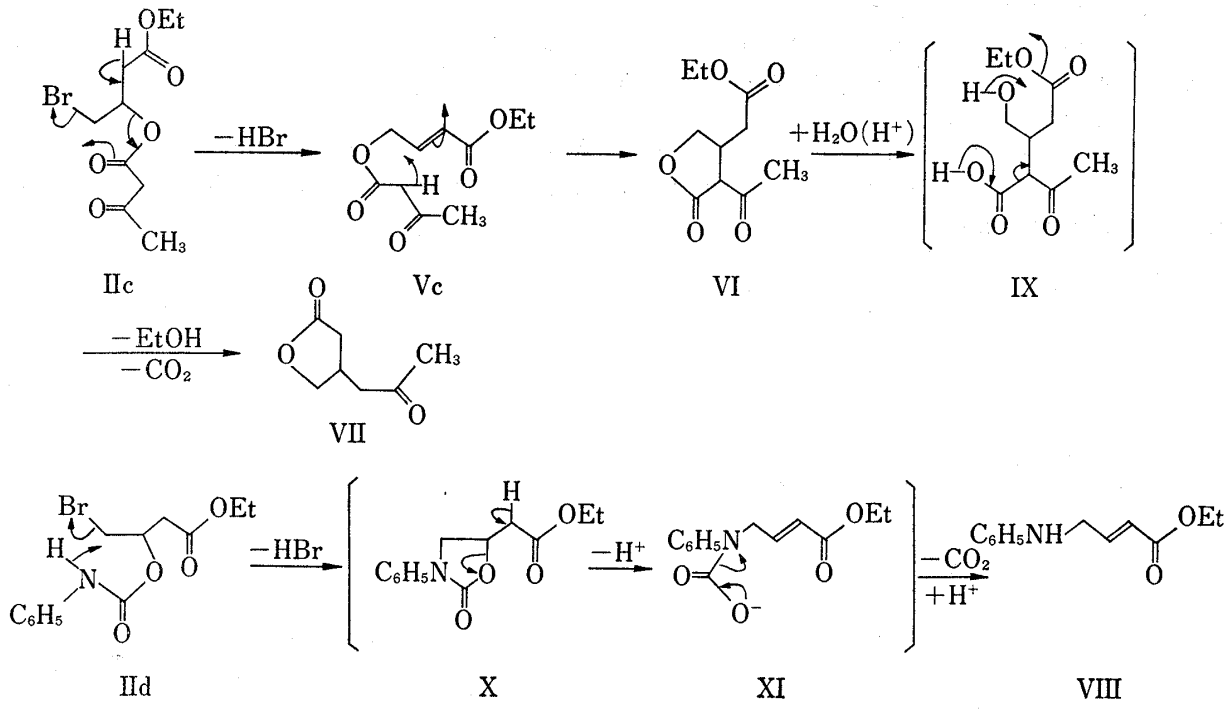

Chart 3

Experimental

Ethyl 4-Bromo-3-hydroxybutanoate (I)——To a solution of ethyl 4-bromoacetoacetate[7] (58 g, 0.28 mol) in ethanol (700 ml), was added dropwise a solution of sodium borohydride (3.5 g, 0.09 mol), during which time temperature was kept below 10° with ice-cooling. After stirring at the same temperature for additional 30 min, the reaction mixture was allowed to stand at room temperature for 4 hr. Acetic acid (16.7 g, 0.28 mol) was added, and the mixture was condensed *in vacuo*. The residue was extracted with ether. The ether solution was condensed, and the oily residue was purified by distillation to give a colorless oil (I), bp 77—79° (0.5 mmHg) (lit.[5b] 93—95° (0.8 mmHg)). Yield, 44.5 g (75%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 1721 (C=O). NMR (CCl_4) ppm: 1.27 (3H, t, J=7 Hz, CH_3), 2.66 (2H, ABX, d, J=6 Hz, CH_2CO), 3.34 (1H, s, OH), 3.39 (2H, d, J=6 Hz, $BrCH_2$), 4.00—4.25 (1H, m, CH), 4.12 (2H, q, J=7 Hz, CH_2).

Ethyl 3-Acetoxy-4-bromobutanoate (IIa)——1) A solution of compound I (1.05 g) in acetic anhydride (5 ml) was heated at 80° for 2 hr. After evaporation of excess acetic anhydride the resulting oily residue was purified by vacuum distillation to give a colorless oil, bp 104—105° (3 mmHg). Yield, 1 g (80%). *Anal.* Calcd. for $C_8H_{13}BrO_4$ (IIa); C, 37.96: H, 5.18. Found: C, 38.27; H, 5.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1737. NMR ($CDCl_3$) ppm: 1.29 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 2.10 (3H, s, CH_3CO), 2.78 (2H, d, J=6 Hz, $\underline{CH_2}CO$), 3.61 (2H, d, J=4.5 Hz, CH_2Br), 4.18 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$), 5.25—5.50 (1H, m, CH).

7) F. Chick, N. and Wilsmore, *J. Chem. Soc.*, **97**, 1978 (1910).

2) A mixture of compound I (0.5 g) and acetyl chloride (1 g) was heated at reflux for 1 hr. After removal of excess acetyl chloride by distillation, the residue was purified by distillation to give a colorless oil, bp 104—105° (3 mmHg), whose IR spectrum was identical in every respect with that of IIa obtained above. Yield, 0.43 g (71%).

3) To a solution of compound I (1.05 g, 0.005 mol) and a catalytic amount of triethylamine in benzene (10 ml), was bubbled ketene gas generated by a ketene lump (1.2 mmol/min)[8] for 30 min (0.036 mol). The reaction mixture was condensed and the residue was distilled to give 1.1 g (88%) of compound IIa.

Ethyl 3-Benzoyloxy-4-bromobutanoate (IIb)——To a solution of compound I (4.2 g) in pyridine (20 ml), was added dropwise benzoyl chloride (4.5 g) with cooling. After allowing to stand at room temperature for 3 hr, the reaction mixture was poured into ice-water, and then extracted with benzene. The benzene layer was washed with 10% sodium carbonate and 10% hydrochloric acid. After drying over sodium sulfate, the benzene solution was condensed, and the residue was distilled to give a colorless oil, bp 128—130° (0.07 mmHg). Yield, 4.6 g (73%). *Anal.* Calcd. for $C_{13}H_{15}BrO_4$ (IIb): C, 49.68; H, 4.78. Found: C, 49.88; H, 4.87. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. NMR ($CDCl_3$) ppm: 1.21 (3H, t, J=8 Hz, $\underline{CH_3}CH_2O$), 2.90 (2H, d, J=6.5 Hz, CH_2CO), 3.73 (2H, d, J=5 Hz, $BrCH_2$), 4.15 (2H, q, J=8 Hz, $CH_3\underline{CH_2}O$), 5.4—5.8 (1H, m, CH), 7.4—7.65 (3H, m, ring-H), 7.95—8.30 (2H, m, ring-H).

Ethyl 3-Acetoacetoxy-4-bromobutanoate (IIc)——A mixture of compound I (6.3 g, 0.03 mol), diketene (2.6 g, 0.03 mol) and a catalytic amount of triethylamine in benzene (20 ml) was heated at reflux for 4 hr. The reaction mixture was condensed *in vacuo*, and the residue was distilled to give a colorless oil, bp 95—102° (0.05 mmHg). Yield, 7.6 g (85%). *Anal.* Calcd. for $C_{10}H_{15}BrO_5$ (IIc): C, 40.70; H, 5.12. Found: C, 40.97; H, 5.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. NMR ($CDCl_3$) ppm: 1.27 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 2.29 (3H, s, CH_3CO), 2.78 (2H, d, J=7 Hz, $\underline{CH_2}CO$), 3.48 (2H, s, $CO\underline{CH_2}CO$), 3.61 (2H, d, J=5 Hz, $BrCH_2$), 4.15 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$), 5.30—5.55 (1H, m, CH).

Ethyl 4-Bromo-3-(N-phenylcarbamoyloxy)butanoate (IId)——A mixture of compound I (1.06 g), phenyl isocyanate (0.6 g), and a catalytic amount of pyridine was heated in a water-bath at 80° for 4 hr. After being cooled, the reaction mixture was rubbed with a glass rod in a small amount of petroleum benzine to give a crystalline substance, which was recrystallized from petroleum benzine to colorless needles, mp 56—57°. Yield, 0.97 g (59%). *Anal.* Calcd. for $C_{13}H_{16}BrNO_4$ (IId): C, 47.29; H, 4.88; N, 4.24. Found: C, 47.33; H, 4.72; N, 4.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1738. NMR ($CDCl_3$) ppm: 1.26 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 2.83 (2H, d, J=7.2 Hz, CH_2O), 3.70 (2H, d, J=5.2 Hz, $BrCH_2$), 4.18 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$), 5.25—5.50 (1H, m, CH), 6.65—6.90 (1H, m, NH), 7.25—7.47 (5H, m, ring-H).

Reaction of IIa with Sodium Ethoxide——To a solution of sodium ethoxide prepared from sodium metal (30 mg, 0.0012 atom) in absolute ethanol (10 ml), was added a solution of compound IIa (253 mg, 0.001 mol) in absolute ethanol (5 ml) with stirring, during which time the temperature was kept at −15° by an ice-salt bath. After stirring for 1 hr at the same temperature, the reaction mixture was neutralized with carbon dioxide, and condensed *in vacuo* to give the oily residue to which was added a small amount of water. The mixture was extracted with ether. The ether solution was evaporated under reduced pressure, and the residue was purified by silica gel thin-layer chromatography using chloroform as a solvent to give 43 mg (27%) of ethyl 4-hydroxycrotonate (III), bp 115—120° (15 mmHg) (lit.[4a] bp 119—120° (13 mmHg)), and 72 mg (37%) of ethyl 4-bromocrotonate (IV), bp 72—75° (15 mmHg) (lit.[4a] bp 75.5—76.0° (16 mmHg)), both of which were identified by comparison of their IR spectra with those of authentic samples prepared according to the literature.

Reaction of IIb with Sodium Ethoxide——In a fashion similar to that described above, compound IIb (315 mg, 0.001 mol) was treated with a sodium ethoxide–ethanol solution (prepared from sodium (23 mg, 0.001 atom) and absolute ethanol (20 ml)) at −10° for 1 hr. After neutralizing with carbon dioxide, the mixture was condensed. The residue was extracted with ether. The ether extract was purified by silica gel column chromatography. The benezne elution gave 48 mg (21%) of ethyl 4-benzoyloxycrotonate (Vb), colorless oil, bp 130—131° (1 mmHg), and 65 mg (34%) of ethyl 4-bromocrotonate (IV), bp 98—100° (18 mmHg).[9] *Anal.* Calcd. for $C_{13}H_{14}O_4$ (Vb): C, 66.65; H, 6.02. Found: C, 66.54; H, 5.76. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, NMR ($CDCl_3$) ppm: 1.29 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 4.21 (2H, q, J=7 Hz, $CH_3\underline{CH_2}O$), 4.90—5.02 (2H, m, CH_2O), 5.92—6.31 (1H, m, olefinic H), 6.85—7.30 (1H, m, olefinic H), 7.40—7.75 (3H, m, ring H), 7.98—8.20 (2H, m, ring H).

Reaction of IIc with Sodium Ethoxide——According to the similar fashion as described above, compound IIc (300 mg) was allowed to react with sodium ethoxide prepared from sodium (30 mg) in absolute ethanol (10 ml). After neutralizing with carbon dioxide, the reaction mixture was condensed. The residue was extracted with ether. The ether extract was submitted on silica gel thin-layer chromatography using chloroform as a solvent to give 96 mg (45%) of ethyl 4-acetoacetoxycrotonate (Vc) (colorless oil, bp 100—102° (0.2 mmHg)), 30 mg (19%) of ethyl 4-hydroxycrotonate (III), and 4 mg (2%) of 3-acetyl-4-ethoxycarbonyl-

8) W.E. Hanford and J.C. Saver, "Organic Reactions," Vol. 3, ed. by R. Adams, John Wiley and Sons, Inc. New York, 1946, p. 132.

9) K.E. Schulte and F. Zinnert, *Arch. Pharm.* **288**, 60 (1955).

methyltetrahydrofuran-2-one (VI), bp 148° (3 mmHg). *Anal.* Calcd. for $C_{10}H_{14}O_5$ (Vc): C, 56.07; H, 6.59. Found: C, 55.82; H, 6.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1717. NMR ($CDCl_3$) ppm: 1.30 (3H, t, $J=7$ Hz, $\underline{CH_3}CH_2O$), 2.30 (3H, s, CH_3CO), 3.53 (2H, s, $CO\underline{CH_2}CO$), 4.21 (2H, q, $J=7$ Hz, $CH_3\underline{CH_2}O$), 4.81 (2H, d,d. $J=4.8$ and 2.0 Hz, OCH_2), 5.85—6.23 (1H, m, olefinic H), 6.73—7.20 (1H, m, olefinic H). *Anal.* Calcd. for $C_{10}H_{14}O_5$ (VI): C, 56.07; H, 6.59. Found: C, 56.06; H, 6.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1777, 1725. NMR ($CDCl_3$) ppm: 1.25 (3H, t, $J=7$ Hz, $\underline{CH_3}CH_2O$), 2.44 (3H, s, CH_3CO), 2.50 (2H, d, $J=7$ Hz, $COCH_2$), 3.13—3.65 (1H, m, CH_2–$CH<$), 4.13 (2H, q, $J=7$ Hz, $CH_3\underline{CH_2}O$), 3.85—4.70 (2H, m, ABX type, CH_2O).

Reaction of IId with Sodium Ethoxide——To a sodium ethoxide–ethanol solution prepared from sodium metal (25 mg, 0.001 atom) and abs. ethanol (20 ml), was added a solution of compound IId (330 mg, 0.001 mol) in abs. ethanol (5 ml) with stirring, during which time the temperature was kept at −15° by an ice-salt bath. After stirring for 30 min at the same temperature, the reaction mixture was allowed to stand at room temperature and stirring was continued for additional 2 hr. The reaction mixture was evaporated *in vacuo* at 40°. The residue was extracted with ether. The ether extract was washed with 10% hydrochloric acid and dried over sodium sulfate. The solvent was removed and the residue was submitted on silica gel column chromatography using hexane–ether (7: 3) as an eluant to recover 40 mg (12%) of IId. The acidic aqueous solution was neutralized with 10% sodium hydroxide and extracted with ether. The ether solution was dried over sodium sulfate. After evaporation of the solvent, the residue was absorbed on the preparative silica gel chromatography plate, and developed with hexane–ether (6: 4) to give pale yellow liquid, ethyl 4-anilinocrotonate (VIII). Yield, 40 mg (20%). HCl salt, mp 141—142° (lit.[6] mp 139°), undepressed on admixture with an authentic sample prepared according to the literature.[6] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1715, 1662, 1605. NMR (CCl_4) ppm: 1.22 (3H, t, $J=7.0$ Hz, $\underline{CH_3}CH_2O$), 3.85 (2H, d,d, $J=4.8$ and 2.3 Hz, $NH\underline{CH_2}$), 3.60—3.80 (1H, m, NH), 4.09 (2H, q, $J=7.0$ Hz, $CH_3\underline{CH_2}O$), 5.90 (1H, t of d, $J=16$ and 2.3 Hz, =CH–CO), 6.32—7.20 (6H, m, =CH–CH_2, ring H).

Ethyl 4-Acetoxycrotonate (Va)——A solution of compound III (0.5 g) and a drop of conc. sulfuric acid in acetic anhydride (4 ml) was allowed to stand at room temperature. After 3 hr, the mixture was diluted with water (10 ml) and extracted with ether. The ether solution was condensed and the residue was distilled to give a colorless oil (Va) of bp 121° (18 mmHg) (lit.[10] bp 115—116° (15 mmHg)).

Ethyl 4-Benzoyloxycrotonate (Vb)——To a solution of compound III (0.26 g, 0.002 mol) in pyridine (2 ml) was added benzoyl chloride (0.28 g, 0.002 mol). After allowing to stand at room temperature for 6 hr, the mixture was diluted with water and extracted with ether. The ether solution was washed with 10% hydrochloric acid, and 10% sodium carbonate. After drying over sodium sulfate, the ether solution was evaporated. The resulting residue was purified by vacuum distillation to give a colorless oil (Vb), bp 130—131° (1 mmHg), whose IR spectrum was identical in every respect with that of specimen obtained in the reaction of IIb with sodium ethoxide. Yield, 0.31 g (66%).

Ethyl 4-Acetoacetoxycrotonate (Vc)——To a solution of compound III (2.6 g, 0.02 mol) in benzene (15 ml), were added diketene (1.9 g, 0.02 mol) and a drop of triethylamine. After refluxing for 2 hr, the reaction mixture was condensed *in vacuo*. The residue was distilled under reduced pressure to give a colorless oil (Vc), bp 100—102° (0.2 mmHg), whose IR spectrum was identical with that of sample obtained in the reaction of IIc with sodium ethoxide. Yield, 3.5 g (82%).

Ethyl 4-N-Phenylcarbamoyloxycrotonate (Vd)——Following the similar procedure given for IId, Vd was prepared from III (1.0 g), phenyl isocyanate (1.0 g) and a catalytic amount of pyridine, as colorless needles (petroleum ether), mp 46—47°. Yield, 1.6 g (80%). *Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 6.04; N, 5.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1722, 1670. NMR ($CDCl_3$) ppm: 1.28 (3H, s, $J=7.0$ Hz, $\underline{CH_3}CH_2O$), 4.21 (2H, q, $J=7.0$ Hz, $CH_3\underline{CH_2}O$), 4.80 (2H, d,d, $J=4.4$ and 1.5 Hz, OCH_2), 6.04 (1H, t of d, $J=16$ and 1.5 Hz, =$C\underline{H}$CO), 6.77—7.45 (7H, m, $CH_2\underline{CH}$=, ring H).

3-Acetyl-4-ethoxycarbonylmethyltetrahydrofuran-2-one (VI)——To a solution of sodium ethoxide prepared from sodium (0.6 g, 0.026 atom) in abs. ethanol (100 ml), was added dropwise a solution of compound Vc (5 g, 0.024 mol) in abs. ethanol (20 ml) at room temperature. After stirring for 1.5 hr, the mixture was neutralized with carbon dioxide and condensed *in vacuo*. The residue was diluted with water (10 ml), and extracted with benzene. The benzene extract was distilled to give a colorless oil, bp 148° (3 mmHg), whose IR spectrum was identical in every respect to that of specimen (VI) obtained in the reaction of IIc with sodium ethoxide.

4-Acetonyltetrahydrofuran-2-one (VII)——A solution of compound VI (0.42 g) in 10% hydrochloric acid (10 ml) was refluxed for 1 hr. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography using ether as an eluant giving an oily substance, which was distilled to give a colorless oil, bp 115° (1 mmHg) (bath temperature). Yield, 0.23 g (81%). *Anal.* Calcd. for $C_7H_{10}O_3$ (VII) C, 59.14; H, 7.09. Found: C, 59.05; H, 7.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780, 1717. NMR ($CDCl_3$) ppm: 2.18 (3H, s, CH_3CO), 2.30—3.27 (5H, m) 3.77—4.06 (1H, m, ABX, CH_2O), 4.40—4.68 (1H, m, CH_2O).

Acknowledgement The authors are indebted to all the staffs of Central Analyses Room of Pharmaceutical Institute, Tohoku University, for spectral measurements and elemental analyses.

10) R. Rambaud, *C. R. Acad. Sci.*, **196**, 188 (1933).