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Reaction of *N*-(α-Acetoxycinnamoyl)-*N*-hydroxy Derivatives of DL-Alanine Esters. Formation of Imidazolidinone and Its Transformations into Pyrrolidinedione and Oxazolidinone

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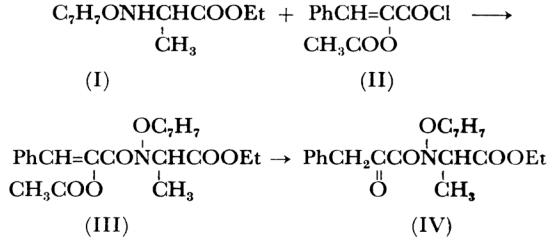
Treatment of *N*-benzyloxy-DL-alanine ethyl ester (I) with α-acetoxycinnamoyl chloride (II) gave *N*-(α-acetoxycinnamoyl)-*N*-benzyloxy-DL-alanine ethyl ester (III), which was treated with aqueous sodium bicarbonate, piperidine or hydroxylamine to afford *N*-benzyloxy-*N*-(phenylpyruvoyl)-DL-alanine ethyl ester (IV). Reaction of III or IV with ammonia afforded 5-benzylidene-2-methyl-4-oxo-2-imidazolidinecarboxylic acid (V), which was transformed into 5-methyl-4-phenyl-2,3-pyrrolidinedione (VI) by treatment with aqueous sodium hydroxide and into methyl 5-benzylidene-2-methyl-4-oxo-2-oxazolidinecarboxylate (VII) by treatment with methanolic hydrogen chloride. VI was also derived from III or IV by treatment with sodium hydroxide. *N*-(α-Acetoxycinnamoyl)-*N*-hydroxy-DL-alanine *t*-butyl ester prepared from *N*-hydroxy-DL-alanine *t*-butyl ester and II, was treated with aqueous sodium hydroxide to give *t*-butyl 5-benzylidene-2-methyl-4-oxo-2-oxazolidinecarboxylate.

In the preceding paper we described the preparation of 3-benzylidene-6-isobutyl-2,5-piperazinedione by the reaction of esters of *N*-(α-acetoxycinnamoyl)-L-leucine with ammonia.[1] In an extention of the reaction to *N*-(α-acetoxycinnamoyl)-*N*-benzyloxy-DL-alanine ethyl ester, it might be expected that 1-benzyloxy-3-benzylidene-6-methyl-2,5-piperazinedione would be formed. This paper deals with an unexpected formation of imidazolidinone in such a reaction and its transformations into pyrrolidinedione and oxazolidinone.

Reaction of *N*-benzyloxy-DL-alanine ethyl ester (I) with α-acetoxycinnamoyl chloride (II) gave *N*-(α-acetoxycinnamoyl)-*N*-benzyloxy-DL-alanine ethyl ester (III), which was confirmed by infrared and NMR spectrum. The acetyl group of III could be easily removed by treatment with aqueous sodium bicarbonate, piperidine or hydroxylamine, and *N*-benzyloxy-*N*-(phenylpyruvoyl)-DL-alanine ethyl ester (IV) was obtained. The product was characterized by its conversion to the 2,4-dinitrophenylhydrazone.



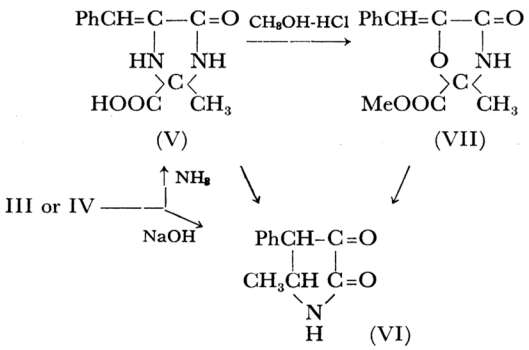
(I) (II)

(III) (IV)

Treatment of IV with ammonia failed to give the expected 2,5-piperazinedione but instead furnished a crystalline product with mp 228—229°C in 60% yield. This compound was also obtained directly from III by treatment with ammonia. Elemental analysis and determination of molecular weight indicated a molecular formula, $C_{12}H_{12}N_2O_3$ for the product, which gives a negative ferric chloride reaction and is insoluble in 1 N hydrochloric acid and in aqueous sodium bicarbonate. These properties as well as the infrared and NMR spectrum revealed the product to be 5-benzylidene-2-methyl-4-oxo-2-imidazolidinecarboxylic acid (V). The

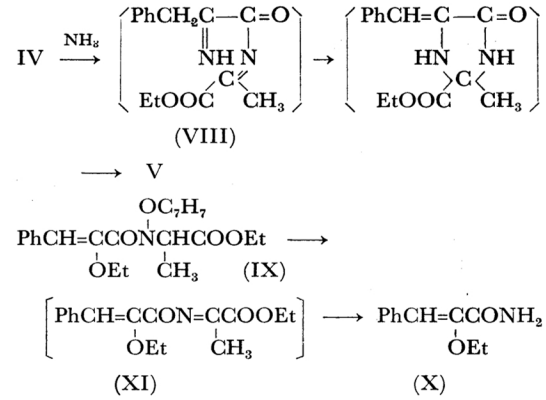
1) Y. Chigira, M. Masaki and M. Ohta, This Bulletin, **42**, 224 (1969).

infrared spectrum showed absorption bands at 3440, 3250 (NH), 3170 (NH), 1710 (COOH), 1690 (CONH), 1680 (C=C) and 1360 cm^{-1}, and the NMR spectrum exhibited signals at τ 8.3 (s, 3H), 7.95 (s, 1NH), 3.85 (s, 1H), 2.6, 2.25 (m, 5H), 2.3 (s, 1NH) and −0.1 (s, 1COOH).[2] 4-Imidazolidinones have been reported to show the infrared absorptions at 1690—1710 (C=O) and 1400—1420 cm^{-1}.[2d]

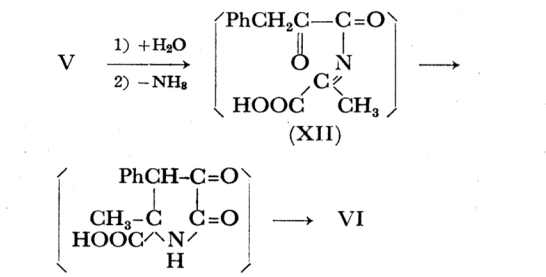


A probable pathway for this reaction would involve an initial elimination of benzyl alcohol from IV, followed or accompanied by the reaction of the ketonic group with ammonia to give ethyl 2 - (2 - imino - 3 - phenylpropionylimino)propionate (VIII) which then cyclized to the ethyl ester of V, and hydrolysis of the ester would yield V. The elimination of benzyl alcohol from IV appeared to be an unexpected reaction, since hydroxamic acids or *N*-acyl-*N*-(benzyloxy)amines are generally stable under the conditions used in the above reaction. However the ease with which benzyl-alcohol was eliminated from *N*-acyl-*N*-benzyloxy amino acid esters was supported by our previous observation: the alkaline treatment of ethyl *N*-(α-ethoxycinnamoyl)-*N*-benzyloxy-DL-alanine ethyl ester (IX) gave α-ethoxycinnamic amide (X).[1] This reaction was also explained by initial elimination of benzyl alcohol from IX followed by hydrolysis of the resultant ethyl 2-(α-ethoxycinnamoylimino)-propionate (XI) to give the amide (X).

When V was dissolved in aqueous sodium hydroxide and then neutralized with hydrochloric acid, the imidazolidinone (V) could not be recovered but instead pyrrolidinedione (VI) was obtained in 80% yield. The structure of VI was derived from elemental analysis, a positive ferric chloride reaction and spectral studies. The ultraviolet spectrum



showed absorption maxima at 221, 227 and 287 mμ and the infrared spectrum showed absorption bands at 3200 (NH), 1710 (C=O) and 1670 (CONH) cm^{-1}. This infrared absorption pattern is virtually identical with that described for pyrrolidinediones, *i. e.*, 1700—1730 (C=O) and 1670 (CONH) cm^{-1}.[3] The NMR spectrum exhibited a three-proton doublet at τ 8.8, a one-proton multiplet at 5.45 and a six-proton multiplet at 2.5. The transformation of V into VI would be reasonably explained by an initial hydrolytic fission of carbon-nitrogen bond of the enamine moiety in V accompanied by loss of ammonia to give 2-(phenylpyruvoylimino)-propionic acid (XII), a cyclization of which followed by the decarboxylation yielded VI. The involvement of the intermediate XII in this reaction was supported by the direct formation of VI from III or



IV. When III or IV was dissolved in 20% aqueous sodium hydroxide and then acidified with hydrochloric acid, pyrrolidinedione (VI) was obtained in 44% and 49% yield respectively.[4] In these reactions, the initial elimination of benzyl alcohol with base would give the ester of XII as intermediate.

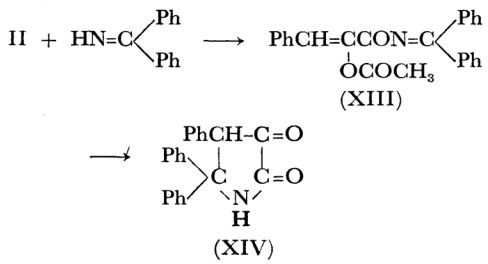
A pyrrolidinedione would be obtained if a α-

2) 4-Imidazolidinones have been prepared by desulfurization of thiohydantoins or by the condensations of α-amino nitriles or α-amino acid amides with carbonyl compounds: a) J. T. Eduards and E. F. Matlem, *Chem. Ind.*, **1954**, 193; b) K. Freter, J. Rabinowitz and B. Witkop, *Ann.*, **607**, 174 (1957); c) A. C. Davis and A. L. Levy, *J. Chem. Soc.*, **1951**, 3479; d) U. Zehavi and D. Ben-Ishai, *J. Org. Chem.*, **26**, 1097 (1961).

3) a) P. L. Southwick and E. F. Barnas, *ibid.*, **27**, 98 (1962); b) P. L. Southwick and J. A. Vida, *ibid.*, **27**, 3075 (1962).

4) 2,3-Pyrrolidinediones have been known to be synthesized by the condensations of α-keto acids or its esters with aldehydes and aromatic amines: a) H. Keskin, *Rev. faculté sci. univ. Istanbul*, **11A**, 1 (1946); *Chem. Abstr.*, **40**, 5427 (1946); b) J. R. Merchant, R. J. Shah and R. M. Bhandarkar, *Rec. Trav. Chim.*, **81**, 131 (1962).

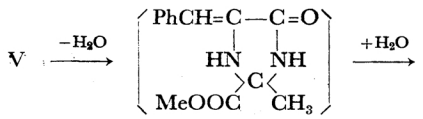
ketoacylimine was formed by an alternative route. Treatment of 1,1-diphenylmethylenimine with α-acetoxycinnamoyl chloride (II) afforded *N*-(α-acetoxycinnamoyl)-1,1-diphenylmethylenimine (XIII) which was unstable and decomposed gradually with atomospheric moisture at room temperature to yield α-acetoxycinnamic amide and benzophenone. When XIII was treated with sodium ethoxide, deacetylation followed by cyclization occurred and 4,5,5-triphenyl-2,3-pyrrolidinedione (XIV) was obtained as expected.



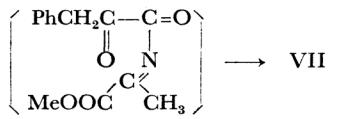
(XIII)

(XIV)

When V was treated with hydrogen chloride in methanol, methyl 5-benzylidene-2-methyl-4-oxo-2-oxazolidinecarboxylate (VII) was obtained in 38% yield. The structure was derived from elemental analysis and spectral studies. The infrared spectrum showed absorption bands at 3070 (NH), 1730 (COOMe), 1710 (CONH) and 1670 (C=C) cm^{-1}. The NMR spectrum exhibited signals at τ 8.15 (s, 3H), 6.2 (s, 3H), 3.65 (s, 1H), 2.6, 2.25 (m, 5H) and 1.05 (s, 1NH).[5] The transformation of V into VII would be rationalized as follows: an initial esterification of V would give the methyl ester (XV) and water, which reacted in the presence of proton to afford methyl 2-phenylpyruvoyliminopropionate (XVI). In contrast to the cyclization of XII into VI under a basic condition, XVI was cyclized to VII in the presence of acid. Treatment of VII with 1 N aqueous sodium hydroxide resulted in the transformation into the pyrrolidinedione (VI) quantitatively. The transformation of



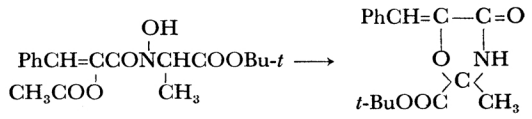
(XV)



(XVI)

VII into VI would involve again the intermediate XII.

In an analogous fashion, *N*-(α-acetoxycinnamoyl)-*N*-hydroxy-DL-alanine *t*-butyl ester (XVII) was prepared by treatment of *N*-hydroxy-DL-alanine *t*-butyl ester with α-acetoxycinnamoyl chloride (II) in the presence of pyridine. Reaction of XVII with 1 N aqueous sodium hydroxide afforded *t*-butyl 5-benzylidene-2-methyl-4-oxo-2-oxazolidinecarboxylate (XVIII). The structure of XVIII was confirmed by elemental analysis and spectral studies. The infrared spectrum showed absorption bands at 3250 (NH), 1735 (COOBu-*t*), 1710 (CONH) and 1680 (C=C) cm^{-1}. The NMR spectrum exhibited a nine-proton singlet at τ 8.5, a three-proton singelt at 8.2, a one-proton singlet at 3.7 and five-proton multiplets centered at 2.3 and 2.7. These absorption patterns were virtually identical with those of VII.



(XVII) (XVIII)

The formation of XVIII from XVII would be also rationalized by dehydration from the hydroxamic moiety of XVII and hydrolysis of the acetoxy moiety followed by a cyclization of the resultant *t*-butyl ester of XII. It is of contrast that the oxazolidinone (XVIII) was formed from *t*-butyl ester of XII under alkaline conditions, while XII was cyclized into the pyrrolidinedione (VI) under similar conditions. The difference should be attributed to the bulkiness of the *t*-butyl group: the formation of pyrrolidinedione from XVII would be impossible since the steric hindrance between phenyl and *t*-butyl groups is so strong that the imino carbon of *t*-butyl ester of XII can not be attacked by the methylene group flanked by phenyl and carbonyl groups, while the steric hindrance would not be so effective in the case of the formation of XVIII.

It is of interest that α-(*N*-acylimino) acid esters (VIII, XI and the esters of XII) were readily formed, but as intermediates, from *N*-acyl derivatives of *N*-benzyloxy- or *N*-hydroxy-DL-alanine esters (IV, IX and XVII) by elimination of benzyl alcohol or water under basic conditions.

Experimental[6]

N-(α-Acetoxycinnamoyl)-N-benzyloxy-DL-alanine Ethyl Ester (III). A solution of α-acetoxycinnamoyl

5) 4-Oxazolidinones have been prepared by the condensations of carbonyl compounds with α-hydroxy nitriles or α-hydroxy acid amides: a) K. Eichenberger, E. Ganz and J. Druey, *Helv. Chim. Acta*, **38**, 284 (1955); b) J. B. Bicking, S. F. Kwong, M. H. Fisher and W. H. Nicholson, *J. Med. Chem.*, **8**, 95 (1965); *Chem. Abstr.*, **62**, 5262 (1965).

6) All melting points were determined in a liquid bath. These and all boiling points are uncorrected. All concentrations and evaporations were carried out under reduced pressure. Infrared spectra were determined on a Hitachi EPI-S2 spectrophotometer as

chloride[1] (II) (3.5 g) in absolute ether (40 ml) was added in portions, with stirring under ice cooling, to a solution of *N*-benzyloxy-DL-alanine ethyl ester[1] (I) (3.5 g) and pyridine (1.2 g) in absolute ether (40 ml). After stirring for 1 hr, the precipitated pyridine hydrochloride (2.1 g) was filtered off. The filtrate was washed successively with water, aqueous sodium bicarbonate, twice with water, 1 N hydrochloric acid, and finally twice with water, and dried over anhydrous sodium sulfate. Evaporation of the ether yielded the product (5.2 g, 81%) as a sirup, which was homogeneous in thin-layer chromatography on silica gel [developed with benzene-alcohol (4:1) or ethyl acetate].

IR (liquid film): 2950, 1765 (CH_3COO), 1740 (COOEt), 1665 (C=C), 1645 (CON<), 1210 and 700 cm^{-1}.

NMR (CCl_4): τ 8.8 (t, 3H), 8.5 (d, 3H), 7.85 (s, 3H), 5.85 (q, 2H), 5.0 (s, 2H), 4.95 (q, 1H), 3.1 (s, 1H), 2.7 (s, 5H) and 2.6 (m, 5H).

***N*-Benzyloxy-*N*-(phenylpyruvoyl)-DL-alanine Ethyl Ester (IV).** *A)* To 1 N methanolic hydroxylamine solution (10 ml) was added III (2.0 g) and the resultant solution was allowed to stand at room temperature for 3 days and then heated at 50—60°C on a water bath for 2 hr. After removal of the methanol, the oily residue was dissolved in ether (20 ml). The ethereal solution was washed successively with water, aqueous sodium bicarbonate, water, 1 N hydrochloric acid and finally with water, and dried over sodium sulfate. The ether was evaporated to afford the product (1.35 g, 75%) as a sirup.

IR (liquid film): 2950, 1740 (COOEt), 1720 (C=O), 1675 (C=C), 1620 (CON<) and 700 cm^{-1}.

2,4-Dinitrophenylhydrazone of IV. To a solution of the product (0.3 g) in methanol (5 ml) was added a methanolic solution of 2,4-dinitrophenylhydrazine sulfate. After a day, the precipitated oily product was separated by decantation and washed twice with methanol. The oily product was dissolved in boiling methanol and the solution was allowed to stand for a week to afford crystalline precipitates. Recrystallization from ethanol afforded yellow needles (0.5 g), mp 135—136°C.

Found: C, 58.97; H, 5.25; N, 12.88%. Calcd for $C_{27}H_{27}N_5O_8$: C, 59.01; H, 4.95; N, 12.75%.

B) A solution of III (1.0 g) and piperidine (0.21 g) in tetrahydrofuran (25 ml) was allowed to stand at room temperature for a day. After removal of the tetrahydrofuran, the oily residue was treated in a manner analogous to the method A to give IV in 70% yield.

C) A solution of III (1.0 g) in tetrahydrofuran was added to a solution of sodium bicarbonate (0.2 g) in water (25 ml) and methanol (2 ml). After a day, the tetrahydrofuran was removed and the aqueous solution was extracted with ether and the ethereal extract was treated in a manner analogous to the method A to give IV in 68% yield.

5-Benzylidene-2-methyl-4-oxo-2-imidazolidinecarboxylic Acid (V). *A) From IV.* A solution of IV (0.8 g) in methanol (20 ml) was saturated with gaseous ammonia under cooling and allowed to stand at room temperature for a day. After removal of the methanol, the crystalline residue was treated with ether. Recrystallization from acetonitrile yielded colorless needles (0.3 g, 60%). A portion of the product was recrystallized from isopropyl alcohol into colorless needles and then from 80% aqueous methanol into colorless prisms, mp 228—229°C.

Found: C, 61.59; H, 5.05; N, 12.07%; mol wt 220. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06%; mol wt 232.

B) From III. A solution of III (0.6 g) in methanol (30 ml) was saturated with gaseous ammonia under cooling and allowed to stand for 2 days. After removal of the methanol, ethyl acetate was added to the residual mixture of an oil and crystals. The insoluble crystals were collected (0.15 g, 44%) and recrystallized from acetonitrile, mp 227—228°C. The product was identical, in melting point and infrared spectrum, with the sample obtained in method A.

5-Methyl-4-phenyl-2,3-pyrrolidinedione (VI). *A)* The imidazolidinone V (0.4 g) was dissolved in 1 N sodium hydroxide (10 ml) and allowed to stand at room temperature overnight. The solution was acidified with 1 N hydrochloric acid to afford gradually crystalline precipitates. The solid was collected and recrystallized from benzene into colorless needles (0.26 g, 80%), mp 228—229°C (with sublimation).

Found: C, 69.45; H, 5.82; N, 7.43%. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40%.

B) From III. A suspension of III (1.0 g) in 20% aqueous sodium hydroxide was stirred for 6 hr. The resultant clear solution was washed with ether, treated with activated charcoal and acidified with 3 N hydrochloric acid. The precipitated oily product was extracted twice with ether. The ethereal extract was dried over anhydrous sodium sulfate and then evaporated. Addition of carbon tetrachloride to the residual oil gave gradually crystalline product (0.2 g, 44%). Recrystallization from benzene afforded colorless needles, mp 228—229°C. The product was identical, in melting point and infrared spectrum, with the sample obtained by method A.

C) From IV. A suspention of IV (0.6 g) in 20% aqueous sodium hydroxide was treated in a manner analogous to method B to afford the product (0.15 g, 49%).

***N*-(*α*-Acetoxycinnamoyl)-1,1-diphenylmethylenimine (XIII).** A solution of *α*-acetoxycinnamoyl chloride (II) (1.5 g) in absolute ether (40 ml) was added in portions, with stirring under ice cooling, to a solution of 1,1-diphenylmethylenimine[7] (2.44 g) in absolute ether (20 ml). After stirring for 2 hr, the precipitated 1,1-diphenylmethylenimine hydrochloride (1.7 g) was filtered off, and the ethereal filtrate was concentrated to dryness. The crystalline residue was treated with dry petroleum ether (bp 30—60°C) to give colorless crystalline product (2.1 g, 84%). A portion of the product was recrystallized from di-*n*-butyl ether to give colorless prisms, mp 98.0—98.5°C.

Found: C, 77.23; H, 5.20; N, 4.35%. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79%.

KBr disks, unless otherwise indicated. NMR spectra were recorded on JUM4H-100 spectrometer (Japan Electron Optics Laboratory Co.) with tetramethylsilane as internal standard. Molecular weight was measured with a Hitachi-Perkin-Elmer 115 apparatus in dimethylformamide.

7) A. Lachman, "Organic Syntheses," Coll. Vol. II, p. 234 (1943).

IR: 1765 (CH_3COO), 1675 (C=C), 1635 (CON=), 1600, 1210 and 700 cm^{-1}.

This compound is very unstable and decomposed on recrystallization into benzophenone and α-acetoxycinnamic amide. The latter compound was recrystallized from benzene to give colorless needles, mp 143°C.

Found: C, 64.64; H, 5.38; N, 7.01%. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%.

4,5,5-Triphenyl-2,3-pyrrolidinedione (XIV). A solution of XIII (0.7 g) in methanol (20 m*l*) was added to sodium methoxide solution [from sodium (0.05 g) and methanol (10 m*l*)] with stirring at room temperature. After a day, the crystalline solid was collected, washed with ether, and then suspended in 1 N hydrochloric acid (10 m*l*). The suspension was extracted with ether and the ethereal extract was dried over anhydrous sodium sulfate. Evaporation of the ether afforded the crystalline product, which was recrystallized from benzene to give colorless needles (0.45 g, 73%), mp 257—258°C.

Found: C, 80.01; H, 5.23; N, 4.55%. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28%.

IR: 3250 (NH), 1690 (C=O), 1430, 1300, 890, 760 and 700 cm^{-1}.

NMR ($CDCl_3$-DMSO-d_6): τ 6.6 (s, 1H), 2.7 (15H) and 1.65 (s, 1H).

Methyl 5-Benzylidene-2-methyl-4-oxo-2-oxazolidinecarboxylate (VII). A solution of V (0.1 g) in absolute methanol (10 m*l*) was refluxed for 1 hr, while dry hydrogen chloride was passed through the solution, and allowed to stand at room temperature overnight. After removal of the methanol, ether was added to the crystalline residue and the insoluble ammonium chloride (0.035 g) was filtered off. The ethereal filtrate was evaporated to give the crystalline product (0.04 g, 38%). Recrystallization from di-*n*-butyl ether afforded colorless needles, mp 124.5—125.0°C.

Found: C, 62.88; H, 5.36; N, 5.88%. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.69%.

Reaction of VII with Sodium Hydroxide. A solution of VII (0.13 g) in 1 N aqueous sodium hydroxide (5 m*l*) was allowed to stand at room temperature overnight. Neutralization of the solution with 3 N hydrochloric acid afforded crystalline precipitates (0.1 g, 100%) which were collected and recrystallized from benzene, mp 228—229°C. The product was identical, in melting point and infrared spectrum, with the pyrrolidinedione (VI) obtained from V.

***N*-(*α*-Acetoxycinnamoyl)-*N*-hydroxy-DL-alanine *t*-Butyl Ester (XVII).** A solution of II (1.3 g) in absolute ether (20 m*l*) was added portionwise, with stirring, to a solution of *N*-hydroxy-DL-alanine *t*-butyl ester (0.93 g) and pyridine (0.4 g) in absolute ether (20 m*l*). After 1 hr, water was added to the mixture and the ethereal layer was washed successively with water, aqueous sodium bicarbonate, water, 1 N hydrochloric acid, and finally twice with water, and dried over anhydrous sodium sulfate. The ether was evaporated to afford the product as a pale yellow sirup (1.5 g, 74%), which gives a deep red color with a methanolic ferric chloride solution. The product was used in a succeeding reaction without further purification.

IR (liquid film): 1780 (CH_3COO), 1730 (COOBu-*t*), 1675, 1370, 1160 and 700 cm^{-1}.

***t*-Butyl 5-Benzylidene-2-methyl-4-oxo-2-oxazolidinecarboxylate (XVIII).** A solution of XVII (1 g) in 1 N aqueous sodium hydroxide was allowed to stand at room temperature overnight. The solution was washed twice with ether, treated with activated charcoal and then saturated with carbon dioxide to separate a mixture of crystals and a yellow oil, which was extracted four times with ether. The combined ethereal extracts were dried over anhydrous sodium sulfate and concentrated to give a crystalline residue (0.3 g, 36%). Rapid recrystallization from di-*n*-butyl ether (lower than 90°C) yielded colorless needles, mp 154.5—155.5°C.

Found: C, 66.20; H, 6.24; N, 4.87%. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84%.