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3-Pyrrolidinones by Intramolecular Condensation[1]

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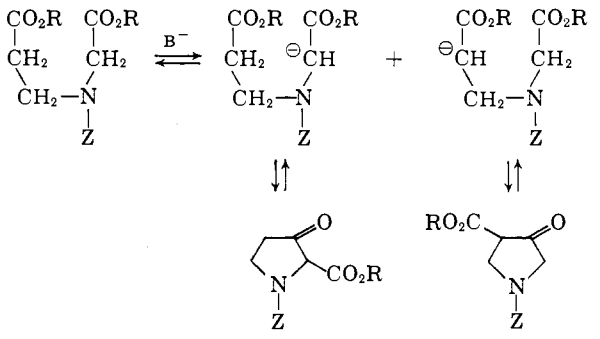
RECEIVED JULY 9, 1964

A study has been made of some base-catalyzed intramolecular condensations of the Dieckmann type, leading to 3-pyrrolidinones. From ethyl N-ethoxycarbonyl-N-(2-ethoxycarbonylethyl)glycinate (IIa), under non-equilibrating conditions, both ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IIIa) and ethyl 1-ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa) have been obtained in roughly equal yield. It has been shown that the rates of formation of the isomers are about the same, and previous failures to obtain the 2,3-isomer IVa were undoubtedly caused in part by its extreme sensitivity to hydrolysis. A number of differences between the two isomers have been delineated, deriving from the resistance of the 2,3-isomer IVa to enolize, which, in turn, is the result of steric factors. The 2,3-isomer IVa and a cyanopyrrolidinone derived from the cyclization of a cyano ester have been converted to 3-hydroxyproline in good yield.

Introduction

In conjunction with our interest in 3-pyrrolidinones as intermediates for the preparation of pyrroles, we undertook an investigation of the Dieckmann condensation as a useful entry into the 3-pyrrolidinone series. The reaction is summarized below, where Z is a blocking group, which, for general applicability, should be removable after condensation.



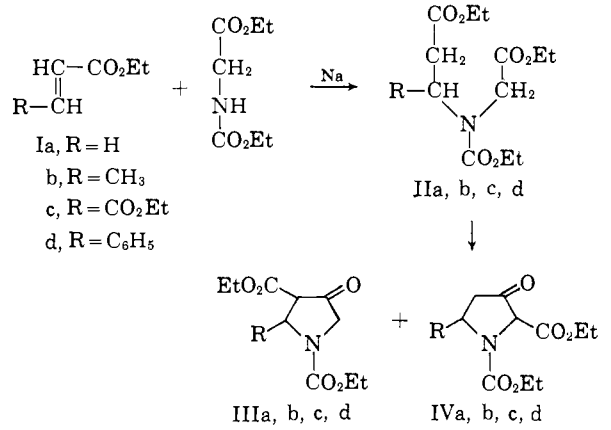
There are two possible products, and maximum utility would obtain if synthetic control enabled preparation of each isomer as desired.

There are no examples[4] of product control leading to both possible keto ester isomers *via* condensation of such unsubstituted diesters. In cases where one of the α-methylenes has been monosubstituted,[4-9] condensation presumably has occurred at the unsubstituted methylene, although the direction of closure usually has not been rigidly established. The reason for the lack of condensation at a substituted methylene is attributed primarily to the inability of the resulting β-keto ester to enolize and partly to a rate retardation by steric and inductive effects. A β-keto ester which cannot form an enolate ion under equilibrating conditions in strong base (equilibrating conditions are normally employed in these ring closures) is susceptible to ring opening and reclosure to a β-keto ester which can form an enolate ion, as is clearly demonstrated in the alicyclic series.[10,11]

If both methylenes are monosubstituted, then neither β-keto ester product will be capable of forming an enolate salt, and the yields of β-keto ester will be reduced.[12] In cases where one of the methylenes is disubstituted,[13] condensation at that methylene is, of course, precluded.

Our main interest has been the condensation of unsubstituted diesters, which, in theory at least, are capable of giving either β-keto ester (at least none of the limitations mentioned above for α-methylene substituted diesters will apply), and in which the nitrogen substituent can be removed after ring closure.

The Dieckmann reaction was first used for such a case by Kuhn and Osswald,[14] who condensed ethyl N-ethoxycarbonylglycinate with substituted ethyl acrylates and claimed that the only product formed was III.



Structural assignments were not rigorously established, since further reactions were carried out after decarboxylation, which would give the same product from III and IV. Also, in connection with the synthesis of kainic and allokainic acid, the diester IIa was treated with sodium in xylene in an attempt to synthesize ethyl 1-ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate; however, the only product isolable was assigned the structure ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carbox-

(1) Sponsored in part by Grant AI-04888 from the National Institutes of Health, United States Public Health Service.

(2) Public Health Service Predoctoral Research Fellow of the National Institutes of Health.

(3) Public Health Service Predoctoral Research Fellow of the National Institute of Mental Health.

(4) See N. J. Leonard, F. E. Fischer, E. Barthel, Jr., J. Figueras, Jr., and W. C. Wildman, *J. Am. Chem. Soc.*, **73**, 2371 (1951), for a discussion of the literature to 1950 of Dieckmann closures leading to 3-pyrrolidinones.

(5) J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, and D. M. Temple, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

(6) British Patent 873,303; *Chem. Abstr.*, **57**, 16566 (1962).

(7) M. Miyamoto, H. Morimoto, T. Sugawa, M. Uchibayashi, Y. Sanno, and K. Tanaka, *J. Pharm. Soc. Japan*, **77**, 571 (1957).

(8) S. Umio, *ibid.*, **78**, 725 (1958).

(9) (a) Y. H. Wu, W. A. Gould, W. G. Lobeck, Jr., H. R. Roth, and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 752 (1962); (b) Y. H. Wu, W. G. Lobeck, Jr., and R. F. Feldkamp, *ibid.*, **5**, 762 (1962).

(10) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 941 (1937); N. N. Chatterjee, B. K. Das, and G. N. Barpujari, *J. Indian Chem. Soc.*, **17**, 161 (1940); N. N. Chatterjee and A. Bose, *Sci. Cult.* (Calcutta), **6**, 724 (1941).

(11) N. S. Vul'fson and V. I. Zaretskii, *J. Gen. Chem. USSR*, **28**, 1951 (1958); **29**, 2704 (1959).

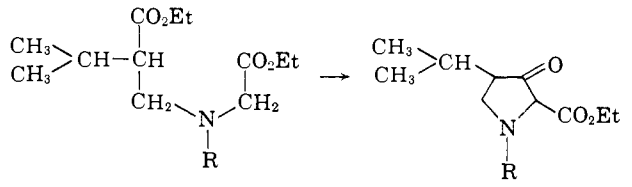
(12) *E.g.*, W. B. Renfrow, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **60**, 463 (1938).

(13) C. W. Ryan and C. Ainsworth, *J. Org. Chem.*, **27**, 2901 (1962).

(14) R. Kuhn and G. Osswald, *Ber.*, **89**, 1423 (1956).

ylate (IIIa).[15] Conclusive evidence for these structures was provided by a study[16] of the condensation of ethyl N-ethoxycarbonylglycinate-1-^{14}C with Ia, b, and c. By decarboxylation and determination of the radioactivity of the evolved carbon dioxide and the residual ketone, the reaction product was established as solely of type III. This also was true when the isolated diester IIa was used as starting material. Similarly, an analog of diester IIa was found[17] to give the same result.

Although it is clear that until now condensations of diester IIa have given only keto ester IIIa, there have been three claims for the synthesis of 2,3-keto esters—analogs of IVa. In two cases, no justification was given for the structural assignments.[18,19] Only in the example of the α-substituted diesters IIe is cyclization to the 2,3-keto esters IVe valid.[7,8] This is clear from the sub-



IIe, R = CO_2Et, CH_3, $C_6H_5CH_2$ IVe

sequent reactions of these keto esters and from the considerations above of the effect of α-methylene substitution on the direction of condensation. Thus, in the cyclization of diesters II, the literature reports the isolation only of keto esters III; keto esters IV, with the exception of IVf, have yet to be isolated and established as products from this reaction.

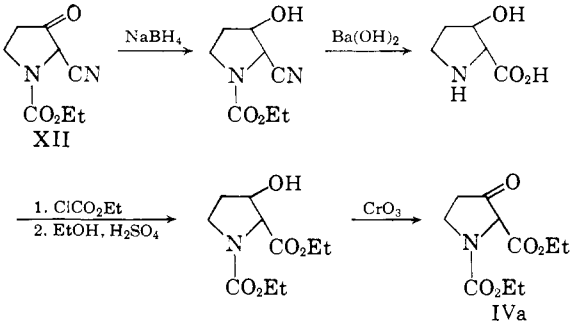
We now would like to report that product control has been achieved in the 3-pyrrolidinone series, and that the condensation of IIa has afforded the previously unknown IVa. In addition, we would like to report on the cyclization of cyano ester XI, and on the facile conversion of the product, cyanoketone XII, and keto ester IVa, to 3-hydroxyproline.

Discussion

Since the reaction conditions which had given ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IIIa) were undoubtedly equilibrating, and since IIIa could be quantitatively recovered from treatment with sodium ethoxide in refluxing ethanol, it was clear that keto ester IIIa was equilibrium favored over IVa. Therefore, we investigated the condensation of diester IIa under nonequilibrating conditions, hoping thereby to synthesize keto ester IVa; in fact, we expected that a rate-determined condensation would favor formation of IVa because of the expected higher acidity of the acetic methylene, owing to the inductive effect of the N-ethoxycarbonyl group.

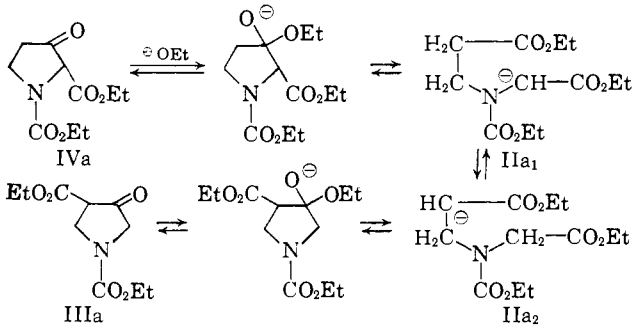
For nonequilibrating conditions, toluene was chosen as a solvent because of its requisite properties of low polarity but good solvent properties and low melting point which allowed low temperature reactions; potassium *t*-butoxide was chosen as a base because it was expected to be relatively inactive in the equilibration of unstable keto ester to stable keto ester.[20]

In order to develop an analytical procedure for the detection of keto ester IVa in mixture with IIIa, authentic samples of each were desirable. Compound IIIa was readily available from condensation of diester IIa, and IVa was synthesized from 1-ethoxycarbonyl-2-cyano-3-pyrrolidinone (XII) which was available in quantity from the cyclization of cyano ester XI (see below for further discussion). With both keto esters in hand, a gas chromatographic (v.p.c.) analysis was developed to distinguish between them.



When diester IIa was condensed with potassium *t*-butoxide in toluene at 0°, v.p.c. analysis of the reaction mixture after 30 min. showed the presence of keto esters IIIa and IVa in yields of 50 and 40%, respectively, with only a trace of recovered diester. Lowering the temperature, ultimately to −70°, had very little effect on this ratio. For preparative purposes, the mixture of IIIa and IVa was easily separated by partition between toluene and aqueous pH 9.5 buffer. Under these conditions, IIIa is quantitatively extracted into the aqueous phase while IVa remains completely in the toluene. The IVa thus obtained was identical in all respects with ethyl 1-ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate synthesized from 1-ethoxycarbonyl-2 cyano-3-pyrrolidinone.

As expected, when keto ester IVa was subjected to equilibrating conditions (sodium ethoxide in refluxing ethanol) it was converted completely to IIIa. Also of considerable interest was the relative instability of IVa

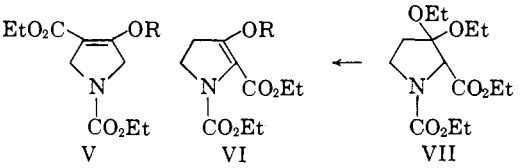


to alkaline hydrolysis. The half-lives in aqueous solution at pH 9.5 were approximately 10 days for IIIa and 2 min. for IVa. Thus, it is easily understood why IVa has not been isolated previously from the condensation of diester IIa; *i.e.*, any IVa formed would be equili-

(15) M. Miyamoto, *J. Pharm. Soc. Japan*, **77**, 568 (1957).
(16) H. Rapoport and C. D. Willson, *J. Am. Chem. Soc.*, **84**, 630 (1962).
(17) K. Morita, F. Irreverre, F. Sakiyama, and B. Witkop, *ibid.*, **85**, 2832 (1963), footnote 5.
(18) L. Ruzicka and C. Seidel, *Helv. Chim. Acta*, **5**, 715 (1922).
(19) H. Sasaki, *J. Chem. Soc. Japan*, **76**, 35 (1955).
(20) It is interesting to note that H. Plieninger and S. Leonhauser, *Ber.*, **92**, 1579 (1959), used potassium *t*-butoxide in toluene at 0° in the condensation of ethyl N-acetyl-N-(3-ethoxycarbonylpropyl)glycinate to synthesize ethyl N-acetyl-3-oxopiperidine-2-carboxylate which, in analogy to the five-membered ring series, should be the less stable of the two possible keto esters.

brated to IIIa, and even if the reaction conditions were not completely equilibrating, IVa would be extremely susceptible to destruction by hydrolysis in the reaction mixture (if the solvents used in the reaction had not been scrupulously dried) or in the isolation.

We observed some other interesting differences in the behavior of keto esters IIIa and IVa; *viz.*, (1) IIIa showed an infrared absorption at 6.1 μ, attributed to the carbonyl absorption of the enolic form of a β-keto ester[21] which was missing in IVa; (2) IIIa exhibited an ultraviolet absorption (Table I) in methanol and an alkali shift attributable to the enolic form of a β-keto ester and the enolate anion, respectively, whereas the ultraviolet spectrum of IVa was that of a β-keto ester in its keto form[22] which was not cleanly converted to its enolate anion in alkali; (3) IIIa showed the usual color reaction with ferric chloride, characteristic of enolic β-keto esters, which was not shown by IVa; (4) IIIa reacted rapidly with diazomethane to form an enol ether,[16] whereas IVa gave a complex mixture with diazomethane, indicative of reaction with both the keto and enol forms of IVa; (5) IIIa was extracted from an organic phase by aqueous pH 9.5 buffer while IVa was not. From these observations, it can be concluded that ethyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IIIa) is much more easily enolized[23] than is ethyl 1-ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa). The diazomethane reaction, in particular, suggests that the difference in the tautomeric behavior of the two keto esters IIIa and IVa is attributed to a particular instability of compounds of the type VI as compared to type V. This is supported by our unsuccess-



ful attempts to prepare enol ether VI by eliminating ethanol from ketal VII. Sodium ethoxide treatment gave no appreciable reaction and heating at 200° did cause elimination but gave a complex mixture containpyrroles and 3-pyrrolines.

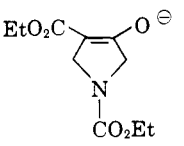
TABLE I

ULTRAVIOLET ABSORPTION OF INTRAMOLECULAR CONDENSATION PRODUCTS

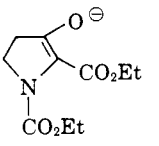
	In CH_3OH		In KOH–CH_3OH	
Compound	λ_{max}, mμ	ϵ	λ_{max}, mμ	ϵ
IIIa	246	5000	275	14,000
IVa	280	53	[a]	
XII	270	150	285	10,000
XIII	273	15,000	Same	

[a] Not reproducible; general slow increase of extinction on addition of alkali by factor of less than 10 and sharpening of absorption at about 275 mμ; most of IVa destroyed in KOH–CH_3OH.

The relative instability of VI with respect to V can be used to explain the observation that IIIa is equilibrium favored over IVa. At equilibrium, in strong base, IIIa and IVa should exist as anions IIIaa and IVaa and, in accordance with what has been outlined above, IVaa should be much less stable than IIIaa, and therefore equilibrium should favor IIIaa. The reason for the relative instability of VI can be seen by examining models which indicate the possibility of significant steric interaction between the 1- and 2-ethoxycarbonyl groups in the rigid pyrroline ring system; on the other hand, V shows no interaction between the two 1,3-ethoxycarbonyl groups.



IIIaa



IVaa

It is possible at this time to draw some conclusions concerning the relative rates of formation of keto esters IIIa and IVa in the Dieckmann condensation of diester IIa.

When IVa was resubmitted to the reaction conditions (potassium *t*-butoxide in toluene, plus 1 mole of ethanol, at 0°), it was recovered in 70–75% yield along with a 5–10% yield of IIIa. This indicates that the maximum equilibration of IVa → IIIa under the reaction conditions was 5–10% and the relative yields of IIIa/IVa in the condensation of IIa were approximately equal to the relative rates of formation of IIIa/IV; *i.e.*, 5/4. However, the relative rates of cyclization can be divided into two parameters: the relative acidities of the acetic and propionic α-methylenes, and the relative rates of closure of the anions IIa_1 and IIa_2.

Although we have no specific data on the acidities of the acetic and propionic methylenes of diester IIa, we can infer that the acetic methylene is more acidic than the propionic methylene on the basis of the inductive effect of the N-ethoxycarbonyl groups; *e.g.*, N-ethoxycarbonylacetic acid has a pK of 3.66 while that of acetic acid is 4.76.[24] Since the inductive effect falls off rapidly with distance, one would expect a greater effect of the N-ethoxycarbonylgroup on an adjacent (acetic) methylene as compared to a methylene (propionic) which is one carbon removed. Thus, the acetic methylene hydrogens of IIa should have a significantly higher acidity than those of the propionic methylene.

The fact that the relative rate of formation of IIIa/IVa is close to one, therefore, suggests that the specific rate of closure of anion IIa_2 is faster than the rate of closure of anion IIa_1. This can be explained by postulating a 1,2-diethoxycarbonyl steric interaction in the transition state leading to keto ester IVa. Since such an interaction would be absent in the transition state leading to keto ester IIIa, the latter should be relatively more stable, and thus the rate of closure of anion IIa_2 should be faster than the rate of closure of anion IIa_1.

The above postulate is supported by our results in the condensation of the *t*-butyl ester analog of diester IIa, namely, *t*-butyl N-ethoxycarbonyl-N-(2-*t*-butoxycarbonylethyl)glycinate-1-^{14}C (VIII). When VIII was treated under the same conditions as diester IIa (potassium *t*-butoxide in toluene at 0°) and the total organic material was examined by decarboxylation and radioactivity analysis, the only keto ester formed was

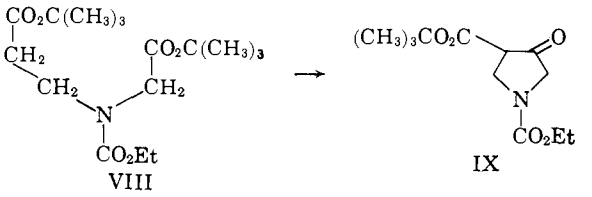
(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

(22) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkeit, *Tetrahedron*, **19**, 1625 (1963).

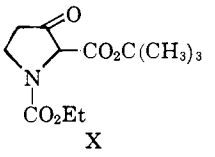
(23) The enol content of IIIa has been found to be 66% in ethanol.[14]

(24) *Pure Appl. Chem.*, 1, 190 (1961).

found to be *t*-butyl 1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IX); no keto ester X could be detected.



VIII IX

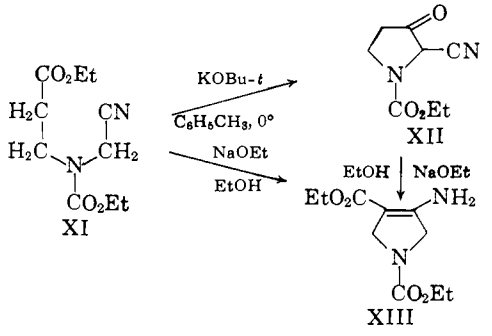


X

Since a *t*-butyl ester (compared to an ethyl ester) would not be expected to change the relative acidities of the acetic and propionic α-methylenes, the lack of formation of X must be explained by a slower rate of closure of the acetic carbanion compared to the propionic carbanion of VIII. This agrees with the idea of a 1,2-alkoxycarbonyl interaction in the transition states leading to IVa of X, which is increased if one of the alkyl groups is *t*-butyl—increased to the point where the transition state leading to X is sufficiently destabilized effectively to prevent formation of X.[25]

Condensation of Cyano Ester.—It is interesting, at this point, to compare the condensation of diester IIa with that of the cyano ester XI.

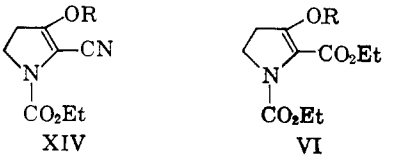
The cyclization of N-ethoxycarbonyl-N-cyanomethyl-β-alanine ethyl ester (XI) was first studied[26] using sodium hydride in benzene. The only product isolated, and that in low yield, was 1-ethoxycarbonyl-2-cyano-3-pyrrolidinone (XII). However, our results differ. Using the same conditions, we obtained as the chief product the pyrroline XIII, which is the only product if the reaction is carried out under equilibrating conditions. Under nonequilibrating conditions, potassium *t*-butoxide in toluene at 0°, the cyanoketone XII was obtained in 55% yield along with about 7% of XIII.



XI XII XIII

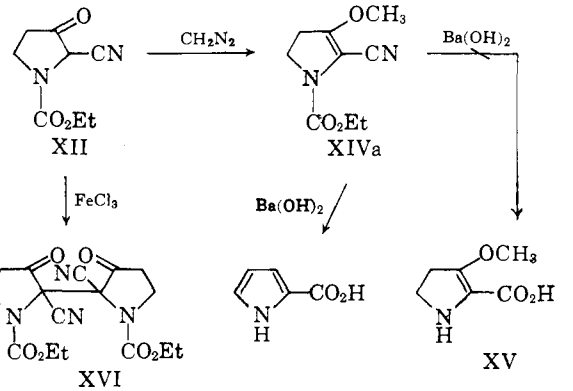
In analogy to the keto ester case (IVa → IIIa), XII could be quantitatively converted to XIII under equilibrating conditions.

Some interesting comparisons can be made between the tautomeric behavior of keto ester IVa and cyanoketone XII. The ultraviolet spectrum of XII (Table I) indicates that, like IVa, it exists mainly in the keto form. However, when XII is subjected to a suitable driving force, such as base or removal of its enol form by a facile conversion to an enol ether with diazomethane, it can easily enolize, unlike keto ester IVa. This difference of behavior is due, of course, to the differences between the ethoxycarbonyl and cyano groups at C-2 in IVa and XII, respectively. Although some of this difference might be ascribed to the electronic characters of the cyano and ethoxycarbonyl groups, we believe the most important difference is that of geometry. That is, the smaller size of the cyano group and its linear geometry suggests that compounds of the type XIV should be more stable than VI, because of the weaker steric interactions in the former than in the latter.



XIV VI

In connection with the conversion of cyanoketone XII to keto ester IVa (through 3-hydroxyproline), which was outlined above, it should be mentioned that the shorter more obvious conversion procedures were not successful. The reported[26] ethanolysis of cyanoketone XII to keto ester IVa in good yield gave very little isolable product in our hands. Similarly, basic hydrolysis of the readily available enol ether XIVa did not give the desired XV, which conceivably could be converted to IVa, but gave instead 2-pyrrolecarboxylic acid. A similar reaction has been observed previously in the alkaline hydrolysis of ethyl 1-ethoxycarbonyl-4-methoxy-Δ^3-pyrroline-3-carboxylate to 3-pyrrolecarboxylic acid.[27]



XII XIVa XVI XV

In analogy with the report[28] that oxidative treatment of methyl 3-oxotetrahydrothiophene-2-carboxylate produced a dimer, we observed that the action of ferric chloride on 1-ethoxycarbonyl-2-cyano-3-pyrrolidinone (XII) gave a quantitative yield of the dimer XVI. Treatment of ethyl 1-ethoxy-carbonyl-3-oxopyrrolidine-2-carboxylate (IVa) under the same conditions gave no evidence of dimer formation.

3-Hydroxyproline.—There recently has been considerable interest in 3-hydroxyproline, concerned with its isolation from natural sources and its synthesis.[17,29-32]

(25) An obvious way to remove the possibility of 1,2-alkoxycarbonyl interaction is by condensing a free amino diester; *e.g.*, ethyl N-(2-ethoxycarbonylethyl)glycinate. However, in this case, difficulties arise from intermolecular condensation between NH and ester leading to diketopiperazine formation, and instability of the free amino β-keto ester.

(26) M. Uchibayashi, *J. Pharm. Soc. Japan*, **78**, 845 (1958).

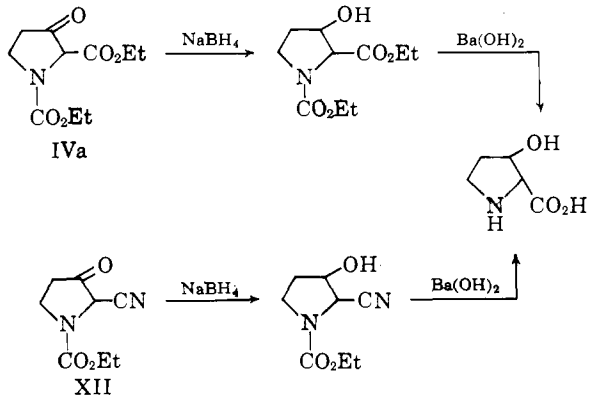
(27) H. Rapoport and C. D. Willson, *J. Org. Chem.*, **26**, 1102 (1961).

(28) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946).

(29) F. Irreverve, K. Morita, A. V. Robertson, and B. Witkop, *ibid.*, **85**, 2824 (1963).

(30) J. Sheehan and J. Whitney, *ibid.*, **84**, 3980 (1962).

Since we could prepare both ethyl 1-ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa) and 1-ethoxycarbonyl-2-cyano-3-pyrrolidinone (XII) in quantity, we investigated the conversion of these two compounds to 3-hydroxyproline. The sequence outlined was straightforward and gave good yields of 3-hydroxyproline: 75% from IVa and 55% from XII.



The ratio of *cis* to *trans* isomers[33] was 1:2 for either synthetic route, and, indeed, it was shown that refluxing aqueous barium hydroxide equilibrated each steroisomer to a mixture of *cis* and *trans* isomers in the ratio of 1:2. Each stereoisomer was characterized as the N-tosyl acid, N-tosyl methyl ester, and N-2,4-dinitrophenyl acid.

Determination of the pK's of each isomer by potentiometric titration led to results which differ from those previously reported. The pK'_1 and pK'_2 for both isomers are reported[29] to be indistinguishable: 1.92 and 9.73, respectively. We found that for the *trans* isomer, $pK'_1 = 1.69$ (± 0.05), $pK'_2 = 9.88$ (± 0.05); for the *cis* isomer, $pK'_1 = 2.13$ (± 0.05), and $pK'_2 = 10.03$ (± 0.05).

Of further interest are the spectrometric studies directed toward the stereochemical question. A comparison of the infrared spectra of *cis*- and *trans*-N-tosyl-3-hydroxyproline methyl esters in methylene chloride shows essentially the same O–H stretch absorption, 3590 cm.$^{-1}$, indicating little, if any, intramolecular hydrogen bonding in the *cis* isomer. This phenomenon was also reported for the N-carbobenzyloxy methyl esters,[29] and is certainly unexpected considering the strong intramolecular hydrogen bonding shown in the methyl 2-hydroxycyclopentanecarboxylate series.[34,35]

The nuclear magnetic resonance spectra of *cis*- and *trans*-3-hydroxyproline studied[29] in D_2O using spin decoupling technique showed coupling constants, J_{23}, of 4 c.p.s. and less than 1 c.p.s. for the *cis* and *trans* isomers, respectively. We measured J_{23} in D_2O–CF_3CO_2H, and thus of the protonated forms of 3-hydroxyproline, and observed values of 3.7 and 2.3 c.p.s. for the *cis* and *trans* isomers, respectively, as compared to the Karplus theoretical values of about 8.2 and 2.2 c.p.s. It is clear that use of the Karplus relation between coupling constant and dihedral angle is not valid in this system, or there are significant bond distortions compared to those expected from models.

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(32) J. Sheehan and J. Whitney, *J. Am. Chem. Soc.*, **85**, 3863 (1963).

(33) Stereochemical designation is based on the assignment of Sheehan and Whitney.[32]

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Experimental[36]

Ethyl 1-Ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa) and Ethyl 1-Ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IIIa).—To a solution of 51.8 mmoles of potassium *t*-butoxide in 120 ml. of toluene at 0° (prepared by the method of Plieninger and Leonhauser[20] using solvents which had been freshly distilled from sodium), under nitrogen, was added 10 g. (36.4 mmoles) of ethyl N-ethoxycarbonyl-N-(2-ethoxycarbonylethyl)-glycinate-1-^{14}C (IIa)[16] in 20 ml. of toluene over a 10-min. period. The solution was stirred for 30 min. at 0° and 4 ml. of glacial acetic acid was added, immediately followed by 20 g. of $NaH_2PO_4 \cdot H_2O$ in 200 ml. of ice-cold water. The resultant mixture was extracted twice with 150-ml. portions of chloroform, and the combined organic extracts were washed twice with 20 ml. of pH 7 phosphate buffer, dried, and evaporated to a residue which was analyzed by v.p.c. (2% QF-1 on Chromosorb W, acid-washed, 170–175°, 60 ml. of He/min.), indicating 50% IIIa (R_t 1.2–1.5 min.) and 40% IVa (R_t 2–2.5 min.).

The above residue was dissolved in 250 ml. of toluene, cooled to 0°, and extracted with three 125-ml. portions of cold pH 9.5 carbonate buffer. The aqueous extracts were converted to pH 3 with phosphoric acid, and extracted with five 100-ml. portions of chloroform which were combined, dried, and evaporated to a residue. Distillation at 130–140° (0.4 mm.) gave 3.7 g. (45% yield) of IIIa, m.p. 60–62° (reported[14] m.p. 59–62°). Decarboxylation of IIIa showed that all of the radioactivity remained in the residual ketone, 1-ethoxycarbonyl-3-pyrrolidinone.

The toluene fraction was washed with 20 ml. of water, dried, and evaporated to a residue which was distilled in a molecular still at 90–100° (0.02 mm.), giving 2.9 g. (35% yield) of a colorless oil, ethyl 1-ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa).

Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.4; H, 6.6; N, 6.1. Found: C, 52.5; H, 6.7; N, 6.0.

Decarboxylation of the above oil showed that essentially all of the radioactivity was in the evolved carbon dioxide.

N-Cyanomethyl-β-alanine Ethyl Ester.—Ethyl 3-aminopropionate hydrochloride[37] (56.2 g., 0.366 mole) was dissolved in 125 ml. of water, and 10 *N* sodium hydroxide was added to pH 9.5. The aqueous solution was extracted with two 200-ml. and four 100-ml. portions of chloroform, readjusting the pH to 9.5 after every extraction. Evaporation of the combined, dried chloroform extracts left a residue to which was added 35 ml. of dry benzene containing 11.65 g. (0.154 mole) of chloroacetonitrile, and the mixture was stirred at 60° for 5 hr. in a dry atmosphere. Benzene (250 ml.) was added to the cooled reaction mixture which was then extracted with three 70-ml. portions of pH 4.9 phosphate buffer. The combined aqueous phase was then extracted with three 100-ml. portions of benzene, and the combined benzene extracts were dried and evaporated to a residue which was distilled at 98–99° (0.5 mm.), yielding 19 g. (79% based on chloroacetonitrile) of N-cyanomethyl-β-alanine ethyl ester.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.8; H, 7.7; N, 17.9. Found: C, 53.3; H, 7.7; N, 18.3.

The above aqueous extracts could be adjusted to pH 9–10 and extracted with chloroform to recover about half of the starting ethyl 3-aminopropionate which could be recycled.

N-Ethoxycarbonyl-N-cyanomethyl-β-alanine Ethyl Ester (XI).—To a mixture of 40.5 g. (0.26 mole) of N-cyanomethyl-β-alanine ethyl ester and 27.5 g. of sodium carbonate in 200 ml. of water (ice bath cooling) was added dropwise 29 g. (0.267 mole) of ethyl chloroformate. The resulting mixture was vigorously stirred at room temperature for 3 hr. Then, 120 ml. of water was added, and the mixture was extracted with six 100-ml. portions of benzene. The combined benzene extracts were dried and evaporated to a residue which was fractionally distilled (spinning band column), the main fraction boiling at 128–130° (0.8 mm.); yield 54 g. (91%) of XI as a colorless oil.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.6; H, 7.1; N, 12.3. Found: C, 52.8; H, 7.0; N, 12.3.

(36) All melting points are corrected, and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley; all evaporations were *in vacuo* using a rotary evaporator.

(37) W. J. Hale and E. M. Honan, *J. Am. Chem. Soc.*, **41**, 770 (1919).

The Cyclization of N-Ethoxycarbonyl-N-cyanomethyl-β-alanine Ethyl Ester (XI). A. With Potassium *t*-Butoxide in Toluene at 0°.—To a mixture of 0.15 mole of potassium *t*-butoxide in 600 ml. of toluene at 0°, under nitrogen, was added 33.5 g. (0.15 mole) of XI in 200 ml. of toluene, dropped in over a period of 30 min. The resultant mixture was stirred for 1 hr. and then extracted with one 400-ml. portion, one 200-ml. portion, and four 100-ml. portions of ice-cold pH 7.1 phosphate buffer. The combined aqueous extracts were adjusted to pH 3.8 and extracted with one 400- and five 200-ml. portions of chloroform. Evaporation of combined, dried chloroform extracts left a residue which was distilled in a molecular still at 110–120° (0.03 mm.), yielding 14.6 (55%) of **1-ethoxycarbonyl-2-cyano-3-pyrrolidinone (XII)** as an extremely viscous liquid.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.7; H, 5.5; N, 15.5. Found: C, 52.5; H, 5.5; N, 15.4.

On smaller scale preparation, the yield of XII was close to 70%. The extreme difficulty in distillation resulted in significant losses.

From the above toluene fraction could be obtained, after drying, evaporating, and subliming (100° (0.5 mm.)), 2.3 g. (7% yield) of **ethyl 1-ethoxycarbonyl-4-amino-Δ³-pyrroline-3-carboxylate (XIII)**, m.p. 119–121°.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.6; H, 7.1; N, 12.3; OC_2H_5, 39.5. Found: C, 52.3; H, 7.1; N, 12.1; OC_2H_5, 39.2.

B. **With Sodium Ethoxide in Ethanol. Ethyl 1-Ethoxycarbonyl-4-amino-Δ³-pyrroline-3-carboxylate (XIII).**—To a solution of 22 mmoles of sodium ethoxide in 100 ml. of absolute ethanol was added 5 g. (22 mmoles) of XI in 25 ml. of ethanol. The reaction mixture was stirred for 12 hr. at room temperature, then diluted with 800 ml. of water. The resulting solution was extracted five times with 80-ml. portions of benzene, and the combined benzene extracts were washed with two 50-ml. portions of 1 *N* sodium hydroxide, dried, and evaporated to a residue which was fractionally distilled, yielding 250 mg. (5%) of recovered starting material, XI, at 147–149° (2.3 mm.), and 4.7 g. (94% yield) of XIII at 158–159° (2.5 mm.) as a colorless liquid which crystallized in the receiver; m.p. 119–121°, identical with that of XIII prepared above by potassium *t*-butoxide condensation of XI in toluene at 0°.

1-Ethoxycarbonyl-2-cyano-3-pyrrolidinol.—Into a solution of 3.2 g. of sodium borohydride and 2 g. of dipotassium hydrogen phosphate in 50 ml. of water at 10° was quickly dropped a solution of 1.58 g. of cyanoketone XII in 20 ml. of ethanol. The resultant mixture was stirred at 5–10° for 5 min., then 1 *M* sulfuric acid was added to pH 2.5. After being stirred a few minutes, the solution was adjusted to pH 6 and evaporated to *ca.* 150 ml., followed by extraction with five 100-ml. portions of chloroform. The combined chloroform extracts were dried and evaporated to a residue which was distilled at 180–190° (0.03 mm.), yielding 1.20 g. (75%) of 1-ethoxycarbonyl-2-cyano-3-pyrrolidinol.

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.2; H, 6.6; N, 15.2. Found: C, 52.2; H, 6.6; N, 15.4.

3-Hydroxyproline. Hydrolysis of 1-Ethoxycarbonyl-2-cyano-3-pyrrolidinol.—A mixture of 700 mg. (3.8 mmoles) of 1-ethoxycarbonyl-2-cyano-3-hydroxypyrrolidine plus 3.72 g. of $Ba(OH)_2 \cdot H_2O$ (19.7 mmoles) in 115 ml. of water was boiled under a nitrogen sweep for 46 hr. The exit gas was bubbled through aqueous boric acid, and the amount of ammonia evolution determined by titration with hydrochloric acid.[38] After 46 hr., ammonia evolution ceased at 90% of the theoretical. The pH of the reaction mixture was adjusted to 4 with sulfuric acid, the barium sulfate precipitate was removed after the addition of filter-aid, and the filtrate was evaporated to *ca.* 50 ml.

The above solution was chromatographed on AG50W-X8 (Bio-Rad Lab) exchange resin, hydrogen form, 50–100 mesh, using a 25-ml. water wash and 1 *N* hydrochloric acid for elution. The eluent was evaporated to give the hydrochloride of 3-hydroxyproline, *cis* and *trans*. This was then chromatographed on AG50W-X8, sodium form, 200–400 mesh, 2.8 × 99 cm., using pH 3.20 citrate buffer for elution, and the eluent fractions were analyzed by the ninhydrin method.[39,40] Two distinctly separated peaks were observed: the first corresponding to *trans*-3-hydroxyproline and the second corresponding to *cis*-3-hydroxyproline. The combined fractions for each amino acid were immediately desalted on AG1-X8, hydroxide form, using a water wash and cold 1 *N* acetic acid elution. The acetic acid eluent could be tested for 3-hydroxyproline by spotting on filter paper with a drop of ninhydrin solution (0.3% in absolute ethanol) and heating at 100° for *ca.* 5 min. Fractions containing 3-hydroxyproline, *cis* or *trans*, gave a yellow color when tested by this procedure. The appropriate fractions were combined and evaporated to yield 250 mg. (50%) of *trans*-3-hydroxyproline and 119 mg. (24%) of *cis*-3-hydroxyproline after recrystallization from water–ethanol; *trans*-3-hydroxyproline, m.p. 222–224° dec. (reported m.p. >200° dec.[29]; 224–230 dec.,[32] 232° dec.[31]); *cis*-3-hydroxyproline, m.p. 223–225° dec. (reported[32] m.p. 225–235°).

Anal. Calcd. for $C_5H_9NO_3$: C, 45.8; H, 6.9; N, 10.7. Found: *trans* isomer, C, 45.8; H, 6.6; N, 10.8; *cis* isomer, C, 45.9; H, 6.7; N, 10.8.

p*K'* Determinations.—An aqueous solution of each isomer was titrated with standard hydrochloric acid, under a nitrogen atmosphere, to determine pK'_1, and then back titrated with sodium hydroxide to determine pK'_2. The pH was measured with a pH meter (Beckman, Model G), calibrated with buffer at pH 4, 7, 10 to within ±0.02 pH unit. Equilibrium constants were calculated by the equations

$$K'_1 = \frac{[H^+](H_3\overset{+}{N}RCO_2^-)}{(H_3\overset{+}{N}RCO_2H)}$$

$$K'_2 = [H^+]\frac{(H_2NRCO_2^-)}{(H_3N^+RCO_2^-)}$$

where $[H^+]$ = hydrogen ion activity measured by the pH meter, and parentheses represent the concentrations of the different amino acid forms, calculated by balance of charges, assuming that the activity coefficients of hydrogen ion and hydroxyl ion are the same as their activity coefficients in solutions of equivalent HCl or NaOH concentrations.[41] Results: *trans*-3-hydroxyproline, pK'_1 = 1.69 ± 0.05, pK'_2 = 9.88 ± 0.05; *cis*-3-hydroxyproline, pK'_1 = 2.13 ± 0.05, pK'_2 = 10.03 ± 0.05.

Use of the above procedure for the p*K'* determination of 4-hydroxy-L-proline gave values of 1.82 and 9.87 as compared to the reported values of 1.82 and 9.65,[41] and 1.92 and 9.73.[42]

3-Hydroxyproline from Ethyl 1-Ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa).—To a solution of 1 g. of K_2HPO_4 in 30 ml. of ice-cold water was added solid $NaH_2PO_4 \cdot H_2O$ until the pH was 7–7.5. Then, 1 g. of sodium borohydride was added and, immediately thereafter, 440 mg. (1.92 mmoles) of IVa in 20 ml. of cold ethanol was quickly dropped in with stirring. More $NaH_2PO_4 \cdot H_2O$ was periodically added to keep the pH between 8 and 9. The mixture was stirred 1 min. at 0°, then 0.5 g. of sodium borohydride was added and stirring continued for 4 min., after which sulfuric acid was added to pH 3. The pH was then readjusted to 7 with NaOH, the aqueous solution was extracted with five 100-ml. portions of chloroform, the combined chloroform extracts were dried and evaporated, and the residue was hydrolyzed and worked up as described above; yield 120 mg. (48%) of *trans*-3-hydroxyproline and 60 mg. (24%) of *cis*-3-hydroxyproline.

***cis*- and *trans*-N-tosyl-3-hydroxyproline** were prepared by treating 20 mg. (0.15 mmole) of each isomer of 3-hydroxyproline with 33 mg. of sodium carbonate and 2 ml. of water; the aqueous solution was *vigorously* stirred with a solution of 47 mg. (0.25 mmole) of toluenesulfonyl chloride in 2.5 ml. of ether for 6 hr. at room temperature, after which the aqueous phase was separated and evaporated to *ca.* 0.3 ml. Hydrochloric acid, 6 *N*, was added to pH 1, and the solid formed, after 6 hr. at 0°, was separated by centrifugation. Recrystallization from 0.4 ml. of 10% ethanol gave 18 mg. (40% yield) of each N-tosyl derivative; *trans* isomer, m.p. 164–168°; *cis* isomer, m.p. 160–164°.

Anal. Calcd. for $C_{12}H_{15}NO_5S$: C, 50.5; H, 5.3; N, 4.9. Found: *trans* isomer, C, 50.7; H, 5.5; N, 6.0; *cis* isomer, C, 50.2; H, 5.6; N, 5.0.

***cis*- and *trans*-N-tosyl-3-hydroxyproline methyl ester** were prepared by treating 15 mg. (0.05 mmole) of each isomer of N-tosyl-3-hydroxyproline in 1.5 ml. of methanol at 0° with a diazomethane–ether solution until the yellow color persisted. After

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(42) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943.

standing at 0° with excess diazomethane for 15 min., the solution was evaporated and the residue was dissolved in ethanol, concentrated to 0.1 ml., and crystallized by adding 0.4 ml. of water. The yield of each isomer was 10–12 mg. (70%); *trans* isomer, m.p. 101–102° (reported[29] m.p. 99–100°); *cis* isomer, m.p. 127–129°.

Anal. Calcd. for $C_{13}H_{17}NO_5S$: C, 52.2; H, 5.7; N, 4.7. Found: *trans* isomer, C, 52.6; H, 5.8; N, 4.8; *cis* isomer, C, 52.6; H, 6.1; N, 5.0.

***cis*- and *trans*-N-2,4-dinitrophenyl-3-hydroxyproline** were prepared by treating a solution of 21 mg. (0.16 mmole) of each isomer of 3-hydroxyproline in 5 ml. of water and 5 ml. of 95% ethanol containing 0.4 ml. of pH 9.5 carbonate buffer (55 g. of sodium carbonate plus 61.1 g. of sodium bicarbonate in 2.5 l. of water) with 34 mg. (0.18 mmole) of 1-fluoro-2,4-dinitrobenzene. The solution was stirred at room temperature for 3.5 hr., the ethanol was evaporated, and the aqueous solution was washed with three 10-ml. portions of ether. After concentrating the aqueous solution to 2 ml., it was made strongly acidic with 6 *N* hydrochloric acid and placed in the cold. The yellow crystals which formed were washed with ice–water, and dried at 30° (1.5 mm.) for 48 hr.; yield, about 80%.

N-2,4-Dinitrophenyl-*trans*-3-hydroxyproline, m.p. 89–91°, $\lambda_{max}^{CH_3OH}$ 364 mμ (ε 18,400), $\lambda_{max}^{1\ N\ NaOH-H_2O}$ 387 mμ (ε 17,400).

Anal. Calcd. for $C_{11}H_{11}N_3O_7 \cdot H_2O$: C, 41.9; H, 4.2; N, 13.3. Found: C, 41.9; H, 4.0; N, 13.3.

N-2,4-Dinitrophenyl-*cis*-3-hydroxyproline, m.p. 173–176°, $\lambda_{max}^{CH_3OH}$ 365 mμ (ε 18,800), $\lambda_{max}^{1\ N\ NaOH-H_2O}$ 385 mμ (ε 17,200).

Anal. Calcd. for $C_{11}H_{11}N_3O_7 \cdot 0.5H_2O$: C, 43.1; H, 3.9; N, 13.7. Found: C, 42.9; H, 3.9; N, 13.6.

Ethyl 1-Ethoxycarbonyl-3-hydroxypyrrolidine-2-carboxylate from 3-Hydroxyproline.—A mixture of 200 mg. (1.53 mmoles) of 3-hydroxyproline, 200 mg. of sodium carbonate, and 165 mg. (1.53 mmoles) of ethyl chloroformate in 10 ml. of water was stirred 4 hr. at room temperature. Hydrochloric acid was added to pH 5, the solution was passed through an AG50W-X8, hydrogen form, column with a water wash, and the eluent was adjusted to pH 3 with sodium hydroxide and evaporated to dryness. To the resulting residue was added 10 ml. of absolute ethanol and 1 ml. of concentrated sulfuric acid and the mixture was boiled for 3 hr. After cooling, a concentrated solution of sodium bicarbonate was added to pH 8, the alcohol was evaporated, and the mixture was diluted to 50 ml. with water and extracted with four 50-ml. portions of chloroform. The combined chloroform extracts were dried and evaporated, leaving a residue which was distilled at 120° (0.01 mm.) in a molecular still to give 235 mg. (67%) of ethyl 1-ethoxycarbonyl-3-hydroxypyrrolidine-2-carboxylate.

Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.9; H, 7.4; N, 6.1. Found: C, 52.4; H, 7.6; N, 6.0.

Ethyl 1-Ethoxycarbonyl-3-oxopyrrolidine-2-carboxylate (IVa) from Oxidation of Ethyl 1-Ethoxycarbonyl-3-hydroxypyrrolidine-2-carboxylate.—To a solution of 218 mg. (0.95 mmole) of ethyl 1-ethoxycarbonyl-3-hydroxypyrrolidine-2-carboxylate in 114 ml. of acetone was added a solution of 258 mg. (2.58 mmoles) of chromic oxide in 0.65 ml. of water and 0.30 ml. of sulfuric acid. The mixture stood at room temperature for 60 min., then 2 ml. of ethanol was added and the mixture was concentrated to 20 ml. and distributed between 140 ml. of chloroform and 40 ml. of water. The chloroform extract was washed with two 20-ml. portions of water, dried, and evaporated to a residue which was chromatographed on silica gel (column washed with benzene, and product eluted with chloroform). The chloroform eluent was evaporated to a residue which was distilled in a molecular still at 100–120° (0.01 mm.), yielding 151 mg. (70% yield) of IVa; infrared absorption, $\lambda_{max}^{CHCl_3}$ 5.64, 5.75, 5.89 μ; v.p.c. (2% QF-1 on Chromosorb W, acid washed, 170–175°, 60 ml. of He/min.) R_t 2–2.5 min.

Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.4; H, 6.6; N, 6.1; OR, 2/229. Found: C, 52.3; H, 6.6; N, 5.9; OR, 2/229.

***t*-Butyl N-(2-*t*-Butoxycarbonylethyl)glycinate-1-^{14}C.**—Three 350-ml. pressure bottles were each charged with 75 ml. of diglyme, 8.9 ml. of sulfuric acid, 10.2 g. of N-(2-carboxyethyl)glycine-1-^{14}C,[43,44] and 90 g. of isobutylene. The bottle was sealed, the mixture was shaken for 55 hr. at room temperature, and the content of each bottle was poured into a solution containing 300 ml. of water, 60 g. of sodium hydroxide, and 40 g. of ice. The precipitated sodium sulfate was removed, the filtrate was extracted with five 100-ml. portions of ether, the ether extracts were washed with two 50-ml. portions of water and dried, and the residue left on evaporating the ether was fractionally distilled. *t*-Butyl N-(2-*t*-butoxycarbonylethyl)glycinate-1-^{14}C was collected at 104–105° (0.4 mm.); yield 18.5 g., 34.3%.

Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.2; H, 9.7; N, 5.4. Found: C, 60.5; H, 9.7; N, 5.2.

***t*-Butyl N-Ethoxycarbonyl-N-(2-*t*-butoxycarbonylethyl)glycinate-1-^{14}C (VIII).**—To a solution of 13.4 g. of sodium carbonate in 210 ml. of water was added 32.6 g. of *t*-butyl N-(2-*t*-butoxycarbonylethyl)glycinate-1-^{14}C. Then, 13.9 g. of ethyl chloroformate was dropped in with external ice cooling. The mixture was stirred at room temperature for 4 hr., cooled to 10° with ice, adjusted to pH 2 with concentrated phosphoric acid, and extracted with four 100-ml. portions of benzene. The combined benzene extracts were washed with three 50-ml. portions of 1 *M* phosphoric acid, 50 ml. of 0.5 *M* sodium bicarbonate, two 50-ml. portions of water, and dried. Evaporation of the benzene and distillation of the residue at 130–133° (0.6 mm.) yielded 36.1 g. (86%) of VIII as a colorless oil.

Anal. Calcd. for $C_{16}H_{29}NO_6$: C, 58.0; H, 8.8; N, 4.2. Found: C, 58.2; H, 9.0; N, 4.1.

Cyclization of *t*-Butyl N-Ethoxycarbonyl-N-(2-*t*-butoxycarbonylethyl)glycinate-1-^{14}C (VIII).—To a mixture of 44.6 mmoles of potassium *t*-butoxide in 300 ml. of toluene at 0°, under nitrogen, was added dropwise 6.05 g. (18.3 mmoles) of VIII in 40 ml. of toluene. The reaction mixture was stirred for 3 hr., and then extracted with 100 ml. of 2.5 *N* acetic acid and two 70-ml. portions of water. Evaporation of the dried toluene solution left a residue which was decarboxylated,[16] the carbon dioxide evolved indicating a 70% yield of β-keto ester. There was no activity in the evolved carbon dioxide, and the residue, 1-ethoxycarbonyl-3-pyrrolidinone, had a specific activity equal to that of the starting material VIII, demonstrating that the sole product was *t*-butyl-1-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate (IX).

1-Ethoxycarbonyl-2-cyano-3-methoxy-Δ²-pyrroline (XIV).—To a solution of 3 g. (16.5 mmoles) of 1-ethoxycarbonyl-2-cyano-3-pyrrolidinone in ether was added an excess of ethereal diazomethane; the resultant solution was kept at 0° for 12 hr. and then evaporated, and the residue was taken up in fresh ether and washed twice with 50-ml. portions of pH 12 phosphate buffer. The ether layer was dried and evaporated to a residue which was fractionally distilled, giving a single fraction, b.p. 152–154° (1.5 mm.), which crystallized on standing; yield 3.0 g. (92%). This material was recrystallized from benzene and sublimed at 48° (1 mm.), yielding 1-ethoxycarbonyl-2-cyano-3-methoxy-Δ²-pyrroline, m.p. 49–50°; ultraviolet absorption: $\lambda_{max}^{CH_3OH}$ 268 mμ (ε 9500).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.1; H, 6.2; N, 14.3; OR, 2/196. Found: C, 54.8; H, 5.8; N, 14.1; OR, 1.9/196.

2,2'-Bis(1-ethoxycarbonyl-2-cyano-3-pyrrolidinone) (XVI).—To a mixture of 3.0 g. (16.5 mmoles) of XII in 10 ml. of methanol and 30 ml. of water was added dropwise a saturated solution of ferric chloride until the orange color persisted. The resultant precipitate was separated by filtration, washed with water, and recrystallized from methanol–chloroform (1:1); yield 2.9 g. (97%) of 2,2'-bis(1-ethoxycarbonyl-2-cyano-3-pyrrolidinone), m.p. 188–190°.

Anal. Calcd. for $C_{16}H_{18}N_4O_6$: C, 53.0; H, 5.0; N, 15.5; OC_2H_5, 24.9; mol. wt., 362. Found: C, 52.9; H, 5.1; N, 15.3; OC_2H_5, 25.2; mol. wt., 345.

(43) L. L. McKinney, E. H. Uhing, E. A. Setzkorn, and J. C. Cowan; *J. Am. Chem. Soc.*, **72**, 2599 (1950).

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