[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis and Reactions of Some Substituted β-Lactams

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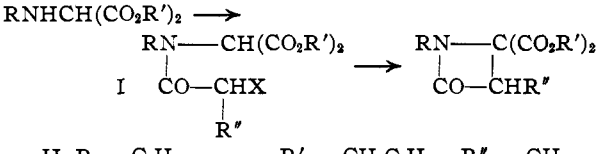
Cyclization to a β-lactam in high yield has been shown to be a general reaction for N-substituted aminomalonic esters N-acylated with α-halo acids. Such diverse bases as triethylamine, diethylamine, benzylamine, ethereal ammonia and alcoholic potassium hydroxide have been used successfully in the ring closure step. The N-substituent can be either aromatic or non-aromatic, but the reaction failed under ordinary conditions when the nitrogen was unsubstituted. When either diethyl chloroacetanilidomalonate or 1-phenyl-4,4-dicarbethoxy-2-azetidinone was treated with alcoholic ammonia an amide tentatively assigned the structure 1-phenyl-4,4-dicarboxamido-2-azetidinone (XIV) was obtained. The structure of XIV was supported by a comparison of its infrared spectrum with that of 1-phenyl-4-carboxanilido-2-azetidinone, which was prepared from 1-phenyl-4,4-dicarboxy-2-azetidinone of known structure. 4,4-Dicarbalkoxy-2-azetidinones were found to be relatively insensitive toward amines and alcohol.

In a previous communcation[2] we have described a convenient new synthesis of β-lactams in which the amide bond is formed first and the four-membered ring is then completed by establishing a carbon-to-carbon linkage. In all previously known cyclization procedures for the preparation of β-lactams, the amide bond is formed last by closing a carboxyl function against an amino group.

Further work has shown the reaction to be general for N-substituted α-haloacylaminomalonic esters (I). The cyclization to the β-lactam proceeds in high yield if the N-substituent is either aromatic or non-aromatic, but the reaction fails under ordinary conditions if the nitrogen is unsubstituted. The reactions involved in our β-lactam synthesis can now be written in a generalized form



II, R = C_6H_5	R′ = $CH_2C_6H_5$	R″ = CH_3
III, R = C_6H_5	R′ = C_2H_5	R″ = C_2H_5
IV, R = C_6H_{11}	R′ = C_2H_5	R″ = H
V, R = C_6H_5	R′ = C_2H_5	R″ = H
VI, R = p-$CH_3C_6H_5$	R′ = C_2H_5	R″ = H
VII, R = 4-$CH_3C_6H_{11}$	R′ = C_2H_5	R″ = H

In our earlier work, we employed an acid anhydride in the acylation step. We have since developed convenient acylation procedures which avoid the separate preparation of the acid anhydride. The acid chloride (or the α-halo acid and phosphorus trichloride) may be heated with either the aminomalonic ester or the corresponding hydrochloride to give the intermediate substituted amide I.

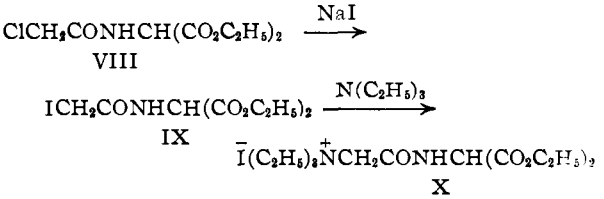
By heating a mixture of α-chloropropionic acid, phosphorus trichloride and dibenzyl anilinomalonate, dibenzyl α-chloropropionanilidomalonate (I, R = C_6H_5, R′ = $CH_2C_6H_5$, R″ = CH_3) was obtained in 86.3% yield. Treatment with triethylamine gave the β-lactam, 1-phenyl-3-methyl-4,4-dicarbobenzyloxy-2-azetidinone (II), in 97.6% yield. In a similar manner, 1-phenyl-3-ethyl-4,4-dicarbethoxy-2-azetidinone (III) was synthesized from diethyl anilinomalonate and α-bromo-*n*-butyric acid in 83% over-all yield.

To demonstrate that an aromatic substituent on the amide nitrogen is not required, 1-cyclohexyl-4,4-dicarbethoxy-2-azetidinone (IV) was prepared. Reduction of diethyl anilinomalonate over Adams catalyst gave diethyl cyclohexylaminomalonate. The interaction of cyclohexylamine and diethyl bromomalonate gave principally high-melting compounds. Diethyl cyclohexylaminomalonate was chloroacetylated by heating under reflux with chloroacetyl chloride in benzene solution. Dehydrohalogenation of the acylation product by interaction with triethylamine afforded IV as a liquid in 90.7% yield.

The β-lactam structure of IV was confirmed by an independent synthesis. The hydrogenation of 1-phenyl-4,4-dicarbethoxy-2-azetidinone (V), the structure of which has been rigorously established[2] gave a liquid with physical properties and infrared spectrum (Curve A, Fig. 1) identical with those of IV. The same compound (XVIII), m. p. 194–195°, was given by the action of ammonia on samples of β-lactam prepared by the two routes.

From diethyl *p*-toluidinomalonate and chloroacetic anhydride was obtained 1-*p*-tolyl-4,4-dicarbethoxy-2-azetidinone (VI), which did not give a satisfactory analysis. However, hydrogenation of VI over Adams catalyst afforded in 91.6% yield 1 - (4′ - methylcyclohexyl) - 4,4 - dicarbethoxy - 2-azetidonine (VII), which gave the expected analysis and an infrared spectrum (Curve B, Fig. 1) similar to that of IV.

Diethyl chloroacetamidomalonate (VIII) did not cyclize on treatment with triethylamine under the usual conditions. In fact, one of the preparative methods for VIII involved the treatment of diethyl aminomalonate with chloroacetyl chloride and triethylamine.[3] Diethyl iodoacetamidomalonate (IX) was obtained by the action of sodium iodide on VIII. Treatment of VIII with triethylamine under forcing conditions led to the formation of a quaternary ammonium salt (X) instead of a β-lactam.[3]



The failure of VIII to cyclize under the conditions tried is in sharp contrast with the unusual ease of cyclization shown by the corresponding N-substituted compounds under similar reaction

(1) Overseas Scholar of the Government of India.

(2) J. C. Sheehan and A. K. Bose, THIS JOURNAL, 72, 5158 (1950).

(3) Work done in this Laboratory by Dr. P. T. Izzo.

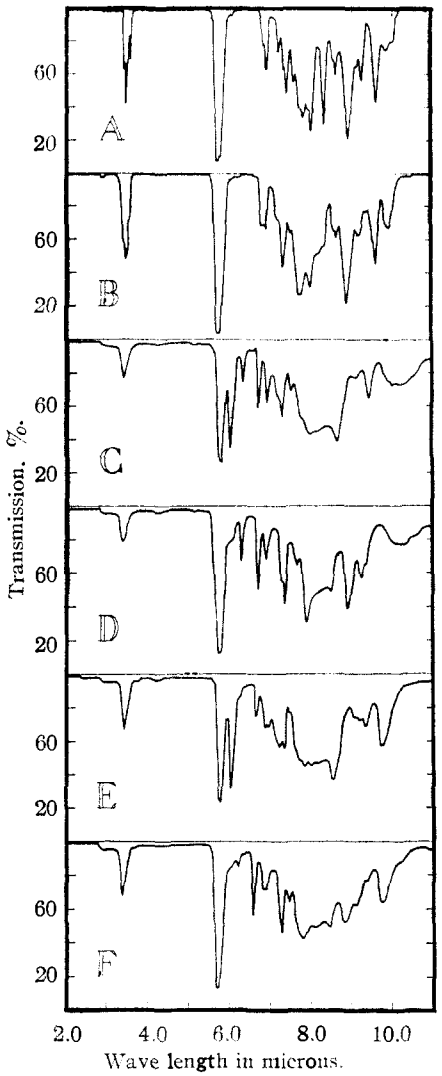


Fig. 1.—Infrared absorption spectrum: A, 1-cyclohexyl-4,4-dicarbethoxy-2-azetidinone (IV); B, 1-(4'-methylcyclohexyl)-4,4-dicarbethoxy-2-azetidinone (VII); C, dibenzyl (α-chloropropionyl)-anilinomalonate; D, 1-phenyl-3-methyl-4,4-dicarbobenzyloxy-2-azetidinone (II); E, diethyl N-(α-bromo-*n*-butyryl)-anilinomalonate; F, 1-phenyl-3-ethyl-4,4-dicarbethoxy-2-azetidinone (III).

conditions. It is interesting to note that only one of the β-lactams reported so far has no substituent on the nitrogen. The exception is the parent β-lactam, 2-azetidinone, prepared in less than 1% yield by Holley and Holley,[4] using Breckpot's method.[5]

Our method of β-lactam synthesis is reminiscent of the Perkin[6] synthesis of small ring compounds, especially the preparation of diethyl 1,1-cyclobutanedicarboxylate (XI) from trimethylene bromide and diethyl malonate, but there are important differences.

In the Perkin method intermolecular condensation competes with the ring-forming intramolecular dehydrohalogenation.[7] We have not observed intermolecular dehydrohalogenation (linear polymerization) in any of the cases we have tried so far.

Walborsky[8] was able to cyclize Perkin's intermediate, 1,1-dicarbethoxy-4-bromo-*n*-butane (XII), by treatment with sodium ethoxide. However, when a benzene solution of XII was treated with trimethylamine, the corresponding quaternary ammonium salt was obtained instead of ring closure.

In our synthesis we have found that a variety of reagents lead to cyclization under mild conditions. Very good yields of β-lactams have been obtained by using such varied bases as triethylamine, diethylamine, ammonia, benzylamine, alcoholic potassium hydroxide and potassium bicarbonate.

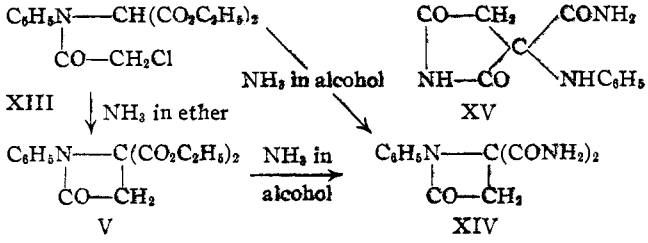
The reaction of diethyl chloroacetanilidomalonate (XIII) with an excess of diethylamine or benzylamine was carried out by heating under reflux overnight a benzene solution of the components. It is evident that these amines played no part other than causing dehydrohalogenation of XIII. The insensitivity of the β-lactam V toward these amines is noteworthy. The β-lactam ring of penicillin opens very easily with amines. During the war-time researches on penicillin,[9] it was found that a few β-lactams react readily with benzylamine but that most others do not. A striking example of difference in reactivity is provided by an observation that 1-phenyl-4-carboxy-4-carbethoxy-2-azetidinone reacts with benzylamine at room temperature to afford the dibenzylamide of anilinosuccinic acid (30% yield) by undergoing simultaneous decarboxylation and ring opening,[2] although 1-phenyl-4,4-dicarbethoxy-2-azetidinone (V) is unaffected even on heating under reflux with benzylamine in benzene for several hours. When V was heated overnight under reflux with an alcoholic solution of diethylamine, the starting β-lactam was again recovered in 86% yield. Apparently V is as resistant to alcoholysis as to aminolysis.

The action of one equivalent of alcoholic potassium hydroxide on diethyl chloroacetanilidomalonate, causing dehydrohalogenation and ring closure in 83% yield in preference to the saponification of an ester group, is remarkable because malonic esters are readily saponified, and 1-phenyl-4,4-dicarbethoxy-2-azetidinone (V) reacts rapidly with an equivalent of alcoholic potassium hydroxide to give the monopotassium salt.[2] Evidently the dehydrohalogenation of XIII is much faster than the saponification of either the starting material XIII or the reaction product V.

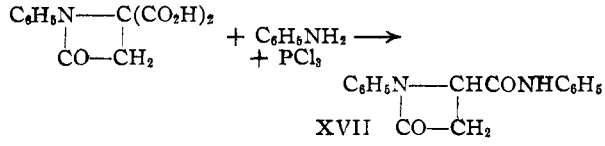
When diethyl chloroacetanilidomalonate (XIII) was treated with an ethereal solution of ammonia, ammonium chloride separated and a 92% yield of the β-lactam V was obtained. However, when alcoholic ammonia was used, a compound tentatively assigned the structure 1-phenyl-4,4-dicarboxamido-2-azetidinone (XIV) was formed in 80% yield. The same compound (XIV) was obtained in 98% yield by allowing V to react with alcoholic ammonia. The alternative structure XV cannot

(4) R. W. Holley and A. D. Holley, THIS JOURNAL, **71**, 2129 (1949).
(5) R. Breckpot, *Bull. soc. chim. Belg.*, **32**, 412 (1923).
(6) W. H. Perkin, Jr., *Ber.*, **16**, 1793 (1883).
(7) *Org. Syn.*, **23**, 16 (1943).
(8) H. M. Walborsky, THIS JOURNAL, **71**, 2941 (1949).
(9) H. T. Clarke, J. R. Johnson and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 979.

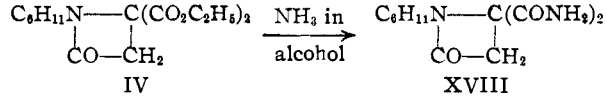
be eliminated rigorously on the basis of present evidence, but the formation of a succinimide derivative under the mild conditions employed would be surprising. The infrared spectrum (Curve A, Fig. 2) of a nujol mull of XIV shows two strong bands at 5.87 and 6.0 μ and a weak band at 5.60 μ. Although the carbonyl bond in a monocyclic β-lactam was assigned the position 5.70–5.74 μ during the war-time researches on penicillin[10] we have found an intense band to occur at 5.60–5.65 μ in the infrared spectrum of most of the 4,4-dicarboxy-2-azetidinones we have synthesized. The 5.60 μ band in the infrared spectrum of XIV, although unusually weak, may be interpreted as an indication of the presence of the β-lactam ring. The 6.0 μ band is apparently due to the amide carbonyl. No ready explanation is available for the band at 5.87 μ. A dioxane solution of XIV shows a slight displacement of the bands in the infrared spectrum (Curve B, Fig. 2). The infrared spectrum of XIV can also be interpreted in terms of the succinimide structure XV.



By heating under reflux a benzene suspension of 1-phenyl-4,4-dicarboxy-2-azetidinone (XVI) with aniline and phosphorus trichloride, 1-phenyl-4-carboxanilido-2-azetidinone (XVII) was obtained in 93.5% yield. The infrared spectrum (Curve C, Fig. 2) of a dioxane solution of XVII was similar to that of XIV except that the band at 5.61 μ was as intense as the bands at 5.86 and 6.01 μ.



Treatment of 1-cyclohexyl-4,4-dicarbethoxy-2-azetidinone (IV) for a week with alcoholic ammonia afforded XVIII in excellent yield. On the basis of elemental analyses and by analogy with XIV, this product was assigned tentatively the structure 1-cyclohexyl-4,4-dicarboxamido-2-azetidinone. The infrared spectrum (Curve D, Fig. 2) of a nujol mull of XVIII showed strong bands at 5.70–5.76 μ and at 5.94 μ, in addition to shoulders at 5.86 and 6.0 μ.



The formation of the diamides XIV and XVIII in nearly quantitative yields is noteworthy because esters of disubstituted malonic acid are known to be very unreactive toward ammonia. Fischer and Dilthey[11] obtained only a 1.1% yield of the diamide by allowing diethyl diethylmalonate to react with liquid ammonia for two months. Russell[12] obtained a 3.5% yield by using methanolic ammonia in the presence of sodium methoxide.

Experimental[13]

1-Phenyl-3-methyl-4,4-dicarbobenzyloxy-2-azetidinone (II).—A solution of 2 g. of dibenzyl anilinomalonate, 2 g. of α-chloropropionic acid, and 1 ml. of phosphorus trichloride in 50 ml. of benzene was heated under reflux for 2 hours. After removal of solvent, the residue was taken up in ether and washed with 5% solution of sodium bicarbonate and with water. On removing the solvent from the dried ethereal solution, there was obtained a slightly yellow, viscous oil (2.14 g., 86.3%, based on the malonic ester), which showed strong infrared (Curve C, Fig. 1) absorption bands at 5.74 and 5.99 μ expected of dibenzyl N-(α-chloropropionyl)-anilinomalonate.

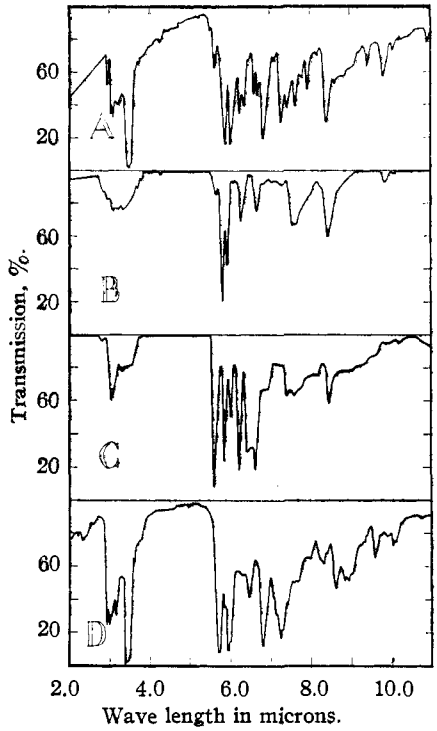


Fig. 2.—Infrared absorption spectrum: A, 1-phenyl-4,4-dicarboxamido-2-azetidinone (XIV); B, 1-phenyl-4,4-dicarboxamido-2-azetidinone (XIV); C, 1-phenyl-4-carboxanilido-2-azetidinone (XVII); D, 1-cyclohexyl-4,4-dicarboxamido-2-azetidinone (XVIII).

A benzene solution of 1 g. of the aforementioned crude acylation product and 0.7 g. of triethylamine was maintained overnight at 50–60°. After removal of triethylamine hydrochloride and solvent, the residual oil (0.9 g., 97.6%) solidified. The absence of a band at 6 μ and the presence of a strong broad band at 5.67–5.77 μ in the infrared spectrum (Curve D, Fig. 1) indicated that this solid, m.p. 75–83°, was substantially pure β-lactam. Recrystallization from cyclohexane raised the m.p. to 86–90° (85% recovery). This β-lactam exhibits dimorphism; on very slow cooling of a saturated solution, rhombic crystals, m.p. 90–92°, are obtained. Rapid cooling deposits needle-shaped crystals with a melting range of 75–90°.

Anal. Calcd. for $C_{26}H_{23}O_5N$: C, 72.71; H, 5.40; N, 3.26. Found: C, 72.80; H, 5.66; N, 3.39.

(10) Ref. 9, p. 973.

(11) E. Fischer and A. Dilthey, *Ber.*, **35**, 849 (1902).

(12) P. B. Russell, THIS JOURNAL, **72**, 1853 (1950).

(13) All melting points are corrected. We are indebted to Mr. S. M. Nagy and his associates for the microanalyses.

1-Phenyl-3-ethyl-4,4-dicarbethoxy-2-azetidinone (III).—The procedure was essentially the same as described in the preceding experiment. The interaction of 2 g. of α-bromo-*n*-butyric acid, 1 ml. of phosphorus trichloride, and 2 g. of diethyl anilinomalonate yielded 2.84 g. (89%, based on the malonic ester) of crude diethyl N-(α-bromo-*n*-butyryl)-anilinomalonate as a viscous oil which showed strong bands (Curve E, Fig. 1) at 5.77 and 6.01 μ. From 1.5 g. of the crude product there was obtained 1.29 g. (93%) of the unpurified 2-azetidinone III (strong infrared, Curve F, Fig. 1, band at 5.67–5.74 μ). By an evaporative distillation (130–145° at 0.4 mm.), a colorless, viscous oil (94% recovery), $n^{25}D$ 1.5108, was obtained. An analytical sample, $n^{25}D$ 1.5106, was prepared by redistillation.

Anal. Calcd. for $C_{17}H_{21}O_5N$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.88; H, 6.75; N, 4.41.

Diethyl (N-Chloroacetyl)-cyclohexylaminomalonate.—An alcoholic solution of 5 g. of diethyl anilinomalonate was hydrogenated overnight in the presence of Adams catalyst (0.05 g.) and a trace of hydrogen chloride. The calculated amount (three moles) of hydrogen was absorbed. Removal of the catalyst and the solvent gave a fluffy material, half of which, without purification, was heated under reflux for 3 hours in benzene solution with 3 g. of chloroacetyl chloride. Isolation as in the other acylation steps afforded an oil (3.1 g., 93% over-all yield) which slowly crystallized. Colorless needles, m.p. 69–70°, were obtained after recrystallization from ligroin.

Anal. Calcd. for $C_{15}H_{24}O_5N$: C, 53.97; H, 7.25; N, 4.20. Found: C, 53.98; H, 7.41; N, 4.56.

1-Cyclohexyl-4,4-dicarbethoxy-2-azetidinone (IV).—(a) By interaction of triethylamine with 2.5 g. of crude diethyl (N-chloroacetyl)-cyclohexylaminomalonate and following the same isolation procedure as in the case of II, the β-lactam IV was obtained as a liquid (2.02 g., 90.7%), $n^{25}D$ 1.4715 (after two evaporative distillations at 140–150° at 0.25 mm.).

(b) The hydrogenation of 0.5 g. of 1-phenyl-4,4-dicarbethoxy-2-azetidinone dissolved in 6 ml. of glacial acetic acid was carried out in the presence of 0.5 g. of Adams catalyst. One hour was required for the absorption of 96–98% of the calculated amount of hydrogen. Removal of the catalyst by filtration and the acetic acid by evaporation under reduced pressure led to an oily product. After washing with dilute sodium bicarbonate solution and water, followed by purification by evaporative distillation (140–150° at 0.3 mm.), the yield of 1-cyclohexyl-4,4-dicarbethoxy-2-azetidinone (IV) was 0.48 g. (93%), $n^{25}D$ 1.4725. An analytical sample, $n^{25}D$ 1.4710, d^{25}_{25} 1.1213, was prepared by two more evaporative distillations (140–150° at 0.3 mm.).

Anal. Calcd. for $C_{15}H_{23}O_5N$: C, 60.58; H, 7.80; N, 4.71; MR, 74.70. Found: C, 60.66; H, 7.76; N, 4.83; MR, 74.12.

1-(*p*-Tolyl)-4,4-dicarbethoxy-2-azetidinone (VI).—Diethyl *p*-toluidinomalonate[14] (2.65 g.) was treated with chloroacetic anhydride to give diethyl (N-chloroacetyl)-(*p*-toluidine)-malonate (91%), which was cyclized without further purification by treatment with triethylamine to give 1-(*p*-tolyl)-4,4-dicarbethoxy-2-azetidinone (90%), m.p. 89.5–91° (from cyclohexane).

Anal. Calcd. for $C_{16}H_{19}O_5N$: C, 63.80; H, 6.31; N, 4.65. Found: C, 63.20; H, 6.22; N, 4.95.

1-(4′-Methylcyclohexyl)-4,4-dicarbethoxy-2-azetidinone (VII).—The hydrogenation of a mixture of 0.15 g. of 1-(*p*-tolyl)-4,4-dicarbethoxy-2-azetidinone and 0.15 g. of platinum oxide suspended in 3 ml. of glacial acetic acid was carried out at room temperature and under atmospheric pressure. The reduction was over in 100 min.; 90–92% of the calculated amount of hydrogen was absorbed. The reduction product was isolated as described for IV. After one evaporative distillation (135–150° at 0.3 mm.), 0.14 g. (91.6%) of a colorless oil, $n^{25}D$ 1.4722, was obtained. An analytical sample, $n^{25}D$ 1.4723, was prepared by a second evaporative distillation.

Anal. Calcd. for $C_{16}H_{25}O_5N$: C, 61.71; H, 8.09; N, 4.50. Found: C, 61.59; H, 7.72; N, 4.71.

Diethyl Chloroacetamidomalonate[3] (VIII).—Diethyl aminomalonate hydrochloride was prepared by hydrogenation of diethyl nitrosomalonate[15] in the presence of palladium-on-charcoal catalyst. To a mixture of 30 g. of this hydrochloride and 11 g. of chloroacetyl chloride suspended in 300 ml. of ethylene dichloride at 0–5° was added slowly a solution of 42 ml. of redistilled triethylamine in 100 ml. of ethylene dichloride. After the addition was complete, the mixture was brought rapidly to the boiling point and then allowed to stand overnight. By filtration 34.5 g. (91%) of triethylamine hydrochloride was obtained. After washing the filtrate with dilute acid and water, the solvent was removed, leaving a pink, crystalline solid (30.6 g., 87%).

Recrystallization from ethylene dichloride–methylcyclohexane gave diethyl chloroacetamidomalonate, m.p. 97.5–98.5°.

Anal. Calcd. for $C_9H_{14}O_5NCl$: C, 42.94; H, 5.61; N, 5.57. Found: C, 42.95; H, 5.65; N, 5.53.

Diethyl Iodoacetamidomalonate[3] (IX).—A solution of 22 g. of diethyl chloroacetamidomalonate and 13 g. of sodium iodide in acetone was heated under reflux with stirring for 9 hours and then stored overnight. After removal of sodium chloride (4.8 g., 94.5%) and acetone, the solid residue was recrystallized from toluene, giving a tan solid (25 g., 83.5%), m.p. 92–96°. An analytical sample prepared by recrystallization from a mixture of toluene and methylcyclohexane melted at 96.5–97°.

Anal. Calcd. for $C_9H_{14}O_5NI$: C, 31.51; H, 4.11; N, 4.08. Found: C, 31.60; H, 4.16; N, 4.13.

The Action of Triethylamine on Diethyl Iodoacetamidomalonate (IX).—A solution of 2 g. of diethyl iodoacetamidomalonate and 1 g. of triethylamine in 50 ml. of benzene was heated under reflux for 1 hour. After removal of solvent under diminished pressure, the residue was purified by crystallization from absolute alcohol. The colorless, crystalline quaternary ammonium iodide X, m.p. 163° (dec.), was obtained.

Anal. Calcd. for $C_{15}H_{29}O_5N_2I$: C, 40.54; H, 6.57; N, 6.30. Found: C, 40.25; H, 6.53; N, 6.29.

Cyclization of Diethyl Chloroacetanilidomalonate (XIII) (a) **Using Amines.**—A benzene solution of XIII was heated overnight under reflux with a large excess of an amine. After removal of the amine hydrochloride, the filtrate was washed with dilute hydrochloric acid, water, and then dried over sodium sulfate. The solvent was evaporated, and the residue was distilled under reduced pressure, giving a distillate which crystallized either spontaneously or on seeding. The following yields of 1-phenyl-4,4-dicarbethoxy-2-azetidinone (V) were obtained by using different amines: triethylamine, 95%; diethylamine, 99%; benzylamine, 80%.

(b) **Using Ethereal Ammonia.**—To an ethereal solution of 1.5 g. of diethyl chloroacetanilidomalonate (XIII) was added 20 ml. of ether saturated with ammonia. The clear solution became opalescent within a minute, and an appreciable amount of a colorless solid precipitated by the end of an hour. The reaction mixture was filtered after storage at room temperature for 2 days; the solid residue (0.23 g., 94%) was ammonium chloride. After removing ammonia and the solvent from the filtrate, the residual oil was submitted to evaporative distillation. The colorless distillate (1.23 g., 92%), which crystallized on storage, was identified as 1-phenyl-4,4-dicarbethoxy-2-azetidinone by a mixed melting point determination with an authentic sample.

(c) **Using Alcoholic Potassium Hydroxide.**—To 5 g. of XIII dissolved in 15 ml. of ethanol was added 0.96 g. (one equivalent) of potassium hydroxide dissolved in ethanol (15 ml.). Potassium chloride started to separate almost immediately. After two days the reaction mixture was filtered and the solvent was removed from the filtrate. By an evaporative distillation (150–160° at 0.4 mm.) 3.7 g. (83%) of 1-phenyl-4,4-dicarbethoxy-2-azetidinone was obtained.

1-Phenyl-4,4-dicarboxamido-2-azetidinone (XIV). (a) **From Diethyl Chloroacetanilidomalonate (XIII).**—To a solution of 14 g. of diethyl chloroacetanilidomalonate (XIII) in 100 ml. of alcohol was added 100 ml. of alcohol containing 12 g. of dissolved ammonia. After a few hours a colorless solid, which was largely ammonium chloride, started to separate. After two weeks, the solvent was removed, and the solid residue was washed with water; 8 g. (80%) of a colorless solid, m.p. 250–255° (dec.) was obtained. Recrystallization from alcohol gave 6.5 g. (65%) of the colorless diamide, m.p. 250–260° (dec.).

(14) R. Blank. *Ber.*, **31**, 1816 (1898).

(15) R. Locquin and V. Cerchez, *Bull. soc. chim. France*, [4] **47**, 1274 (1930).

Anal. Calcd. for $C_{11}H_{11}O_5N$: C, 56.60; H, 4.72; N, 18.00. Found: C, 56.44; H, 5.01; N, 17.97.

(b) **From 1-Phenyl-4,4-dicarbethoxy-2-azetidinone (V).**—To an alcoholic solution of 2 g. of V was added 40 ml. of alcohol saturated with ammonia. After one week, the solvent was removed, leaving 1.57 g. (98%) of a colorless solid, m.p. 255–256° (dec.). A sample recrystallized from alcohol, m.p. 258.5–260° (dec.), when mixed with the diamide (XIV) prepared by procedure (a), showed no depression in melting point.

1-Phenyl-4-carboxanilido-2-azetidinone (XVII).—A suspension of 0.150 g. of 1-phenyl-4,4-dicarboxy-2-azetidinone (XVI) in benzene was heated overnight under reflux with 0.190 g. of aniline and 0.05 ml. of phosphorus trichloride. Removal of benzene and digestion with a 5% solution of sodium bicarbonate gave a colorless solid (0.158 g., 93.5%), m.p. 247–251°. Recrystallization from alcohol gave colorless needles, m.p. 254–255° (80% recovery). The m.p. was constant at 254.5–255.5° on further recrystallization.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52. Found[16]: C, 71.96; H, 5.07; N, 10.90.

(16) A trace of ash was obtained on combustion; the percentages are corrected values.

1-Cyclohexyl-4,4-dicarboxamido-2-azetidinone (XVIII).—To an alcoholic solution of 0.55 g. of 1-cyclohexyl-4,4-dicarbethoxy-2-azetidinone (IV) was added 20 ml. of alcohol saturated with ammonia. After one week, the solvent and excess ammonia were removed under reduced pressure. A colorless, crystalline solid (0.44 g., 100%), m.p. 165–171°, was obtained. After several recrystallizations from a mixture of acetone and cyclohexane, colorless needles, m.p. 190–192°, 77% recovery, were obtained. An analytical sample, m.p. 194–195°, was prepared by further recrystallization.

Anal. Calcd. for $C_{11}H_{17}O_3N_3$: C, 55.22; H, 7.16; N, 17.97. Found: C, 55.50; H, 7.32; N, 17.76.

Infrared Absorption Spectra.—The infrared absorption spectra were determined with a Baird Infrared Spectrophotometer, Model B. For curves in Fig. 1, the following solvents and concentrations were used: A, carbon tetrachloride, 5%; B, C, D, E and F, chloroform, 5%.

For curves in Fig. 2, the following solvents and concentrations were used: A, nujol mull; B, dioxane, 1.7%; C, dioxane, 3.8%; D, nujol mull.

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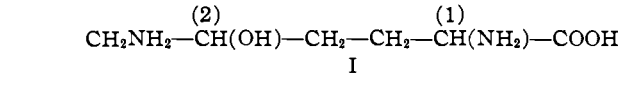
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOPE COLLEGE]

A Synthesis of Hydroxylysine

BY GERRIT VAN ZYL, EUGENE E. VAN TAMELEN AND GEORGE D. ZUIDEMA

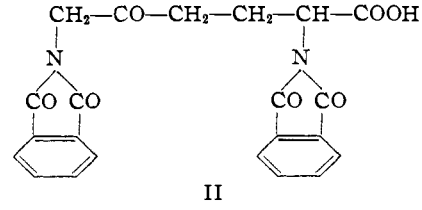
The synthesis of hydroxylysine (I) has been accomplished by the catalytic reduction and subsequent hydrolysis of diethyl (γ-hydroxy-δ-nitro-*n*-butyl)-acetamidomalonate, which was obtained directly by condensing diethyl acetamidomalonate, acrolein and nitromethane. An explanation accounting for the racemization of hydroxylysine during its isolation from natural sources is proposed.

The amino acid hydroxylysine (I) has been isolated from isinglass by S. B. Schryver, H. W. Buston



I

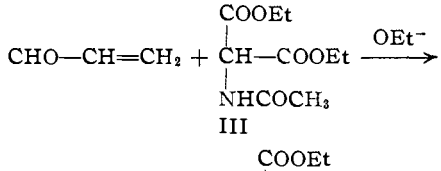
and O. H. Mukherjee,[1] and from gelatin by D. D. Van Slyke, A. Hiller, R. T. Dillon and D. A. MacFadyen.[2] In spite of having on hand only inconclusive evidence, the former group was the first to propose a structure for hydroxylysine: α,ϵ-diamino-β-hydroxycaproic acid. Van Slyke, *et al.*,[2,3] were able to demonstrate, however, that the acid probably possessed either structure (I) or α,δ-diamino-ϵ-hydroxycaproic acid, since periodic acid released one mole of ammonia and one mole of formaldehyde, indicating that the hydroxyl and one of the amino groups were on adjacent carbon atoms at the end of the chain. More recently, Sheehan and Bolhofer[4] confirmed structure (I) by converting hydroxylysine to methyl α,ϵ-diphthalimido-δ-keto-DL-caproate (II), which was found to be identical with the material synthesized by an independent route. These coworkers were also successful in effecting the synthesis of structure (I),[5] identifying their product



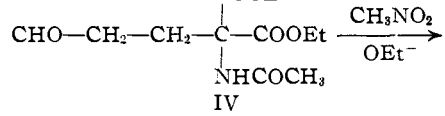
II

through the preparation of two derivatives, the monohydrochloride and the dipicrate. This paper describes an alternate synthesis of (I)—carried out in this Laboratory prior to the appearance of the publication of Sheehan and Bolhofer—as well as its conversion to derivatives identical with those obtained by these authors.

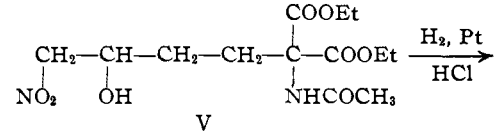
Hydroxylysine monohydrochloride (VII) was obtained in an over-all yield of 26% according to the following



III



IV



V

(1) S. B. Schryver, H. W. Buston and O. H. Mukherjee, *Proc. Roy. Soc.* (*London*), **98B**, 58 (1925).

(2) D. D. Van Slyke, A. Hiller, R. T. Dillon and D. A. MacFadyen, *Proc. Soc. Exp. Biol. Med.*, **38**, 548 (1938).

(3) D. D. Van Slyke, A. Hiller, D. A. MacFadyen, A. B. Hastings and F. W. Klemperer, *J. Biol. Chem.*, **133**, 287 (1940); F. W. Klemperer, A. B. Hastings and D. D. Van Slyke, *ibid.*, **143**, 433 (1942).

(4) J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2469 (1950).

(5) J. C. Sheehan and W. A. Bolhofer, *ibid.*, **72**, 2472 (1950).