were also performed in which aliquots were withdrawn and quenched by addition to 10% aqueous Na_2SO_3 and 10% aqueous $NaHCO_3$ with subsequent analysis of the CCl_4 layer.

The relative second-order rate constants were calculated with the following equation[8]

$$\ln (\mathbf{1a}_t/\mathbf{1a}_0) = [k_2(\mathbf{1b})/k_2(\mathbf{1a})][\ln (\mathbf{1b}_t/\mathbf{1b}_0)]$$

where $k_2(\mathbf{1b})/k_2(\mathbf{1a})$ is the second-order rate constant ratio for olefins **1a** and **1b**, respectively, $\mathbf{1a}_0$ and $\mathbf{1b}_0$ are the initial areas of olefins **1a** and **1b** normalized to the internal standard area, and $\mathbf{1a}_t$ and $\mathbf{1b}_t$ are the areas of the compounds normalized to the internal standard area at any time (t).

The order of elution for the compounds was olefin **1a**, methylene chloride, olefin **1b**, and cyclohexane.

When the competitive rate of appearance of products was analyzed it was limited to small per cent olefin conversion due to the reactivity of the enone products **4a** and **4b** to peracid. During the course of our studies, we noticed that during the first 3% reaction, olefins **1a** and **1b** reacted in an abnormally fast manner and gave a surprising $k_2(\mathbf{1b})/k_2(\mathbf{1a}) = ca.$ 3.0. This phenomenon is presumably due to a mixing period during which the peracid and olefin concentrations are not homogeneous and the temperature may have fluctuated. A similar situation is indicated in the peracid kinetic results that have been reported by Lynch and Pausaker.[24]

Iodometric Analysis of Peracid Loss.[25] A magnetically stirred solution containing known amounts of olefin and MCPBA was prepared at 0° in a 10-ml volumetric flask. A short time thereafter (1–2 min to allow mixing and thermal equilibration), a 1-ml aliquot was withdrawn in two portions with a calibrated (at 0°) 500-μl syringe which was cooled to 0°. The aliquot was added to a solution of 1 ml of acetic acid and 1 mol of 10% aqueous potassium iodide. The liberated iodine was titrated with $Na_2S_2O_3$ ($ca.$ 1×10^{-3}–1×10^{-4} M) which had been previously normalized with KIO_3. A stopwatch was started during the addition of the reaction solution to the acetic acid–KI solution. The peracid loss during the initial 1–2-min period from the prepared concentration was calculated and an appropriate correction made in the time zero olefin concentration used in subsequent calculations.

The reaction solution was subsequently monitored at recorded times by withdrawing 0.5- or 1.0-ml aliquots with a chilled (0°) 500-μl volumetric syringe. Ice was replaced in the cooling bath as needed to maintain a bath temperature of 0°. The reaction solution was analyzed repeatedly until 20–70% MCPBA loss was noted. Usually, several (5–12) samples were analyzed at various times for each run. For olefins which were relatively unreactive two separate aliquots were analyzed (±10 sec) for each time recorded.

The data were analyzed first by a least-squares program on a Hewlett-Packard Model 9820 A advanced programming calculator. The normal second-order rate equation was rearranged into terms of observables, for conditions of initial olefin concentration greater than initial peracid concentrations

$$\frac{1}{A_\infty}\ln\left(\frac{2V_aA_\infty}{M\mathrm{ml}_t}+1\right) = \frac{1}{A_\infty}\ln\left(\frac{2V_aA_\infty}{M\mathrm{ml}_0}+1\right) + k_2t$$

where A_∞ is the difference in the time zero concentration of olefin and peracid, respectively, V_a is the volume in milliliters of the reaction aliquot analyzed, M is the molarity of the thiosulfate stock solution, and ml_t and ml_0 are the volumes (milliliters) of thiosulfate solution at time t and time zero required to titrate the liberated iodine for the respective samples.

Subsequently, the data were analyzed with a nonlinear iterative least-squares computer program[26] on an IBM-360/65 computer. This program accounts for random errors present in all observables. In all cases, the data gave linear plots with the second-order rate equation and the rate constants were invariant over a range of initial reactant concentrations.

Acknowledgments. We wish to thank the National Science Foundation and the Merck Company Foundation for financial support. Computer time was provided by the Computing Center at the University of Rochester.

(24) B. M. Lynch and K. H. Pausaker, *J. Chem. Soc., London*, 1525 (1955).

(25) D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1966, pp 485–493.

(26) Louis E. Friedrich, unpublished program, University of Rochester, Rochester, N. Y., 1969.

Carboxy β-Lactams by Photochemical Ring Contraction

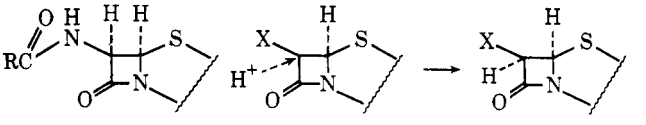
Gilbert Stork* and Richard P. Szajewski

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. *Received June 2, 1973*

Abstract: The potential and limitations of the photochemical ring contraction of 3-diazo-2,4-pyrrolidinediones as a route to carboxy β-lactams (2-azetidinone-3-carboxylic acids) are explored. Although the method seems to be a fairly general route from α-amino acids to β-lactams, the difficulty of achieving steric control makes the process not especially promising as a route to natural penicillins and cephalosporins.

Considerable ingenuity has been demonstrated over many years in devising syntheses for the β-lactam system which forms the most salient feature of the penicillin and cephalosporin antibiotics.[1]

An intriguing feature which gives additional complexity to the problem is that the amino substituent next to the lactam carbonyl is in the less stable arrangement in these molecules, cis to the sulfur atom. Such an arrangement could, in principle, be the result of kinetic protonation, from the less hindered side, of a trigonal center bearing a substituent X, which could be either an amino group or any other function capable of transformation into an amino group with retention of configuration.[2]

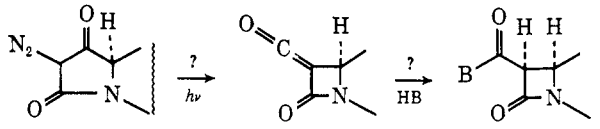


One of the most versatile possibilities would be to have X present as a carboxyl group. Indeed, the conversion of carboxy β-lactams to amino β-lactams has

(1) For a recent review of β-lactam syntheses, *cf.* A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 327 (1973).

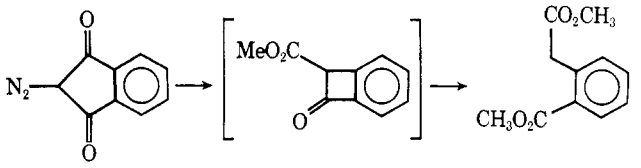
(2) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).

already been described.[3] It thus became of considerable interest to see whether such carboxy β-lactams (3-carboxy-2-azetidinones) might be derivable *via* photochemical ring contraction of 3-diazo-2,4-pyrrolidinediones, as shown below.

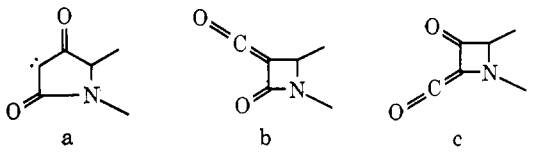


As will be demonstrated in the sequel, the photochemical ring contraction route is indeed a rather general new synthesis of β-lactams functionalized on the α carbon, although the stereoselectivity which we have so far achieved as the result of trapping the intermediate ketene with various nucleophiles has been disappointingly small.[4]

It should be pointed out that the success of this photochemical ring contraction route to β-lactam was by no means assured; a related case, that of 2-diazo-1,3-indandione, actually leads to ring cleavage of the presumed intermediate to the corresponding homophthalic acid.[5] We presumed, however, that the relative stability of the 2-azetidione system should prevent this cleavage. A more serious question arises from the fact that there are two possible initial products, *i.e.*, b



and c, of the ring contraction in the pyrrolidinedione



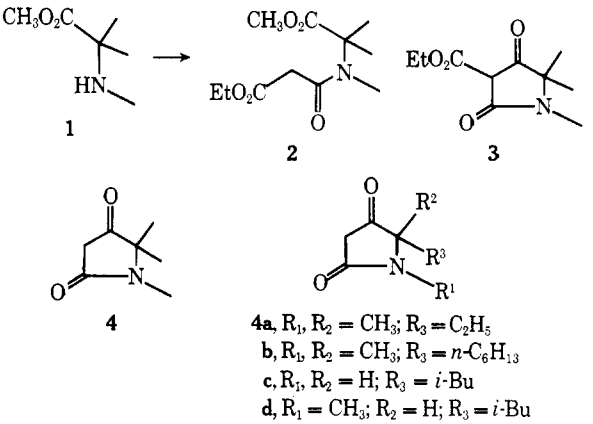
a b c

case, *via* an electron deficient species such as a. Only b can lead to the desired β-lactam.

We anticipated that the rearrangement would take the desired course *via* b because involvement of the nitrogen in amide resonance should impede electron donation to the photochemically generated carbenoid center. It is thus the carbon and not the nitrogen that should migrate.

We now describe the reactions which substantiate these expectations.

The 2,4-pyrrolidinediones ("tetramic acids") used as starting materials were synthesized by standard procedures;[6] condensation of methyl 2-*N*-methylaminoisobutyrate (**1**) with carbethoxyacetyl chloride (benzene, room temp, 1 equiv of triethylamine) followed by cyclization of the resulting malonamic ester **2** (refluxing in sodium methoxide–methanol) led, after acidification, to the carbethoxypyrrolidinedione **3** which could be decarbethoxylated by hydrolysis with 1% aqueous hydrochloric acid to the tetramic acid **4**, mp 76–78°, thus ob-

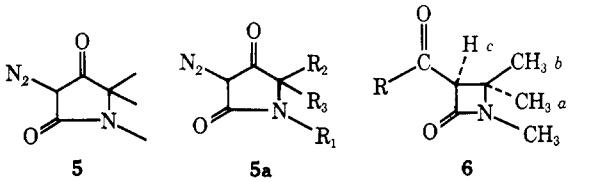


4a, $R_1, R_2 = CH_3$; $R_3 = C_2H_5$
b, $R_1, R_2 = CH_3$; $R_3 = n\text{-}C_6H_{13}$
c, $R_1, R_2 = H$; $R_3 = i\text{-Bu}$
d, $R_1 = CH_3$; $R_2 = H$; $R_3 = i\text{-Bu}$

tained in ~80% yield from the initial α-amino ester. The preparation of the tetramic acids **4a** (mp 111–113°), **4b** (oil), **4c** (mp 114–116°), and **4d** (oil) was carried out in a similar manner.

The related diazo compounds were prepared by the Regitz procedure of diazo transfer,[7] using either *p*-toluenesulfonyl azide or methylsulfonyl azide in cold methylene chloride in the presence of triethylamine. By this method the required diazo tetramic acids **5** (oil), **5a** (mp 73–76°d), **5b** (oil), **5c** (mp 138–141°d), and **5d** (oil) were obtained in excellent yields. Photolysis of the diazo tetramic acids was conducted in ether at 0°, using a medium pressure mercury lamp and a Pyrex filter, in the presence of various nucleophiles to trap the intermediate ketene.

Under these conditions, the diazo tetramic acid **5** was converted, in excellent yields (*ca.* 95%), to the corresponding β-lactam carboxylic acid **6**, R = H, mp 84–87° dec, which showed the typical β-lactam absorption at 1751 cm^{-1} (in KBr). The corresponding methyl ester and hydrazide (**6**, R = OCH_3 and R = $NHNH_2$)



5 **5a** **6**

were obtained similarly. The two methyl groups attached to carbon had their resonances between δ 1.3 and 1.5 ppm and were clearly separated singlets. The β-lactams **6**, derived from photolysis of **5**, present no stereochemical problem, in contrast to the more complex representatives of the series to be considered shortly. It was thus of considerable interest, in order to facilitate assignment of stereochemistry to these substances, to correctly assign the nmr resonances of the methyl groups in **6** and its derivatives. We anticipated that the higher field methyl resonance was probably that of the methyl cis to the carbonyl of the β-lactam acid

(3) A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, 3797 (1973); D. M. Brunwin, G. Lowe, and J. Parker, *Chem. Commun.*, 865 (1971).

(4) After much of this work had been completed and communicated at the Symposium on Organic Synthesis (Vancouver, Canada, August 1972) there appeared a preliminary communication (G. Lowe and D. D. Ridley, *Chem. Commun.*, 328 (1973)) in which the same approach was explored. This very fine work has recently appeared in a full paper: G. Lowe and D. Ridley, *J. Chem. Soc., Perkin Trans. 1*, 2024 (1973)). For this reason our early communication was withdrawn and we are presenting the full details of those of our results which involve compounds not reported by Lowe, *et al.*

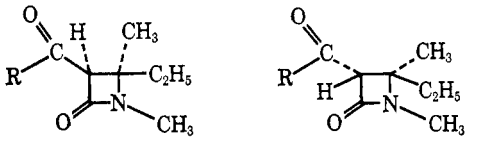
(5) M. P. Cava and R. J. Spangler, *J. Amer. Chem. Soc.*, **89**, 4550 (1967).

(6) For this type of tetramic acid synthesis, *cf.* K. Achiwa and S. Yamada, *Chem. Pharm. Bull.*, **14**, 537 (1966).

(7) M. Regitz, *Angew Chem., Int. Ed. Engl.*, **6**, 733 (1967); *cf.* M. Rosenberger, P. Yates, J. B. Hendrickson, and N. Wolf, *Tetrahedron Lett.*, 2285 (1964).

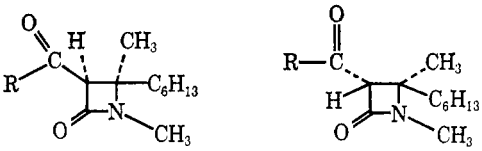
derivatives, but possible complications because of the particular ring system made confirmation desirable. This was done easily by nuclear Overhauser effect experiments on the trifluoroethyl ester **6**, R = OCH_2CF_3, prepared in the usual manner. In that substance, the two methyl resonances appear at δ 1.35 and 1.48 and the ring hydrogen H_c is at δ 3.85. The expectation that the resonance at δ 1.35 belongs to the methyl labeled b was confirmed by showing that irradiation at δ 1.35 gave no enhancement, while irradiation at δ 1.48 gave a 12% enhancement of the H_c signal.

By the same procedure, irradiation of **5a** in the presence of water or methanol gave the two epimeric β-lactam carboxylic acids (**7** and **8**, R = OH) and the two



7 **8**

corresponding methyl esters (**7** and **8**, R = OCH_3) in 80 and 65% yield, respectively. The steric discrimination in the ring protonation of the enol derived from the ketene intermediate was small (**7**:**8** = 57:43) but in the expected direction, since the major isomer in each case had the ring hydrogen cis to the smaller methyl group. Increasing the size difference between the two alkyl groups resulted in greater discrimination in the expected direction. Photolysis of **5b** in the presence of the appropriate nucleophiles gave the mixture of epimeric carboxy β-lactams **9** and **10**, R = OH, and the corre-

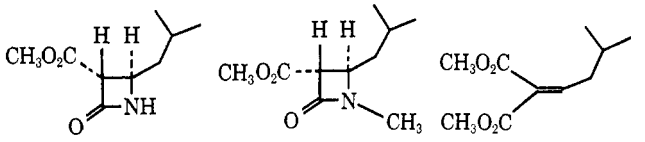


9 **10**

sponding methyl esters, amides, and hydrazides (**9** and **10**, R = OCH_3, NH_2, and $HNNH_2$). In all cases, the predominant isomer **9** (ratio **9**:**10** = 3:1) had the methyl group resonance at lower field (δ ~1.45) while the methyl resonance (δ 1.39 ± 0.05) of the minor isomer confirmed the orientation of the carboxyl as cis to the methyl.

The conclusion that the major isomer **9** is the less stable one, as a result of kinetic protonation, was confirmed by showing that equilibration of a mixture of the methyl esters (**9** and **10**, R = OCH_3) (initially 76% **9** and 24% **10**) with lithium methoxide at 0° for 1 hr led to a mixture which now was ~30% **9** and 70% **10**.

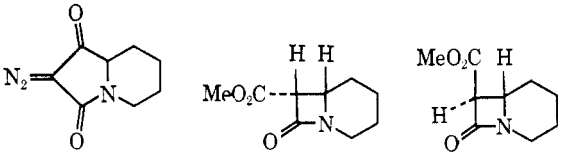
The observed kinetic protonation of the enol intermediates leading to a preponderance of **9** over **10** naturally led to the expectation that a single bulky group would give essentially complete control in the desired direction. This expectation was surprisingly not fulfilled. Indeed, photolysis of the diazo tetramic acids **5c** and **5d** in the presence of methanol led in about 50% yield to only one isolable carbomethoxy β-lactam in each case, *i.e.*, **11** and **12**, respectively. These appeared to have the trans stereochemistry (more stable product) shown, on the basis of the coupling constant (*ca.* 2.5 Hz) between the two ring hydrogens.[8] None of the isomeric lactams could be found. Instead, the photolysis of **5c** was accompanied by 22% of dimethyl isopentylidenemalonate (**13**). Although it would be



11 **12** **13**

tempting to ascribe the formation of **13** to a pathway involving the cis isomer of **11**, thus rationalizing its absence from the reaction products, it is unfortunately also possible to derive **13** from the carbene intermediate between **5c** and **11**.

Photolysis of the bicyclic diazo tetramic acid **14** (mp 44–46°) gave in 65% yield a 2:5 mixture of the easily separable β-lactams **15** and **16**.[9] Lactam **15**, however,



14 **15** **16**

proved to epimerize to **16** with great ease, even in the apparent absence of a proton carrier, thus leaving the relative amounts of **15** and **16** initially formed open to question.

In any event, protonation is apparently not sufficiently sensitive to steric hindrance to allow the use of this sequence as a stereospecific route to cis-disubstituted β-lactams in general or of penicillin in particular. The photolysis of diazotetramic acids remains, however, a convenient method for the construction of functionally substituted β-lactams from a variety of α-amino acids.

Experimental Section

Unless otherwise noted, nuclear magnetic resonance spectra were obtained on Varian T60 and A60A spectrometers and are reported in parts per million δ downfield of internal TMS, ir spectra were obtained on a Perkin-Elmer 137, and mass spectra were obtained on a JEOL Model 07 spectrometer. Elemental analyses were performed by Micro-Tech Laboratories Inc., Skokie, Ill. Melting points were determined using a Büchi capillary apparatus and are uncorrected.

Methyl 2-*N*-Methylaminoisobutyrate (1). Following a procedure used by Leonard and Barthel[10] in a similar case, 87 g of acetone and a solution of 33 g of methylamine hydrochloride in 40 ml of water were stirred for 15 min at room temperature. A solution of 33 g of potassium cyanide in 70 ml of water was then added over a 15-min period and the mixture was stirred at room temperature for 22 hr. The solution was extracted with 4 × 100 ml CH_2Cl_2, dried over Na_2SO_4, and evaporated to give 47.4 g of cyanoamine as a clear oil: ν (film) 3350 and 2220 cm^{-1}; δ ($CDCl_3$) 1.4 (6 H, s), 2.5 (4 H, b s). Slow addition of the cyanoamine (39.2 g) with occasional cooling in ice to 81 g of concentrated H_2SO_4 was followed by heating on a steam bath for 30 min. Addition of ~100 g of crushed ice was followed by refluxing for 5 hr, cooling, and addition of 64 g of NaOH in 75 ml of water. The solution was then evaporated to dryness and the residue was refluxed 12 hr with 800 ml of methanol saturated with anhydrous hydrogen chloride. The solution was then evaporated and the amino acid ester was liberated by the method of Hillman.[11] Treatment with 1 l. of $CHCl_3$ saturated with ammonia for 1 hr, followed by filtration and evaporation, gave 22 g of **1**, bp 49–50° (15 mm): ν (film) 3350 and 1725 cm^{-1}; δ ($CDCl_3$) 1.3 (6 H, s), 2.0 (1 H, s), 2.3 (3 H, s), 3.7 (3 H, s).

(8) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 3325 (1965).

(9) D. R Bender, L. F. Bjeldanes, D. R. Knapp, D. R. McKean, and H. Rapoport, *J. Org. Chem.*, **38**, 3439 (1973).

(10) N. J. Leonard and E. Barthel, *J. Amer. Chem. Soc.*, **72**, 3632 (1950).

(11) G. Hillman, *Z. Naturforsch.*, **1**, 682 (1946).

Methyl 2-*N*-Carbethoxyacetyl-*N*-methylaminoisobutyrate (2). To a solution of 5.5 g of **1** and 5.3 g of triethylamine in 400 ml of benzene was slowly added 6.3 g of carbethoxyacetyl chloride[12] in 50 ml of benzene. The mixture was stirred at room temperature for several hours, diluted with 400 ml of anhydrous ether, and filtered to give 8.7 g (85%) of a light red oil which could be used without further purification: ν (film) 1735 and 1655 cm^{-1}; δ ($CDCl_3$) 1.2 (3 H, t, J = 7 Hz), 1.4 (3 H, s), 3.0 (3 H, s), 3.4 (2 H, s), 3.6 (3 H, s), 4.2 (2 H, q, J = 7 Hz).

1,5,5-Trimethyl-2,4-pyrrolidinedione (4). A solution of 8.7 g of **2** in 20 ml of methanol was added to a solution made from 1.5 g of 57% NaH in mineral oil and 300 ml of methanol,[13] and the mixture was refluxed for 2 hr under nitrogen. Evaporation of volatile materials and partition of the residue between ether and water, followed by acidification of the aqueous fraction and extraction with methylene chloride, gave, after evaporation, 6.4 g (90%) of the cyclic dione ester **3** as a yellowish, waxy solid: δ ($CDCl_3$) 1.3 (6 H, s), 1.3 (3 H, t, J = 7 Hz), 3.0 (3 H, s), 4.4 (2 H, q, J = 7 Hz), 10.7 (1 H, b s).

A solution of 5.0 g of **3** in 20 ml of 1% aqueous HCl, heated on a steam bath for 15 min, followed by addition of 200 ml of ether, drying (Na_2SO_3), filtration, and evaporation gave 3.4 g of crude product which was purified by chromatography on silica gel, using chloroform as eluant, to give 3.0 g (92%) of the dione **4** which slowly crystallized on standing in the cold: mp 76–78°; ν (film) 3450, 1775, 1705, 1600–1700 cm^{-1} (b, fine structure); δ ($CDCl_3$) 1.4 (6 H, s), 2.9 (3, H, s), 3.0 (2 H, s)

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.41; H, 7.81.

1,5-Dimethyl-5-ethyl-2,4-pyrrolidinedione (4a). This was prepared by a sequence analogous to that described for compound **4**, starting from methyl ethyl ketone: mp 111–113°; ν ($CHCl_3$) 1775 and 1705 cm^{-1}; δ ($CDCl_3$) 0.8 (3 H, t, J = 7 Hz), 1.3 (3 H, s), 1.8 (2 H, m), 2.9 (3 H, b s), 3.0 (2 H, s).

Anal. Calcd for $C_8H_{13}O_2N$: C, 61.91; H, 8.44. Found: C, 62.08: H, 8.37.

1,5-Dimethyl-5-hexyl-2,4-pyrrolidinedione (4b). By a sequence analogous to that for compound **4**, starting from methyl hexyl ketone (amide formation, cyclization, and hydrolysis decarboxylation proceeded in 94, 51, and 70% yields, respectively), **4b** was obtained as an oil: ν (film) 1775, 1700, 1600–1700 cm^{-1} (b fine structure); δ ($CDCl_3$) 3.0 (2 H, s), 2.9 (3 H, s), 1.3 (3 H, s), 1.0–2.1 (16 H, m).

5-Isobutyl-2,4-pyrrolidinedione (4c). To a suspension of 9.0 g of L-leucine methyl ester hydrochloride in 500 ml of benzene 11.0 g (2 equiv) of triethylamine was added and the mixture was stirred at room temperature. After 0.5 hr, 7.5 g of carbethoxyacetyl chloride[12] in 50 ml of benzene was slowly added and the mixture was stirred at room temperature for 3 hr. Addition of 300 ml of ether, followed by filtration and evaporation, gave 12.5 g (97%) of amido diester: ν (film) 3350, 1735, 1670 cm^{-1}. Cyclization, acid hydrolysis, and decarboxylation, as described above, gave 6.7 g of crude pyrrolidinedione which could be purified by chromatography on silica gel, using chloroform as eluant, to give (60% overall yield from L-leucine) 4.7 g of **4c** as a waxy solid. A sample, recrystallized from ethyl acetate–petroleum ether, showed mp 114–116°; ν ($CHCl_3$) 3350, 1775, 1715 cm^{-1}; δ ($CDCl_3$) 7.9 (H, b s), 4.1 (1 H, M), 3.1 (2 H, s), 1.4–2.0 (3 H, m), 1.0 (6 H, d, J = 6 Hz).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 61.99; H, 8.44.

5-Isobutyl-1-methylpyrrolidine-2,4-dione (4d). Treatment of 4.4 g of *N*-methylleucine methyl ester hydrobromide with carbethoxyacetyl chloride, under conditions identical with those described for the preparation of compound **4c**, gave 4.4 g (85%) of diester amide: ν (film) 1735 and 1650 cm^{-1}. Cyclization, followed by acid hydrolysis, again as described above, gave 2.3 g (78%) of **4d** as an oil: ν (film) 1770 and 1695 cm^{-1}; δ ($CDCl_3$) 3.8 (1 H, t, J = 6 Hz), 2.9 (5 H, b s), 1.4–1.8 (3 H, m), 0.9 (6 H, d, J = 6 Hz).

3-Diazo-1,5-dimethyl-5-ethyl-2,4-pyrrolidinedione (5a). Following the general procedure of Regitz, 595 mg of tosyl azide in 10 ml of CH_2Cl_2 was added to a solution of 465 mg of **4a** in 15 ml of CH_2Cl_2 at 0°. A solution of 220 mg of diethylamine in 3 ml of CH_2Cl_2 was then slowly added, the ice bath was removed, and the mixture was allowed to stir for 1.5 hr. The volatile materials were evaporated at reduced pressure and room temperature and the residue was partitioned between ether and water. The ether solution was washed with 5% NaOH solution to remove tosylamide, dried over Na_2SO_4, and evaporated. Chromatography on silica gel, using ether as eluant, gave 530 mg (98%) of yellow crystalline diazo ketone VIII, mp 73–76° dec: ν (CCl_4) 2123, 1724, 1695, 1667 1650 cm^{-1}; δ ($CDCl_3$) 0.8 (3 H, t), 1.3 (3 H, s), 1.5–2.0 (2 H, m), 2.9 (3 H, s).

Anal. Calcd for $C_8H_{11}O_2N_3$: C, 53.03; H, 6.12. Found: C, 53.23; H, 6.01.

3-Diazo-1,5,5-trimethyl-2,4-pyrrolidinedione (5). Compound **5** was obtained in a similar manner from compound **4** as a distinctly yellow, viscous oil: ν (film) 2120, 1724, 1695, 1678, 1660 cm^{-1}; δ ($CDCl_3$) 1.4 (6 H, s), 2.9 (3 H, s).

3-Diazo-1,5-dimethyl-5-hexyl-2,4-pyrrolidinedione (5b). Compound **5b** was obtained in a similar manner from compound **4b** in 95% yield as a yellow, viscous oil: ν (film) 2125, 1724, 1695, 1678, 1650, 1590 cm^{-1}; δ ($CDCl_3$) 2.8 (3 H, s), 1.32 (3 H, s), 0.8–2.0 (13 H, m).

3-Diazo-5-isobutyl-2,4-pyrrolidinedione (5c). A solution of 105 mg of mesyl azide in 1 ml of CH_2Cl_2 was added at 0° to a solution of 129 mg of **4c** in 7 ml of CH_2Cl_2. After addition of 85 mg of triethylamine in 1 ml of CH_2Cl_2, the mixture was stirred at 0° for 1 hr and at room temperature for 1 hr. Evaporation of volatile materials at room temperature and reduced pressure followed by partition of the residue between ether and water gave, after drying of the ether extracts with Na_2SO_4 and evaporation, 126 mg (85%) of **5c**, mp 138–141° dec: ν (CCl_4) 3450, 3250, 2128, 1690 cm^{-1}; δ ($CDCl_3$) 7.4 (1 H, b, s), 4.0 (1 H, m), 1.2–2.0 (3 H, m), 1.0 (6 H, d, J = 6 Hz).

Anal. Calcd for $C_8H_{11}O_2N_3$: C, 53.03; H, 6.12, Found: C, 52.28; H, 6.17.

3-Diazo-5-isobutyl-1-methylpyrrolidine-2,4-dione (5d). Treatment of 1.0 g of **4d** in CH_2Cl_2 at 0° for 1 hr with 735 mg of mesyl azide and 650 mg of triethylamine followed by work-up as described above gave, after filtration through silica gel using ether eluant, 876 mg (75%) of **5d** as a yellow oil: ν (film) 2123 and 1689 cm^{-1}; δ ($CDCl_3$) 3.8 (1 H, t, J = 6 Hz), 2.9 (3 H, s), 1.4–1.8 (3 H, m), 0.9 (6 H, d, J = 6 Hz).

Photolytic Decomposition of 3-Diazo-2,4-pyrrolidinediones. All photolyses were carried out under essentially identical conditions. The appropriate diazo compound (0.5 to 2 mmol) was dissolved in 100 ml of anhydrous ether and the ketene trapping agent was added. In the case of methanol and trifluoroethanol, this consisted of 5 ml of the alcohol. In the case of hydrazine 1.1 to 1.2 equiv were used. In the case of water or ammonia, the ether was presaturated at 0°. Photolyses were done through a Pyrex filter for 2.5 hr using a Hanovia 450 W medium pressure mercury arc. The whole apparatus was kept at 0° during a photolysis.

3-Carbomethoxy-1,4,4-trimethyl-2-azetidinone (6, R = OCH_3). Photolysis of 168 mg of a methanol solution of **5**, filtration through glass wool, and evaporation gave 161 mg (93%) of **6** (R = OCH_3) as a clear oil: ν (CCl_4) 1767 and 1730 cm^{-1}; δ ($CDCl_3$) 3.73 (4 H, s), 2.72 (3 H, s), 1.46 (3 H, s), 1.35 (3 H, s); mass spectrum, *m/e* 171 (M^+), 156 ($M^+ - CH_3$), 114 ($(CH_3O_2CCH{=}CCH_3)_2^+$, 56 ($O{=}CN{=}CH_2^+$).

Anal. Calcd for $C_8H_{13}NO_3$: *m/e* 171.0895. Found: *m/e* 171.0901.

3-Carbohydrazido-1,4,4-trimethyl-2-azetidinone (6, R = $NHNH_2$). Photolysis and work-up, as described above, of 157 mg of **5** in the presence of anhydrous hydrazine gave 153 mg of **6** (R = NHNHz) (95%) as an oil: ν (CCL_4) 3300, 3060, 1754, 1675 cm^{-1}; δ ($CDCl_3$) 4.0–5.0 (3 H, b s), 3.65 (1 H, s), 2.73 (3 H, s), 1.48 (3 H, s), 1.37 (3 H, s); mass spectrum, *m/e* 171 (M^+), 156 ($M^+ - CH_3$), 114 ($NH_2NHCOCH{=}C(CH_3)_2$), 56 ($O{=}CN{=}CH_2$).

Anal. Calcd for $C_7H_{13}N_3O_2$: *m/e* 171.1007. Found: *m/e* 171.1003.

3-Carboxy-1,4,4-trimethyl-2-azetidinone (6, R = OH). Photolytic decomposition and work-up as described above, in the presence of water, of 159 mg of **5** gave 145 mg (98%) of **6** (R = H) as off-white crystals, mp 84–87° dec: ν (KBr) 2740–2335, 1751, 1760–1700 cm^{-1}; δ ($CDCl_3$) 8.0 (b, s), 3.82 (1 H, s), 2.74 (3 H, s) 1.47 (3 H, s), 1.42 (3 H, s); mass spectrum, *m/e* 157 (M^+), 139 ($M^+ - H_2O$), 129 ($M^+ - CO_2$).

Anal. Calcd for $C_7H_{11}NO_3$: *m/e* 157.0739. Found: *m/e* 157.0741.

3-Carbotrifluoroethoxy-1,4,4-trimethyl-2-azetidinone (6, R = CF_3CH_2O). This ester was prepared from **5** as described above in the presence of trifluoroethanol: ν (CCl_4) 1768 and 1730 cm^{-1}; δ ($CDCl_3$) 4.56 (2 H, q of d, J = 8.5, 2.0 Hz), 3.85 (1 H, d, J =

(12) Y. L. Goldfarb, S. Z. Taitz, and V. N. Bulgakova, *Izv. Akad. Nauk*, 1299 (1963).

(13) To avoid ester exchange, it is necessary to add the diester to the alkoxide solution at room temperature so as to complete salt formation before heating is begun.

0.7 Hz), 2.73 (3 H, d, J = 0.7 Hz), 1.48 (3 H, s), 1.35 (3 H, s). Irradiation at 1.48 ppm (CH_3 a) gave 12% enhancement of H_c signal; irradiation at 1.35 ppm (CH_3 b) gave no enhancement of H_c; mass spectrum, m/e 239 (M^+), 224 ($M^+ - CH_3$), 182 ($F_3CCH_2OCOCH{=}C(CH_3)_2 \cdot^+$), 56 ($O{=}CN{=}CH_2 \cdot^+$).

3-Carbomethoxy-4-ethyl-1,4-dimethyl-2-azetidinone (7 and 8, R = OCH_3). Photolysis of 103 mg of **5a** in methanol gave 112 mg of a mixture of azetidinone together with some **4a** and small amounts of unidentified products. Chromatography on silica gel, using $CHCl_3$ eluant, gave 67 mg (64%) of the epimeric mixture **7** and **8** (R = OCH_3) in a ratio of 56:44 as shown by nmr analysis: ν (CCl_4) 1767 and 1739 cm^{-1}; δ ($CDCl_3$) 3.67 (4 H, b s), 2.76 (3 H, s), 1.6–2.0 (2 H, m), 1.46 and 1.35 (3 H, s, ratio 56:44), 1.01, 1.03 (3 H, two overlapping triplets); mass spectrum, m/e 185 (M^+), 170 ($M^+ - CH_3$), 156 ($M^+ - C_2H_5$), 128 ($CH_3OCCH{=}C(C_2H_5)(CH_3) \cdot^+$), 56 ($O{=}C{=}N{=}CH_2 \cdot^+$).

Anal. Calcd for $C_9H_{15}NO_3$: m/e 185.1052. Found: m/e 185.1058.

3-Carboxy-4-ethyl-1,4-dimethyl-2-azetidinone (7 and 8, R = OH). Photolysis of 9 mg of **5a** in water gave 94 mg of oil which could be crystallized from CCl_4–$CHCl_3$ (9:1) to give 75 mg (80%) of white needles. A sample, recrystallized from ethyl acetate–hexane, had mp 129–130°. No satisfactory elemental analysis could be obtained for this compound, but all were consistent with partial decarboxylation. Nmr analysis of the mixture indicated that the ratio of epimers **7** and **8** (R = OH) was 58:42: ν (KBr) 2800–2400, 1760, 1750–1700 cm^{-1}; δ ($CDCl_3$) 10.3 (1 H, b s), 3.85 and 3.79 (1 H, two broad singlets), 2.76 (3 H, s), 1.6–2.0 (2 H, m), 1.45 and 1.38 (3 H, s, ratio 58:42), 0.98 and 0.96 (3 H, two overlapping triplets, J = Hz); mass spectrum: m/e 171 (M^+), 156 ($M^+ - CH_3$), 142 ($M^+ - C_2H_5$), 127 ($M^+ - CO_2$), 114 ($HO_2C(H)C{=}C(C_2H_5)(CH_3) \cdot^+$), 56 ($O{=}CN{=}CH_2 \cdot^+$).

Anal. Calcd for $C_8H_{13}NO_3$: m/e 171.0895. Found: m/e 171.0916.

3-Carbomethoxy-4-*n*-hexyl-1,4-dimethyl-2-azetidinone (9 and 10, R = OCH_3). Photolysis of 105 mg of **5b** in ether–methanol gave 89 mg of a 3:1 mixture of **9** and **10** (R = OCH_3) as determined by nmr analysis: (CCl_4) 1770 and 1730 cm^{-1}; δ ($CDCl_3$) 3.73 (4 H, b s), 2.73 (3 H, s), 1.5–2 (2 H, m), 1.42 and 1.29 (3 H, s, relative areas 75:25), 0.8–1.3 (11 H, m); mass spectrum, m/e 241 (M^+), 226 ($M^+ - CH_3$), 184 ($CH_3O_2C(H)C{=}C(C_6H_{13})(CH_3) \cdot^+$), 182 ($M^+ - CO_2CH_3$), 156 ($M^+ - C_6H_{13}$), 56 ($O{=}CN{=}CH_2 \cdot^+$).

Anal. Calcd for $C_{13}H_{23}NO_3$: m/e 241.1678. Found: m/e 241.1693.

Photolysis of 106 mg of **5a** in a 5:1 mixture of methanol–acetic acid gave 99 mg of an essentially identical mixture (76:24) of **9** and **10** (R = OCH_3).

Equilibration of the Lactam Mixture 9 and 10 (R = OCH_3). To a solution of $LiOCH_3$ at 0° (prepared by adding 0.1 mmol of *n*-BuLi–hexane to 4 ml of THF and 1 ml of CH_3OH) was added 0.4 mmol of a 76:24 mixture of **9** and **10**, R = OCH_3. This was stirred at 0° for 1 hr, and 100 μl of acetic acid was then added slowly. The resultant solution was evaporated to dryness at room temperature and reduced pressure. The infrared was superimposable with that of the starting material. The nmr integration indicated that the ratio of **9** to **10** was at most 30:70. Thin-layer chromatography in five solvent systems (CCl_4, $CHCl_3$, C_6H_6, $(C_2H_5)_2O$, EtOAc) showed a reversal in intensity of spots corresponding to **9** and **10**, R = OCH_3 (side products did not appear to be formed).

3-Carboxamido-4-*n*-hexyl-1,4-dimethyl-2-azetidinone (9 and 10, R = NH_2). Photolysis of 104 mg of **5b** in ether–anhydrous ammonia gave 89 mg of a 3:1 mixture of **9** to **10**, R = NH_2, as determined by nmr: ν (CCl_4) 1751 and 1695 cm^{-1}; δ ($CDCl_3$) 6.6 (1 H, b s), 5.9 (1 H, b s), 3.61 (1 H, b s), 2.73 (3 H, d, J = 0.7 Hz), 1.5–2.0 (2 H, m), 1.42 and 1.35 (3 H, s; relative area 77:23), 0.8–1.3 (11 H, m); mass spectrum, m/e 226 (M^+), 211 ($M^+ - CH_3$), 82 ($M^+ - CONH_2$), 141 ($M^+ - C_6H_{13}$), 56 ($O{=}CN{=}CH_2 \cdot^+$).

Anal. Calcd for $C_{12}H_{22}N_2O_2$: m/e 226.1681. Found: m/e 226.1699.

3-Carboxy-4-*n*-hexyl-1,4-dimethyl-2-azetidinone (9 and 10, R = OH). Photolysis of 99 mg of **5b** in ether–water gave 96 mg of a 2:1 mixture of **9** and **10**, R = OH, as determined by nmr analysis: ν (CCl_4) 2800–2500, 1761, 1718 cm^{-1}; δ ($CDCl_3$) 8.0 (1 H, b s), 3.75 (1 H, b s), 2.75 (3 H, b s), 1.5–2.0 (2 H, m), 1.45 and 1.38 (3 H, s; relative areas 66:34), 0.8–1.3 (11 H, m); mass spectrum, m/e 227 (M^+), 212 ($M^+ - CH_3$), 183 ($M^+ - CO_2$), 56 ($O{=}CN{=}CH_2 \cdot^+$).

Anal. Calcd for $C_{12}H_{21}NO_3$: m/e 227.1521. Found: m/e 227.1521.

A similar photolysis of 98 mg of **5b** in a 5:1 mixture of water–acetic acid gave 81 mg of a similar mixture (70:30) of **9** and **10**, R = OH.

3-Carbohydrazido-4-*n*-hexyl-1,4-dimethyl-2-azetidinone (9 and 10, R = NH_2NH). Photolysis of 111 mg of **5b** in ether–anhydrous hydrazine, as described above, gave 106 mg of a 3.5:1 mixture of **9** to **10**, R = NH_2NH, as determined by nmr: ν (CCl_4) 3400, 3100, 1754, 1695 cm^{-1}; δ ($CDCl_3$) 3.5–3.9 (4 H, b), 2.75 (3 H, d, J = 0.7 Hz), 1.5–2.0 (2 H, m), 1.45, 1.32 (3 H, s, relative areas 78:22), 0.8–1.3 (11 H, m). The mass spectrum did not give a parent peak.

Photolysis of 3-Diazo-4-isobutyl-2,4-pyrrolidinedione (5c). Photolytic decomposition of 92 mg of **5c** in ether–methanol, followed by evaporation of the volatile materials, left 101 mg of a mixture of products. Careful chromatography on silica gel, using chloroform eluant, gave 22 mg of material whose mass spectrum showed a parent peak at m/e 200. This was identified as dimethyl isopentylidenemalonate (**13**) by comparison of the nmr and ir spectra with those of an authentic sample. In addition to the 22% yield of **13**, a 47% yield of *trans*-3-carbomethoxy-4-isobutyl-2-azetidinone (**11**) was also isolated: ν (CCl_4) 1776 and 1740 cm^{-1}; δ ($CDCl_3$) 6.81 (1 H, b s), 3.96 (1 H, triplet of doublets, J = 6.5, 2.5 Hz), 3.76 (3 H, s), 3.62 (1 H, d, J = 2.5 Hz), 1.1–1.5 (3 H, m), 0.93 (6 H, d, J = 6 Hz); mass spectrum, m/e 185 (M^+), 142 ($CH_3O_2C(H)C{=}C(H)CH_2CH(CH_3)_2$).

Anal. Calcd for $C_9H_{15}NO_3$: m/e 185.1052. Found: m/e 185.1050.

Dimethyl Isopentylidenemalonate (13). Following a general procedure of Cope[14] 2.62 g of dimethyl malonate and 1.72 g of isovaleraldehyde were refluxed in 15 ml of benzene in the presence of ~100 mg of piperidine and 500 mg of acetic acid for 6 hr with azeotropic removal of water, using a Dean-Stark trap. The residue was washed with water, dried over sodium sulfate, and evaporated. Bulb-to-bulb distillation at 80–90° (0.1 mm) gave 3.3 g (78%) of **13** identical with the substance from the photolysis of **5c**; ν (film) 1740 and 1653 cm^{-1}; δ ($CDCl_3$) 7.05 (1 H, t, J = 7 Hz), 1.4–2.1 (1 H, m), 0.93 (6 H, d, J = 6 Hz).

Photolytic Decomposition of Diazopyrrolidinedione (5d). Photolysis of 127 mg of **5d** in the presence of methanol as described above gave, after chromatography on silica gel using ether eluant, 5 mg (3%) of **13**, identified by comparison of its nmr and ir with that of authentic material, and 69 mg, 54%, of the trans lactam **12** as an oil: ν (CCl_4) 1779 and 1730 cm^{-1}; δ ($CDCl_3$) 3.8–4.0 (1 H, m), 3.75 (3 H, s), 3.60 (1 H, d of d, J = 2.0, 0.7 Hz), 2.81 (3 H, s) 1.1–1.8 (3 H, m), 0.95 (6 H, d, J = 6 Hz); mass spectrum, m/e 199 (M^+), 142 (M^+ – *i*-Bu, $CH_3O{-}CC(H){=}CHCH_2CH(CH_3)_2 \cdot^+$), 100 ($CH_3O_2C{-}C(H){=}C{=}O \cdot^+$). There was no evidence of the formation of the cis isomer of **12**.

8-Diazo-7,9-dioxo-1-azabicyclo[4.3.0]nonane (14). Compound **14** was prepared from ethyl pipecolinate, by acylation with carbethoxyacetyl chloride[12] (91%), cyclization in sodium methoxide followed by acid hydrolysis and decarboxylation (65%), and diazo transfer using mesyl azide (69%), in a manner analogous to that described above, as a yellow crystalline material: mp 44–46°; ν ($CHCl_3$) 2120, 1724, 1695, 1680 cm^{-1}; δ ($CDCl_3$) 4.33 (1 H, dd, J = 3, 14 H), 3.7 (1 H, m), 2.8 (1 H, m), 1.0–2.3 (6 H, m).

Photolysis of 8-Diazo-7,9-dioxo-1-azabicyclo[4.3.0]nonane (14). Photolytic decomposition of 184 mg of **14** in ether–methanol followed by evaporation of volatile materials left 178 mg of a mixture of products. Chromatography on silica gel, using ether eluant, gave two isomeric β-lactams **15** (35 mg) and **16** (87 mg).[9]

β-Lactam 15: R_f 0.58 (ether–silica gel): ν (CCl_4) 1770 and 1730 cm^{-1}; δ ($CDCl_3$) 3.6–4.4 (3 H, m), 3.73 (3 H, s), 2.8 (1 H, m), 1.0–2.3 (6 H, m); mass spectrum, m/e 183 (M^+), 155 ($M^+ - CO$), 124 ($M^+ - CO_2Me$), 83 ($C{-}N{=}CH(CH_2)_4^+$).

β-Lactam 16: R_f 0.4 (ether–silica gel); ν (CCl_4) 1773 and 1735 cm^{-1}; δ ($CDCl_3$) 3.6–4.2 (3 H, m), 3.72 (3 H, s), 2.8 (1 H, m), 1.0–2.3 (6 H, m); mass spectrum, m/e 183 (M^+), 155 ($M^+ - CO$), 124 ($M^+ - CO_2Me$).

Anal. Calcd for $C_9H_{13}NO_3$: m/e 183.0895. Found: 183.0894.

Epimerization of β-Lactam 15. Treatment of a sample of **15** in lithium methoxide–methanol at 0° readily converts it to the isomeric lactam **16** as monitored by tlc. Compound **16** is stable to these conditions. In addition **15** converts to a mixture of **15** and **16** on storage at −10°.

Acknowledgments. We thank the National Institutes of Health for their support of this work. R. S. thanks the National Science Foundation for a predoctoral fellowship.

(14) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Amer. Chem. Soc.*, **63**, 3452 (1941).