NMR spectra, and Professor G. W. Kenner, University of Liverpool, for high-resolution mass spectra.

Registry No.—**1a**, 31951-33-4; **1b**, 41601-98-3; **4a**, 875-30-9; **4a** 1,3,5-trinitrobenzene charge-transfer complex, 54383-93-6; **4b**, 1971-46-6; **4b** 1,3,5-trinitrobenzene charge-transfer complex, 54383-94-7; **6a**, 54383-95-8; **6a** 1,3,5-trinitrobenzene charge-transfer complex, 54383-96-9; **6b**, 54384-25-7; **6c**, 54384-26-8; skatole, 83-34-1; diborane, 19287-45-7.

References and Notes

(1) Part III: K. M. Biswas and A. H. Jackson, *J. Chem. Soc. C*, 1667 (1970).
(2) A. Chatterjee and K. M. Biswas, presented in part at the Golden Jubilee Celebrations of the Indian Chemical Society, Calcutta, India, Dec 23–30, 1973, Abstracts of Papers, Part II, p 204.
(3) (a) B. Robinson, *Chem. Rev.*, **69**, 785 (1969); (b) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, N.Y., 1970, p 131; (c) W. A. Remers and R. K. Brown in "The Chemistry of Heterocyclic Compounds", Vol. 25, W. J. Houlihan, Ed., Wiley-Interscience, New York, N.Y., 1972, p 166; (d) S. A. Monti and R. R. Schmidt, III, *Tetrahedron*, **27**, 3331 (1971), and references cited therein; (e) L. J. Dolby and Z. Esfandiari, *J. Org. Chem.*, **37**, 43 (1972); (f) R. Littell and G. R. Allen, Jr., ibid., **38**, 1504 (1973); (g) R. R. Schmidt, III, *Diss. Abstr. Int. B*, **33**, 4203 (1973); *Chem. Abstr.*, **79**, 5211 (1973).
(4) Reference 3c, pp 170–171.
(5) H. Sirowej, S. A. Khan, and H. Plieninger, *Synthesis*, 84 (1972).
(6) Reference 3c, pp 206–208.
(7) W. B. Wright, Jr., U.S. Patent 3,565,902 (1971); *Chem. Abstr.*, **75**, 36033 (1971).
(8) Reference 3b, pp 109, 113.
(9) Reference 3c, pp 196–199.
(10) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **25**, 227 (1969).
(11) Reference 3b, p 220.
(12) (a) The *N*-(a)-formyl group of a tryptamine derivative was reported to undergo reductive cleavage with $LiAlH_4$: K. Elter and O. Svierak, *Monatsh. Chem.*, **83**, 1474 (1952). (b) The *N*-acetyl groups of two 1,3-diacylindoles were found to be inert to $LiBH_4$: D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.*, 1984 (1956). (c) The *N*-acyl group of an indole derivative resisted reduction under acidic or basic conditions: T. Teitei, *Aust. J. Chem.*, **23**, 185 (1970).
(13) (a) Reference 3b, Chapter 1; (b) Reference 3c, Chapter 1; (c) A. H. Jackson and B. Naidoo, *Tetrahedron*, **25**, 4843 (1969).
(14) J. Wolinsky and J. E. Sundeen, *Tetrahedron*, **26**, 5427 (1970).
(15) G. Casnati, A. Dossena, and A. Pochini, *Tetrahedron Lett.*, 5277 (1972).
(16) Reference 3b, p 2.
(17) A. Chatterjee and K. M. Biswas, *J. Org. Chem.*, **38**, 4002 (1973).
(18) A solution of **1a** in BF_3–OEt_2 did not undergo any appreciable change on keeping at 25° for 3 hr.
(19) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968).
(20) (a) A. H. Jackson and B. Naidoo, *J. Chem. Soc., Perkin Trans. 2*, 548 (1973); (b) R. Iyer, A. H. Jackson, P. V. R. Shannon, and B. Naidoo, ibid., 872 (1973); (c) R. Iyer, A. H. Jackson, and P. V. R. Shannon, ibid., 878 (1973).
(21) (a) P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972); (b) G. Decodts, M. Wakselman, and M. Vilkas, ibid., **26**, 3313 (1970), and references cited therein; (c) Y. Kanaoka, K. Miyashita, and O. Yonemitsu, ibid., **25**, 2757 (1969); (d) G. Casnati, A. Pochini, B. Cardillo, and A. Ricca, ibid., **23**, 3771 (1967); (e) T. F. Spande, A. Fontana, and B. Witkop, *J. Am. Chem. Soc.*, **91**, 6199 (1969); (f) T. F. Spande and G. G. Glenner, ibid., **95**, 3400 (1973); (g) G. Casnati, A. Pochini, M. Francioni, and A. Guareschi, *Tetrahedron Lett.*, 2485 (1969); (h) G. Stöher, G. Salemnick, and G. B. Brown, *Biochemistry*, **12**, 5084 (1973); (i) A. Walser, J. F. Blount, and R. I. Fryer, *J. Org. Chem.*, **38**, 3077 (1973); (j) M. Aiura and Y. Kanaoka, *Heterocycles*, **2**, 319 (1974); (k) A. S. Bailey, A. J. Buckley, and J. F. Seager, *J. Chem. Soc., Perkin Trans. 1*, 1809 (1973), and references cited therein; (l) R. K. Bramely, J. Caldwell, and R. Grigg, ibid., 1913 (1973).
(22) (a) A methoxyl group at the 6 position of 3-alkylindoles was reported to cause 31% direct substitution at the 2 position: ref 20c. (b) Evidence of about 30% direct substitution at the 9a position of a 9-methyltetrahydrocarbazole derivative was also reported earlier: ref 3e.
(23) Prepared by the method described in ref 17.
(24) P. G. Stecher, M. J. Finkel, O. H. Siegmund, and B. M. Szafranski, "The Merck Index of Chemicals and Drugs", 7th ed, Merck and Co., Inc., Rahway, N.J., 1960, p 952.
(25) Similar results were reported earlier: (a) C. W. Whittle and R. N. Castle, *J. Pharm. Sci.*, **52**, 645 (1963); (b) N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **27**, 1049 (1957); *Chem. Abstr.*, **52**, 3763 (1958).
(26) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **70**, 1703 (1948).
(27) T. L. Rebstock, L. E. Weller, and H. M. Sell, *J. Org. Chem.*, **21**, 1515 (1956).
(28) J. Thesing and P. Binger, *Chem. Ber.*, **90**, 1419 (1957).

Synthesis of 4-Keto-4,5,6,7-tetrahydroindoles via Munchnone Intermediates[1]

Fred M. Hershenson

Department of Chemical Research, Searle Laboratories, Chicago, Illinois 60680

Received June 20, 1974

The amino acids, proline and pipecolinic acid, have been converted into the 4-keto-4,5,6,7-tetrahydroindoles, **5a** and **5b**, respectively, in three steps. This sequence involved the preparation of the corresponding *N*-(4-carbomethoxybutyroyl)amino acids and their subsequent reaction with acetic anhydride and dimethyl acetylenedicarboxylate, thereby yielding the pyrrole triesters, **4a** and **4b**. This latter transformation employed a 1,3-dipolar cycloaddition reaction of bicyclic munchnone derivatives generated in situ. The final step in this sequence involved a Dieckmann condensation of **4a** and **4b** using sodium hydride. The application of the sequence to acyclic amino acids was also investigated and with phenylglycine and sarcosine, the tetrahydroindoles, **15** and **16**, respectively, were obtained.

Munchnones (mesoionic oxazolium 5-oxides) have been successfully used in the preparation of pyrroles bearing simple alkyl, aryl, and/or carboalkoxy substituents.[2,3] This paper will describe the synthesis of pyrrole derivatives possessing a functionalized alkyl side chain capable of undergoing further reaction to yield 4-keto-4,5,6,7-tetrahydroindoles. In particular, this involves the reactions of *N*-(4-carbomethoxybutyroyl)amino acids with acetic anhydride and dimethyl acetylenedicarboxylate. The concept of utilizing functionalized 1,3-dipoles has recently been described by Lown and Landberg.[4]

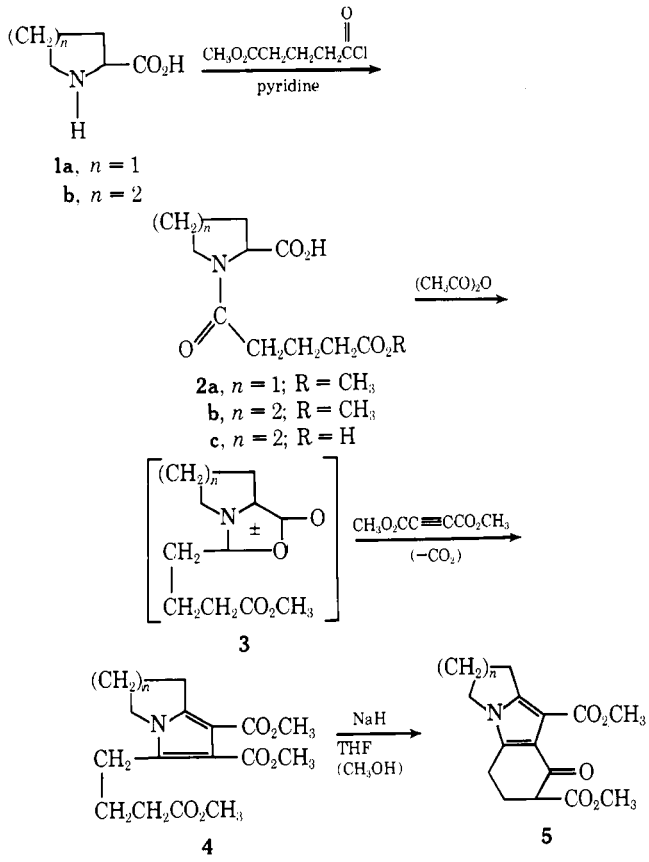
Results and Discussion

Initially, the amino acids, proline and pipecolinic acid, were used in this study, and the reactions involving these compounds are listed in Scheme I.

Treatment of these amino acids with methyl (4-chloroformyl)butyrate in refluxing pyridine afforded the *N*-acyl amino acids, **2a** and **2b**, respectively. Attempts to carry out this acylation reaction under Schotten–Baumann conditions failed to give the desired *N*-(4-carbomethoxybutyroyl)amino acids. When pipecolinic acid was treated with methyl 4-(chloroformyl)butyrate in dilute sodium hydroxide solution, a low yield of the *N*-acyl diacid, **2c**, was obtained. **2a** and **2b** were isolated as viscous oils and were used in the next step without extensive purification, although **2b** was converted into a crystalline dicyclohexylamine salt for the purposes of characterization.

Reaction of **2a** and **2b** with acetic anhydride and dimethyl acetylenedicarboxylate furnished the tetrahydropyrrolizine **4a** and tetrahydroindolizine **4b**, respectively, as oils. The formation of these products involve the intermediacy

Scheme I

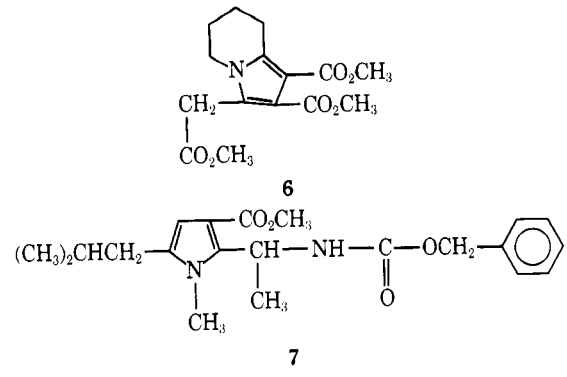


of bicyclic munchnone derivatives (**3a** and **3b**), possessing a functionalized substituent at C-2. Surprisingly, the bicyclic munchnone (**3b**) appears to be formed more readily than munchnones derived from acyclic, *N*-acyl secondary amino acids (vide infra), since carbon dioxide evolution, an indication that the 1,3-dipolar cycloaddition of the munchnone to the acetylenic dipolarophile has occurred, was observed in this case on simply mixing the reactants at room temperature. Reactions involving the acyclic, *N*-acyl amino acids required the use of elevated temperatures (45–60°).

Both the tetrahydropyrrolizine **4a** and the tetrahydroindolizine **4b** possess the requisite spectral characteristics to substantiate their structural assignments. In particular, the ultraviolet spectra of **4a** and **4b** are in good agreement with the reported uv spectrum (λ_{max} (CH_3OH) 268 mμ (log ϵ 3.97) of the homologous tetrahydroindolizine **6**, prepared by Acheson and Taylor.[5]

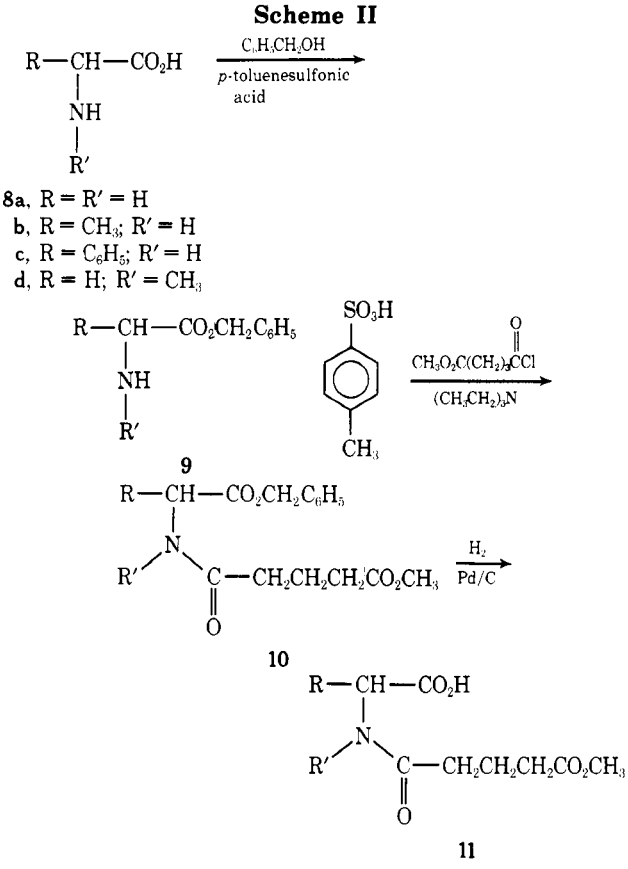
Conversion of **4a** and **4b** into the corresponding 4-keto-4,5,6,7-tetrahydroindoles, **5a** and **5b**, respectively, was accomplished by a Dieckmann condensation using sodium hydride in tetrahydrofuran containing a trace of methanol. In this manner, compound **5a**, a heterocycle which possesses three of the four rings contained in the mitomycin skeleton, was readily made.

Since it appeared that munchnones bearing a functionalized side chain at C-2 could be used in the preparation of complex pyrroles, a study of this reaction with acyclic *N*-acyl amino acids was then made in order to establish the synthetic scope of this approach. An example of such a reaction, somewhat related to the present study, has been recently reported. McDermott and Benoiton have found that treatment of Z-Ala-MeLeu with dicyclohexylcarbodiimide in THF followed by addition of methyl propiolate resulted in the formation of the crystalline pyrrole **7** in 85% yield.[6] The formation of this particular product involves the intermediacy of a mesoionic oxazolium 5-oxide which possesses a functionalized alkyl side chain (aminoalkyl group) at C-2.



In the present study, four amino acids, glycine, alanine, phenylglycine, and sarcosine (*N*-methylglycine), **8a–d**, respectively, were converted into their *N*-(4-carbomethoxybutyroyl) derivatives **11a–d**, by first preparing the benzyl ester, then acylating the benzyl ester with methyl (4-chloroformyl)butyrate in the presence of triethylamine, and finally removing the benzyl ester by hydrogenolysis (Scheme II). Once formed, the *N*-(4-carbomethoxybutyroyl) amino

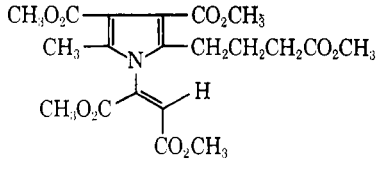
Scheme II



acids, **11a–d**, were dissolved in acetic anhydride containing dimethyl acetylenedicarboxylate and the reaction mixture was heated until carbon dioxide evolution was observed to occur (system vented through a barium hydroxide trap).

The results of the reactions studied here are consistent with earlier findings by Huisgen,[7] namely, reactions involving *N*-acyl amino acids which are derived from amino acids possessing a primary amine group usually fail to give the desired pyrrole products. In our case, reaction of *N*-(4-carbomethoxybutyroyl)glycine (**11a**) with acetic anhydride yielded the corresponding azlactone, which does not appear

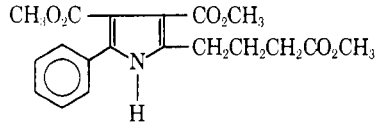
to exist in any appreciable equilibrium with the requisite mesoionic munchnone. No carbon dioxide evolution was observed even up to the reflux temperature of acetic anhydride, and only a small amount of monomethyl glutarate was obtained from the reaction mixture, indicating that hydrolysis of the azlactone had occurred on work-up. Reaction of **11b**, the amide derived from alanine, did furnish a small amount of the pyrrole **12**. This is also consistent with



12

Huisgen's finding that dimethyl 2,5-dialkylpyrrole-3,4-dicarboxylates react with dimethyl acetylenedicarboxylate in a Michael addition fashion.[7]

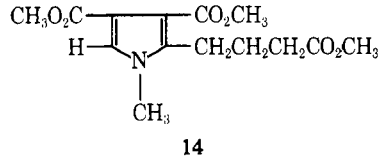
The pyrrole **13** obtained from **11c**, however, does not possess the dimethyl maleate substituent on the pyrrole



13

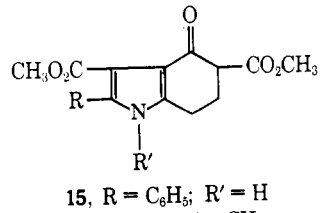
ring nitrogen. Apparently, the presence of the aromatic phenyl substituent at one of the α positions of the pyrrole ring inhibits this further reaction of 1-unsubstituted pyrroles with dimethyl acetylenedicarboxylate. In this particular example, carbon dioxide evolution was observed to occur when the temperature of the reaction mixture reached 45°. This is due to the charge stabilization of the phenyl substituent at C-4 of the munchnone, thereby facilitating the formation of this highly reactive 1,3-dipole.

The use of an *N*-aryl secondary amino acid such as **12d** was uneventful and afforded the desired pyrrole, **14**, in 57%



14

yield. Both **13** and **14** were subsequently converted into the corresponding 4-keto-4,5,6,7-tetrahydroindoles, **15** and **16**, by means of a Dieckmann condensation using conditions just described.



15, R = C_6H_5; R′ = H
16, R = H; R′ = CH_3

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus which was calibrated against known standards. Ultraviolet spectra were recorded in CH_3OH solutions on a Beckman DK-2A spectrometer; infrared spectra were determined in $CHCl_3$ solutions on a Beckman IR-12 spectrometer; ^1H NMR spectra were obtained on a Varian Associates A-60 or T-60 spectrometer from $CDCl_3$ solutions using tetramethylsilane as an internal standard; mass spectra were run on an AEI MS-30. Microanalyses were performed by the Searle Laboratories Microanalytical Department. Mallinckrodt silica gel (CC7) was used in the column chromatographic work-ups.

***N*-(4-Carbomethoxybutyroyl)proline (2a).** A solution of L-proline (23.0 g, 0.2 mol) in anhydrous pyridine (300 ml) was treated with methyl (4-chloroformyl)butyrate (32.9 g, 0.2 mol) and the mixture was heated to reflux for 3 hr. The reaction mixture was cooled and poured into a slurry of concentrated hydrochloric acid (400 ml) and ice (400 ml). The resultant aqueous acidic mixture was extracted with chloroform (3 × 250 ml); the combined chloroform extract was washed with water (250 ml), then dried (Na_2SO_4), and the solvent was removed in vacuo. A thick, orange oil (42.75 g) was isolated: μ_{OH} 3300–3000, $\mu_{C=O}$ 1735 and 1645 cm^{-1}. This product, **2a**, was used without further purification in the next step (synthesis of **4a**).

***N*-(4-Carbomethoxybutyroyl)pipecolinic Acid (2b).** Using the procedure just described, a reaction of pipecolinic acid (25.8 g, 0.2 mol) and methyl (4-chloroformyl)butyrate (32.9 g, 0.2 mol) in anhydrous pyridine (300 ml) furnished **2b** as a brown viscous oil (37.10 g): μ_{OH} 3300–3000, $\mu_{C=O}$ 1735, 1720 (shoulder), and 1645 cm^{-1}. In addition to using this material for the preparation of **4b**, a small portion (1.2 g) of this oil was dissolved in anhydrous ether (50 ml) and a solution of dicyclohexylamine (1.0 g) in ether (10 ml) was added. A colorless, crystalline solid was obtained (0.9 g), mp 139–141°.

Anal. Calcd for $C_{24}H_{42}N_2O_5$: C, 65.72; H, 9.65; N, 6.39. Found: C, 65.95; H, 9.99; N, 6.36.

Dimethyl 2,3-Dihydro-5-(3-carbomethoxypropyl)-1*H*-pyrrolizine-6,7-dicarboxylate (4a). A mixture consisting of **2a** (42.75 g, assumed to be 0.176 mol), dimethyl acetylenedicarboxylate (28.4 g, 0.2 mol), and acetic anhydride (250 ml) was stirred and heated to 65°. At this temperature an exothermic reaction ensued, and the temperature quickly rose to 115°. This temperature was maintained for 18 hr by means of a heating bath. After the blackened reaction mixture was cooled, the solvents were removed in vacuo, and the black tarry residue that remained was dissolved in methylene chloride (250 ml). This solution was washed with brine (6 × 150 ml), dried (Na_2SO_4), and the solvent removed in vacuo. The black tar that remained was chromatographed on a silica gel column (1800 g). Elution of the column with 1% ethanol–99% chloroform furnished **4a** as a brown oil (25.42 g): λ_{max} 266 mμ (log ϵ 3.77); $\mu_{C=O}$ 1735 cm^{-1}. Bulb-to-bulb distillation of a small sample of this material afforded a light orange, viscous oil.

Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: 59.08; H, 6.50; N, 4.01.

Dimethyl 3-(3-Carbomethoxypropyl)-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (4b). A solution of **2b** (23.5 g, assumed to be 0.09 mol), dimethyl acetylenedicarboxylate (21.3 g, 0.15 mol), and acetic anhydride (400 ml) was stirred at room temperature overnight. The reaction mixture was evaporated to dryness in vacuo and the residue obtained was dissolved in ether (300 ml). The ether solution was filtered, washed with water (200 ml), 10% K_2CO_3 solution (200 ml), and water (200 ml), then dried ($MgSO_4$) and evaporated to dryness. The brown oil that was obtained (28.60 g) was divided into two equal portions and each portion was chromatographed on a silica gel column (1000 g). Elution of these columns with 10% ethyl acetate–90% benzene afforded **4b** as a light brown oil (12.12 g). Distillation of a small sample of the brown oil furnished a light yellow, viscous oil: bp 223–224° (0.9 mmHg); λ_{max} 267 mμ (log ϵ 3.82); $\mu_{C=O}$ 1730 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.74; H, 7.07; N, 3.86.

Dimethyl 2,3,5,6,7,8-Hexahydro-8-oxo-1*H*-pyrrolo[1,2-*a*]indole-7,9-dicarboxylate (5a). Sodium hydride dispersion in mineral oil (57%, 8.2 g, 0.2 mol) was washed twice with pentane, the pentane washings were carefully decanted, and distilled THF (250 ml) containing 1 ml of methanol was added. A solution of **4a** (25 g, 0.077 mol) in distilled THF (100 ml) was added in dropwise portions over a 1-hr period to this NaH suspension under a nitrogen atmosphere with stirring at reflux. Heating of the reaction mixture at reflux was continued for an additional 90 min; then it was cooled and cautiously acidified by adding concentrated hydrochloric acid (20 ml). The acidified mixture was then dissolved in water (300 ml) and the resultant solution was extracted with chloroform (2 × 250 ml). After the combined chloroform extract was washed with brine (500 ml), the organic solution was dried (Na_2SO_4) and the solvent was removed in vacuo. Trituration of the residue with ether afforded a brown solid (17.4 g) which was re-

crystallized from ethyl acetate to give a light-tan, powdery solid (5.25 g, 23%): mp 139–141°; λ_{max} 283 mμ (log ε 4.02), 263 (3.94), 225 (3.90); $\mu_{C=O}$ 1740 and 1680 cm^{-1}; in addition to δ 3.73 and 3.81 (s, OCH_3) and 3.90 (t, CH, J = 7 Hz), a series of multiplets are present between δ 2.00 and 3.60, integrating for ten protons.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.73; H, 5.95; N, 4.83.

Dimethyl 1,2,3,4,6,7,8,9-Octahydro-1-oxopyrido[1,2-*a*]indole-2,10-dicarboxylate (5b). Using the procedure described for the synthesis of **5a**, reaction of **4b** (16.08 g, 0.047 mol) with sodium hydride dispersion (57%, 4.20 g, 0.10 mol) in distilled THF (200 ml) containing 1 ml of methanol afforded a light brown solid (11.55 g, 81%), mp 142–146°. A slightly modified work-up was employed here and involved the use of acetic acid in place of concentrated hydrochloric acid during the acidification. Recrystallization of the brown solid from water and decolorization using Darco furnished **5b** as colorless plates: mp 153–157°; λ_{max} 285 mμ (log ε 3.92), 265 (3.85), 229 (3.93); $\mu_{C=O}$ 1735 and 1680 cm^{-1}; a series of multiplets between δ 1.70 and 3.95 with two singlets at δ 3.75 and 3.81 (OCH_3 protons).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.10; H, 6.42; N, 4.43.

Preparation of Amino Acid Benzyl Ester *p*-Toluenesulfonates (9). The synthesis of sarcosine benzyl ester *p*-toluenesulfonate (**9d**) will serve as an example of the synthetic method used in this reaction. A mixture consisting of sarcosine (22.3 g, 0.25 mol), *p*-toluenesulfonic acid monohydrate (48.5 g, 0.255 mol), benzyl alcohol (100 ml), and anhydrous benzene (50 ml) was heated to reflux overnight beneath a Dean-Stark trap. After 19 hr had elapsed, 10.5 ml of water had collected in the trap. The reaction mixture was cooled, ether (300 ml) was added, and the resultant mixture was refrigerated for several days. A colorless solid (58.6 g) was obtained and addition of ether (150 ml) to the mother liquor provided a second crop of solid (76.3 g). The solids were combined and recrystallized from acetone, yielding a colorless solid (63.85 g, 73%), mp 99–102°.

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.75; H, 6.09; N, 3.78.

In a similar manner, alanine benzyl ester *p*-toluenesulfonate (**9b**) was prepared in 65% yield, mp 112–114° (lit.[8] mp 113–114°), and phenylglycine benzyl ester *p*-toluenesulfonate (**9c**) was synthesized in 80% yield, mp 192–194.5° (CH_3CN).

Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.87; H, 5.75; N, 3.12.

Preparation of *N*-(4-Carbomethoxybutyroyl)amino Acid Benzyl Esters (10). The synthesis of **10a** will serve as an example of the experimental procedures used for this reaction. A mixture of glycine benzyl ester *p*-toluenesulfonate[9] (**9a**, 16.85 g, 0.05 mol) in chloroform (300 ml) was cooled to 5° and triethylamine (10.0 g, 0.1 mol) was added. After stirring for a few minutes, a solution of methyl (4-chloroformyl)butyrate (8.25 g, 0.05 mol) in chloroform (25 ml) was added in dropwise portions over a 45-min period. The reaction mixture was allowed to stand overnight at room temperature, and was then washed with dilute hydrochloric acid (2 × 200 ml) and water (300 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by bulb-to-bulb distillation provided **10a** as a light yellow oil (13.15 g, 90%): μ_{NH} 3440 cm^{-1}, $\mu_{C=O}$ 1740 and 1680 cm^{-1}; δ 1.80–2.70 (m, six protons), 3.63 (s, OCH_3), 4.06 (d, CH_2, J = 5.5 Hz), 5.16 (s, OCH_2), 6.25 (broad s, NH), 7.33 (s, phenyl protons).

Anal. Calcd for $C_{15}H_{19}NO_5 \cdot \frac{1}{2}H_2O$: C, 59.58; H, 6.68; N, 4.63. Found: C, 59.39; H, 6.72; N, 4.76.

The following *N*-(4-carbomethoxybutyroyl)amino acid benzyl esters were prepared in an analogous manner.

***N*-(4-Carbomethoxybutyroyl)alanine benzyl ester (10b)** was a colorless oil obtained in 85% yield; μ_{NH} 3440, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 1.40 (d, CH_3, J = 7 Hz), 1.80–2.60 (m, six protons), 3.65 (s, OCH_3), 4.71 (q, CH, J = 7 Hz), 5.16 (s, OCH_2), 6.25 (broad s, NH), 7.33 (s, phenyl protons).

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.23; H, 6.89; N, 4.58.

***N*-(4-Carbomethoxybutyroyl)phenylglycine benzyl ester (10c)** was a colorless solid, mp 68–72° (benzene–hexane), obtained in 90% yield: μ_{NH} 3440, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 1.80–2.60 (m, six protons), 3.56 (s, OCH_3), 5.16 (s, OCH_2), 5.63 (d, CH, J = 7 Hz), 6.66 (broad d, NH), 7.10–7.40 (m, phenyl protons).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.58; H, 6.25; N, 3.81.

***N*-(4-Carbomethoxybutyroyl)sarcosine benzyl ester (10d)** was a colorless oil isolated in quantitative yield: $\mu_{C=O}$ 1730 and 1650 cm^{-1}; δ 1.80–2.60 (m, six protons), 3.06 (s, CH_3N), 3.61 (s, OCH_3), 4.18 (s, CH_2), 5.16 (s, OCH_2), 7.40 (s, phenyl protons).

Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.37; H, 6.93; N, 4.49.

Preparation of *N*-(4-Carbomethoxybutyroyl)amino Acids (11). The following description of the experimental procedures used in preparing **11a** is representative of the method used in this debenzylation reaction. A solution of **10a** (12.3 g, 0.041 mol) in ethyl acetate (200 ml) was treated with 5% palladium on carbon (1.2 g) and the mixture was hydrogenated using a Parr Shaker apparatus at room temperature and atmospheric pressure. Once the theoretical amount of hydrogen had been taken up (this usually occurred within 3 hr), the mixture was filtered and the filtrate was evaporated to dryness in vacuo. **11a** was isolated as a light yellow oil (7.75 g, 93%), which crystallized on standing at room temperature: mp 62–66°; μ_{NH} 3440, μ_{OH} 3300–3000. $\mu_{C=O}$ 1730 and 1675 cm^{-1}; δ 1.80–2.65 (m, six protons), 3.65 (s, OCH_3), 4.03 (d, CH_2, J = 6 Hz), 6.85 (t, NH, J = 6 Hz), 9.30 (s, CO_2H).

Anal. Calcd for $C_8H_{13}NO_5$: C, 47.28; H, 6.45; N, 6.89. Found: C, 46.95; H, 6.55; N, 7.00.

The following *N*-(4-carbomethoxybutyroyl)amino acids were prepared in an analogous manner.

***N*-(4-carbomethoxybutyroyl)alanine (11b)** was obtained as a light yellow oil in 89% yield, which crystallized into a colorless solid: mp 137–140° (EtAc–hexane); μ_{OH} 3690 and 3300–3000, μ_{NH} 3440, $\mu_{C=O}$ 1740 and 1680 cm^{-1}; δ 1.43 (d, CH_3, J = 8 Hz), 1.80–2.60 (m, six protons), 3.65 (s, OCH_3), 4.66 (d of q, CH, J = 8 Hz), 6.80 (d, NH, J = 8 Hz), 8.33 (s, CO_2H).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.72; H, 6.66; N, 6.83.

***N*-(4-Carbomethoxybutyroyl)phenylglycine (11c)** was isolated as colorless needles, mp 102–105° (benzene), in 88% yield: μ_{OH} 3690 and 3300–3000, μ_{NH} 3440, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 1.70–2.60 (m, six protons), 3.60 (s, OCH_3), 5.57 (d, CH, J = 7 Hz), 7.06 (d, NH, J = 7 Hz), 7.33 (s, phenyl protons), 9.68 (s, CO_2H).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.16; H, 6.14; N, 5.01.

***N*-(4-Carbomethoxybutyroyl)sarcosine (11d)** was obtained as a colorless oil in quantitative yield: μ_{OH} 3690 and 3300–3000, $\mu_{C=O}$ 1730 and 1650 cm^{-1}; δ 1.80–2.80 (m, six protons), 3.00 and 3.08 (s, CH_3N),[10] 3.70 (s, OCH_3), 4.10 and 4.16 (s, CH_2N),[10] 9.16 (s, CO_2H).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.94; H, 6.63; N, 6.50.

Reaction of 11b with Acetic Anhydride and Dimethyl Acetylenedicarboxylate. 11b (7.2 g, 0.033 mol) was dissolved in acetic anhydride (125 ml) containing dimethyl acetylenedicarboxylate (5.7 g, 0.04 mol), and the solution was heated to 120° for 24 hr. After the solution was cooled and the acetic anhydride was removed in vacuo, the residue was dissolved in ether (200 ml), filtered, and washed with dilute hydrochloric acid (2 × 100 ml), then water (2 × 100 ml). The ether solution was dried ($MgSO_4$) and evaporated to dryness, leaving a brown oil (10.05 g). This oil was chromatographed on a silica gel column (1200 g) and elution with 5% ethyl acetate–95% benzene afforded **12** as a light brown oil (2.2 g, 15%): λ_{max} 258 mμ (log ε 3.90); $\mu_{C=O}$ 1735 and 1710 (shoulder), $\mu_{C=C}$ 1660 cm^{-1}; δ 2.18 (s, CH_3), 1.55–2.90 (m, six protons), 3.65, 3.70, 3.83, 3.86 (s, five OCH_3), 7.36 (s, vinyl proton).

Dimethyl 2-Phenyl-5-(3-carbomethoxypropyl)pyrrole-3,4-dicarboxylate (13). A solution comprised of **11c** (5.6 g, 0.02 mol), dimethyl acetylenedicarboxylate (4.25 g, 0.03 mol), and acetic anhydride (150 ml) was warmed to 45–55° for 6 hr, then cooled and evaporated to dryness in vacuo. The residue was dissolved in ether (100 ml) and the ether solution was washed with dilute (5%) acetic acid (100 ml), 2% $NaHCO_3$ solution (100 ml), and water (100 ml). After drying ($MgSO_4$), the solution was evaporated to dryness and the residue was triturated with hexane. **13** was obtained as a viscous orange oil (6.85 g) and this material was used without further purification in preparing **15**. A small sample of **13** was purified by bulb-to-bulb distillation and afforded a light yellow oil which had the following spectral characteristics: μ_{NH} 3470 and 3340, $\mu_{C=O}$ 1735 cm^{-1}; δ 1.70–2.50 (m, four protons), 2.93 (t, CH_2, J = 7 Hz), 3.66; 3.80, 3.83 (s, three OCH_3), 7.20–7.57 (m, phenyl protons), 9.50 (broad s, NH).

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.11; H, 5.81; N, 3.46.

Dimethyl 1-Methyl-5-(3-carbomethoxypropyl)pyrrole-3,4-dicarboxylate (14). Using the procedures described for the synthesis of **13**, reaction of **11d** (15.55 g, 0.072 mol), dimethyl acetylenedicarboxylate (12.8 g, 0.09 mol), and acetic anhydride (200 ml)

furnished **14** as a yellow oil: bp 196–198° (0.6 mmHg) (12.25 g, 57%); λ_{max} 258 mμ (log ε 3.90); $\mu_{C=O}$ 1735 cm^{-1}; δ 1.70–3.10 (m, six protons), 3.61 (s, CH_3N), 3.66, 3.78, 3.83 (s, three OCH_3), 7.08 (s, pyrrole ring proton).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.52; H, 6.24; N, 4.42.

Dimethyl 2-Phenyl-4-oxo-4,5,6,7-tetrahydroindole-3,5-dicarboxylate (15). To a suspension of sodium hydride (57% dispersion in mineral oil, 2.1 g, 0.05 mol, washed with pentane to remove the mineral oil) in distilled THF (50 ml) containing 0.2 ml of methanol, a solution of **13** (6.85 g, 0.019 mol) in distilled THF (25 ml) was added in dropwise portions over a 30-min period. The reaction mixture throughout this addition was kept under a nitrogen atmosphere and was stirred while the mixture was heated to reflux. Upon completion of the addition of **13**, the mixture was refluxed for an additional 3 hr, then cooled to 5° and acidified with acetic acid (20 ml) and water (200 ml). The aqueous mixture was extracted with chloroform (2 × 100 ml), and the combined organic extract was washed with brine (200 ml), dried (Na_2SO_4), and evaporated to dryness in vacuo. The brown tarry residue (6.05 g) was then chromatographed on a silica gel column (1000 g) and elution with 20% ethyl acetate–80% benzene furnished a brown semisolid (2.23 g) which was recrystallized from benzene–ether to give **15** as a colorless powder (0.93 g, 15%): mp 121–123°; μ_{NH} 3440 and 3300, $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 2.10–3.10 (m, four protons), 3.45 (t, CH, J = 6 Hz), 3.65 and 3.68 (s, two OCH_3), 7.30–7.50 (m, phenyl protons), 10.13 (broad s, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 66.11; H, 5.15; N, 4.25.

Dimethyl 1-Methyl-4-oxo-4,5,6,7-tetrahydroindole-3,5-dicarboxylate (16). Following the procedure described for the synthesis of **15**, reaction of **14** (4.5 g, 0.015 mol) with sodium hydride (57% dispersion, 2.1 g, 0.05 mol) in distilled THF (50 ml) containing 0.2 ml of methanol furnished a dark orange oil (5.20 g) which was chromatographed on a silica gel column (500 g). Elution of the column with 5% ethanol–95% benzene afforded **16** as a tan solid (1.85 g, 46%): mp 95–100°; $\mu_{C=O}$ 1735 and 1680 cm^{-1}; δ 2.30–3.00 (m, four protons), 3.50 (t, CH, J = 7.5 Hz), 3.56 (s, CH_3N), 3.71 and 3.78 (s, two OCH_3), 7.23 (s, indole ring proton).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.95; H, 5.85; N, 4.88.

Acknowledgment. The author wishes to thank Ms. Mary Anne Oram for technical assistance, Mr. Michael Scaros for carrying out the catalytic hydrogenation reactions, and the Searle Laboratories column chromatography group.

Registry No.—**1a**, 147-85-3; **16**, 535-75-1; **2a**, 54384-27-9; **2b**, 54383-97-0; **2b** dicyclohexylamine salt, 54383-98-1; **4a**, 54383-99-2; **4b**, 54384-00-8; **5a**, 54384-01-9; **5b**, 54384-02-0; **8a**, 56-40-6; **8b**, 56-41-7; **8c**, 69-91-0; **8d**, 107-97-1; **9a**, 1738-76-7; **9b**, 42854-62-6; **9c**, 54384-04-2; **9d**, 54384-06-4; **10a**, 54384-07-5; **10b**, 54384-28-0; **10c**, 54384-08-6; **10d**, 54384-09-7; **11a**, 54384-10-0; **11b**, 54384-29-1; **11c**, 54384-11-1; **11d**, 54384-12-2; **12**, 54384-13-3; **13**, 54384-14-4; **14**, 54384-15-5; **15**, 54384-16-6; **16**, 54384-17-7; methyl (4-chloroformyl)butyrate, 1501-26-4; dicyclohexylamine, 101-83-7; dimethyl acetylenedicarboxylate, 762-42-5; *p*-toluenesulfonic acid, 104-15-4; benzyl alcohol, 100-51-6.

References and Notes

(1) Portions of this material were presented at the Fourth International Congress on Heterocyclic Chemistry, Salt Lake City, Utah, July 1973, Paper D-12.
(2) R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schafer, *Chem. Ber.*, **103**, 2611 (1970).
(3) Recent examples of this reaction include the following: J. W. ApSimon, D. G. Durham, and A. H. Rees, *Chem. Ind. (London)*, 275 (1973); M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).
(4) J. W. Lown and B. E. Landberg, *Can. J. Chem.*, **52**, 798 (1974).
(5) R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 4600 (1960).
(6) J. R. McDermott and . L. Benoiton, *Can. J. Chem.*, **51**, 2562 (1973).
(7) H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 2356 (1970).
(8) M. Winitz, L. Bloch-Frankenthal, N. Izumiya, S. M. Birnbaum, C. G. Baker, and J. P. Greenstein, *J. Am. Chem. Soc.*, **78**, 2423 (1956).
(9) Obtained from Nutritional Biochemicals Corp.
(10) The presence of two signals for both the CH_3N and CH_2N protons is due to the restricted rotation of the tertiary amide group; H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

Rearrangement of Pyruvates to Malonates. Synthesis of β-Lactams

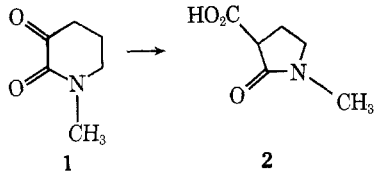
Dean R. Bender, Leonard F. Bjeldanes, Daniel R. Knapp, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received December 11, 1974

The oxidative rearrangement of α-ketoacyl derivatives to malonates has been extended to include a synthesis of β-lactams by oxidative (periodate) ring contraction of α-keto-γ-lactams. The rearrangement introduces a carboxyl group at the α carbon of the β-lactam and is capable of converting β-substituted α-keto-γ-lactams to the α,α-disubstituted ring-contracted derivatives. The application of the reaction to several simple mono- and bicyclic lactams is presented.

The fortuitous observation that periodate treatment of the δ-lactam 1-methyl-3-hydroxy-3-hydroxymethyl-2-piperidinone led to the formation of γ-lactam **2** was followed by the determination that the actual precursor of **2** was the α-keto-δ-lactam **1**.[1] The possibility that related acyclic derivatives might undergo a similar rearrangement was realized with the demonstration that α-keto esters and amides can be rearranged to malonates.[1] Rearrangement of the δ-lactam **1** to the ring-contracted derivative **2** also suggested



1 **2**

the possibility of extending the reaction to provide a synthesis of β-lactams. Formation of β-lactams by this ring-contraction reaction represents a potential synthesis of β-lactams containing either mono- or difunctionality at the α carbon, and the rearrangement conditions of periodate at room temperature and neutral pH suggested compatibility of the approach with the presence of a variety of substituents.

Examination of the numerous methods currently available for β-lactam synthesis[2] reveals that nearly all approaches require ring closure directly to the four-membered ring. Of the few methods utilizing ring expansion or ring contraction,[3] only the photolytic Wolff rearrangement of 3-diazo-2,4-pyrrolidinediones appears to have received more than passing attention.[3d,e] The potential advantages of β-lactam formation by ring contraction under mild and