J = 7 Hz), 4.58 (1 H, s), 7.7–8.2 (1 H, br N–H); IR (NaCl) 3375 (s, weak), 3020, 2980, 1700 (strong), 1600 cm^{-1} (strong).

Anal. Calcd for $C_8H_{13}O_2N$: C, 61.94; H, 8.39; O, 20.64; N, 9.03. Found: C, 61.95; H, 8.41; O, 20.61; N, 9.03.

Preparation of Diester 4. *n*-Butyllithium/hexane (102 mL of 2.3 N, 234 mmol) was added dropwise to a flame-dried 1000-mL three-neck flask containing diisopropylamine (25.6 g, 254 mmol) and 700 mL of THF at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was cooled to −78 °C and enamine ester **3** (30.2 g, 195 mmol) in 100 mL THF was added dropwise over 40 min followed by a 30-min stirring period. Ethyl bromoacetate (48.8 g, 293 mmol) was added and stirring was continued for 2 h. The reaction mixture was allowed to warm to 0 °C for 2 h and acidified with 5% HCl. The THF was removed with a rotary evaporator and the residue was washed twice with ether. The aqueous layer was neutralized with excess solid $NaHCO_3$ and then extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were washed twice with brine, dried over $MgSO_4$, and concentrated to give the diester as a brown solid (34.7 g, 74%). This material is adequate for the cyclization to **5** but can be recrystallized from $CHCl_3$/hexane to give analytically pure material: mp 96.5–98 °C; NMR ($CDCl_3$) 1.3 (6 H, t, J = 7 Hz), 1.8–2.3 (2 H, m), 2.7 (2 H, t, J = 7 Hz), 3.25 (2 H, s), 3.6 (2 H, t, J = 7 Hz), 4.2 (4 H, q, J = 7 Hz), 8.1–8.5 (1 H, br s); IR (KBr) 3350 (w), 1720, 1655, 1580 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}O_4N$: C, 59.50; H, 7.85; O, 26.45; N, 6.2. Found: C, 59.87; H, 8.02; O, 26.36; N, 5.75.

Preparation of Lactam 5. Potassium hydride (6.5 g, 39 mmol, of a 24% oil dispersion) was washed four times with benzene in a flame-dried 500-mL three-neck flask and then suspended in 150 mL of anhydrous THF at 0 °C. The diester **4** (7.23 g, 30.0 mmol) in 70 mL of THF was added over a 20-min period and the reaction mixture was stirred at 0 °C for another 25 min. Aqueous 10% HCl was added to pH 6 and the THF was removed with a vacuum pump. The residue was dissolved in 50 mL of water and extracted with three 50-mL portions of $CHCl_3$. The combined $CHCl_3$ layers were washed with water (2 × 250 mL), dried over $MgSO_4$, and concentrated to give the lactam (5.67 g, 97%) as a light brown solid. Recrystallization from $CHCl_3$/hexane gave an analytical sample: mp 88–89 °C; NMR ($CDCl_3$) 1.3 (3 H, t, J = 7 Hz), 2.2–2.6 (2 H, m), 2.8–3.2 (2 H, m), 3.5–3.8 (4 H, m), 4.3 (2 H, q, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.702, 163.553, 161.485, 98.800, 59.620, 41.514, 41.210, 26.640, 25.664, 14.569.

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 61.54; H, 6.67; O, 24.61; N, 7.18. Found: C, 61.61; H, 6.70; O, 24.49; N, 7.20.

Reduction of Lactam 5 to Lactam 6. Lactam **5** (1.16 g, 6.00 mmol) was dissolved in 15 mL of absolute ethanol and a catalytic amount of 10% Pd/C was added. This was maintained under hydrogen at 1 atm and room temperature overnight (20 h) and filtered through celite and the filtrate was concentrated to give 1.15 g (98%) of the lactam: bp 164–165 °C (0.1 mm); NMR ($CDCl_3$) δ 1.3 (3 H, t, J = 7 Hz), 1.7–2.4 (4 H, m), 2.7–2.9 (2 H, unsym d, J = 6 Hz), 3.0–3.9 (3 H, m), 4.0–4.4 (3 H, q and m, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 174.039, 171.600, 62.729, 60.961, 41.697, 39.868, 36.089, 27.432, 26.432, 14.260; IR (NaCl) 2970, 2900, 1730, 1690, 1190 cm^{-1}.

Preparation of Isoretronecanol (1). Lactam **6** (0.788 g, 4.00 mmol) in 5 mL of THF was added over a 5-min period to a flame-dried 50-mL three-neck flask containing $LiAlH_4$ (0.304 g, 8.00 mmol) in 10 mL of THF. The reaction mixture was refluxed for 17 h and the THF was removed by distillation. Ether (10 mL) and water (0.66 mL) were added and the mixture was stirred for 8 h. This was filtered and the filtrate was concentrated and distilled to give 0.35 g (62%) of isoretronecanol as a clear liquid: bp 120–123 °C (0.1 mm); picrate mp 188–189 °C (lit.[10] mp 188–190 °C); NMR ($CDCl_3$) δ 1.4–2.2 (6 H, m), 2.3–2.6 (6 H, m), 3.8 (2 H, d, J = 7 Hz), 4.0–4.5 (1 H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 66.131, 62.571, 55.597, 54.036, 44.379, 27.310, 26.481, 25.945.

Preparation of Ethyl Isoretronecanolate 7. Lactam **6** (1.15 g, 5.80 mmol) was mixed in a flame-dried three-neck flask with phosphoryl chloride (6 mL) at room temperature for 40 min. Excess $POCl_3$ was removed under vacuum and the residue was dissolved in 4 mL of dimethoxyethane at 0 °C. Sodium borohydride (0.444 g, 11.6 mmol) in 18 mL of absolute ethanol was added at such a rate that the reaction remained vigorous. The reaction mixture was allowed to warm up to room temperature for 30 min and then acidified to pH 2 with 5% HCl. The ethanol was removed (rotary evaporator), the reaction mixture was stirred for 30 min, and 25 mL of water was added. This was extracted with three 10-mL portions of ether and the aqueous phase was basified to pH 9 at 0 °C with solid K_2CO_3 and extracted with four 15-mL portions of ether. The combined ether layers were washed with water, dried over $MgSO_4$, concentrated, and distilled to give ethyl isoretronecanolate (0.70 g, 66%) as a clear liquid: bp 113–115 °C (0.1 mm); picrate mp 120–121 °C (lit.[11] mp 119–121 °C); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.8–2.2 (7 H, m), 2.6–3.4 (4 H, m), 3.5–3.9 (1 H, m), 4.2 (2 H, q, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.369, 65.838, 60.181, 55.584, 53.695, 47.452, 28.481, 26.774, 26.384, 14.289.

Registry No.—1, 18929-90-3; 1·picrate, 61259-90-3; **2**, 18929-91-4; **3**, 25219-53-8; **4**, 67800-66-2; **5**, 67800-67-3; **6**, 67800-68-4; **7**, 34951-60-5; **8**, 34951-61-6; thiopyrrolidone, 2295-35-4; ethyl[(3,4-dihydro-2*H*-pyrrol-5-yl)thio]acetate, 4226-71-5; phosphorus pentasulfide, 1314-80-3; pyrrolidone, 616-45-5; ethyl bromoacetate, 105-36-2.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of Yeong-Ho Chang, University of Georgia, 1978.
(2) Presented at the 30th Southeastern Regional Meeting of the American Chemical Society, Savannah, Ga., Nov. 8–10, 1978.
(3) For example, see the following: (a) N. J. Leonard and T. Sato, *J. Org. Chem.*, **34**, 1066 (1969); (b) R. V. Stevens, Y. Luh, and J. T. Sheu, *Tetrahedron Lett.*, 3799 (1976); (c) S. Danishefsky, R. McKee, and R. K. Singh, *J. Am. Chem. Soc.*, **99**, 4783 (1977).
(4) (a) F. L. Warren in "The Alkaloids-Chemistry and Physiology", Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, 1970, p 319; (b) D. H. G. Crout in "The Alkaloids", Vol. 6, The Chemical Society, London, 1976, p 84; (c) W. M. Hoskin and D. H. G. Crout, *J. Chem. Soc., Perkin Trans. 1*, 538 (1977); (d) E. G. C. Clarke in "The Alkaloids-Chemistry and Physiology", Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, 1970, p 518.
(5) M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).
(6) Unfortunately, ethylene dibromide fails to react with the anion of **3**.
(7) S. Brandange and C. Lundin, *Acta Chem. Scand.*, **25**, 2447 (1971).
(8) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964); M. J. Kornet, P. A. Thio, and S. I. Tan, *J. Org. Chem.*, **33**, 3637 (1968).
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(11) M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).

New Reactions and Reagents. 7. Unusual Reactivity of *N*-Iminoglycyl Peptides. Formation of Substituted Imidazol-4-ones[1]

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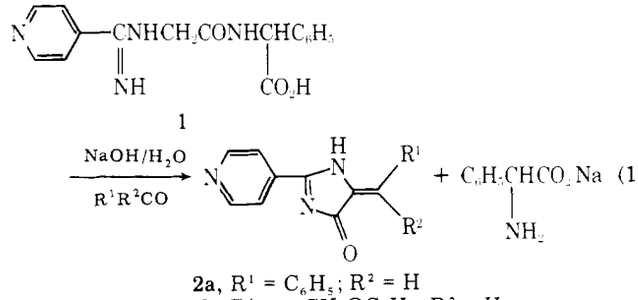
N-(4-Pyridylimino)glycylphenylglycine (**3**) undergoes a novel fragmentation in aqueous alkaline medium which in the presence of a carbonyl compound proceeds to give the corresponding 1,5-dihydro-2-(4-pyridyl)-5-(alkyl- or arylmethylene)-4*H*-imidazol-4-one (**2**) and phenylglycine (eq 1). The structure of **2a–d** is based on IR (–CO–, ~1700 cm^{-1}; –C=N–,



2a, R^1 = C_6H_5; R^2 = H
b, R^1 = *p*-$CH_3OC_6H_4$; R^2 = H
c, R^1 = R^2 = CH_3
d, R^1, R^2 = –$(CH_2)_5$–

~1650 cm^{-1})[2] and ^1H NMR, as well as mass spectral (Table I) and ^{13}C-NMR (Table II) assignments.[3] The formation of **2** from **1** is most likely occurring via the generation of 1,5-dihydro-2-(4-pyridyl)-4*H*-imidazol-4-one (**6**)[4] and its subsequent reaction with the added carbonyl compound (Scheme I).[5,6] It is worthy of note that only one stereoisomer is isolated in the case of **2a,b**.[7] The *Z* stereochemistry assigned for these two compounds is based on close agreement between the calculated and observed shifts for their olefinic protons.[8]

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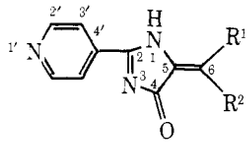
0022-3263/78/1943-4663$01.00/0

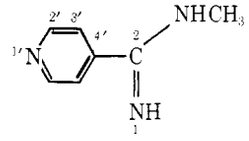
Table I. Characterization Data of 2

compd	mp, °C	IR (KBr), cm^{-1}	^1H NMR, δ (Me_2SO-d_6, Me_4Si)	mass spectrum, *m/e* (ion formula, rel intensity)	anal. calcd	anal. found
2a	267–69	3390, 3030, 1695, 1639, 1600, 1439, 1266, 1205, 938, 897, 775	6.96 (s, 1 H), 7.28 (poor t, 6 H), 7.86 (d, 2 H, J = 6 Hz), 8.13 (pair d, 4 H, J = 6 Hz), and 8.63 (d, 2 H, J = 7 Hz)	249.0915 ($C_{15}H_{11}N_3O$, 52), 117.0583 (C_8H_7N, 100), 105.0446 ($C_6H_5N_2$, 52), 104.0386 ($C_6H_4N_2$, 4), 90.0468 (C_7H_6, 22), 89.0390 (C_7H_5, 19), 78.0338 (C_5H_4N, 30), 51.0236 (C_4H_3, 34)	C 72.28 H 4.41 N 16.86	C 71.70 H 4.37 N 17.11
2b	282–84	3390, 3030, 1695, 1639, 1600, 1515, 1439, 1307, 1266, 1250, 1170, 1026, 940, 826	3.85 (s, 3 H), 7.06 (d, 2 H, J = 8 Hz), 7.11 (s, 1 H), 8.03 (d, 2 H, J = 6 Hz), 8.36 (d, 2 H, J = 8 Hz), and 8.86 (d, 2 H, J = 6 Hz)	280 (18), 279 (100), 147 (99), 132 (57), 105 (55), 104 (16), 78 (32), 51 (30), 44 (28), 40 (22)	C 68.80 H 4.60 N 15.00	C 68.31 H 4.52 N 14.43
2c	209–11	3077, 1704, 1653, 1613, 1445, 1282, 1235, 1170, 925, 833, 790	2.26 (s, 3 H), 2.38 (s, 3 H), 3.6 (br, 1 H), D_2O exch.), 7.8 (d, 2 H, J = 6 Hz), and 8.6 (d, 2 H, J = 6 Hz)	201.0874 ($C_{11}H_{11}N_3O$, 100), 105.0452 ($C_6H_5N_2$, 61), 104.0379 ($C_6H_4N_2$, 6), 78.0334 (C_5H_4N, 32), 69.0571 (C_4H_7N, 70), 68.0494 (C_4H_6N, 18), 54.0222 ($C_2H_2N_2$, 16)	C 65.67 H 5.47 N 20.89	C 65.96 H 5.49 N 20.80
2d	244–46	3390, 3077, 2741, 2857, 1695, 1639, 1600, 1449, 1290, 1227, 1045, 930, 833	1.66 (br, 8 H), 3.23 (br m, 2 H), 4.86 (br s, 1 H, D_2O exch.), 8.06 (d, 2 H, J = 6 Hz), and 8.73 (d, 2 H, J = 6 Hz)	241.1208 ($C_{14}H_{15}N_3O$, 62), 240.1115 ($C_{14}H_{14}N_3O$, 46), 213.0904 ($C_{12}H_{11}N_3O$, 38), 187.0752 ($C_{10}H_9N_3O$, 52), 174.0672 ($C_9H_8N_3O$, 50), 161.0592 ($C_8H_7N_3O$, 40), 106.0547 ($C_6H_6N_2$, 100), 105.0444 (C_6H_5N, 78), 104.0402 ($C_6N_4N_2$, 62), 81.0623 (C_5H_7N, 76)	C 69.71 H 6.22 N 17.43	C 69.33 H 6.45 N 17.47

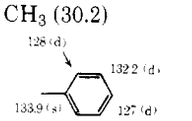
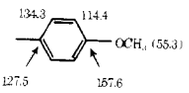
Table II. ^{13}C Chemical Shifts of 2 and Related Model 3[a]



2

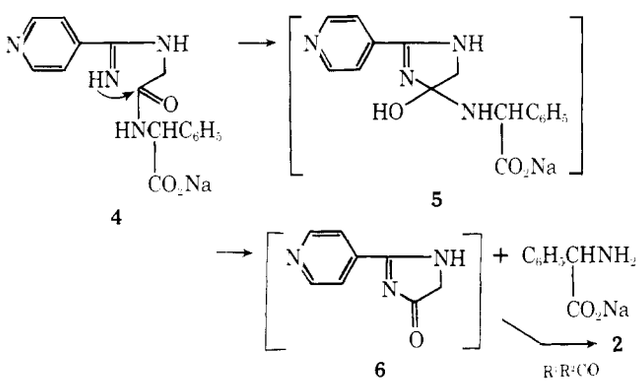


3

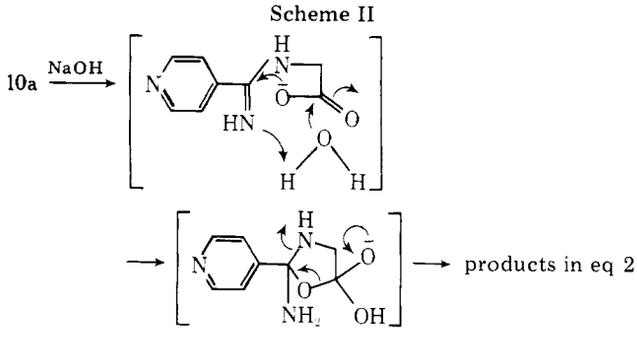
compd	registry no.	C_2	C_4	C_5	C_6	C_2'	C_3'	C_4'	R^1; R^2 substitution
3	67722-39-8	163.3				150.8	122.8	137.7	CH_3 (30.2)
2a	67722-40-1	159 (s)	171 (s)	139.9 (s)	130.3 (d)	150.4 (d)	120.6 (d)	134.9 (s)	
2b	67722-41-2	161.1	171.2	126.6	138	150.3	120.4	135.1	
2c	67722-42-3	153 (s)	169.6 (s)	135.6 (s)	150.5 (s)	150.3 (d)	120.2 (d)	137.8 (s)	CH_3 (19.1, q); CH_3 (22.3, q)
2d	67722-43-4	169.9	170.3	120.2	161.6	150.2	120.4	135.3	not assigned

[a] In ppm downfield relative to Me_4Si in $CDCl_3$ as solvent; ^1H–^{13}C coupling multiplicities are indicated in parentheses.

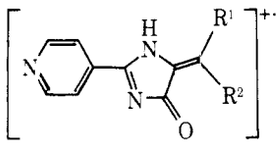
Scheme I



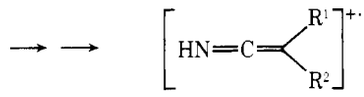
Scheme II



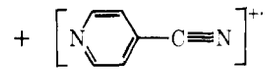
The mass spectral fragmentation of **2a–d** reveals certain interesting characteristics. **2a–c** fragment to provide aza-



[2a]$^+$; *m/e* 249.0915 ($C_{15}H_{11}N_3O$)
[b]$^+$; *m/e* 279
[c]$^+$; *m/e* 201.0874 ($C_{11}N_{11}N_3O$)

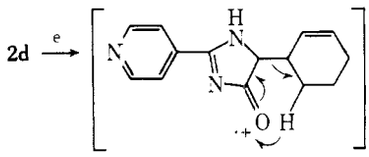


7a, *m/e* 117.0583 (C_8H_7N)
b, *m/e* 147
c, *m/e* 69.0571 (C_4H_7N)

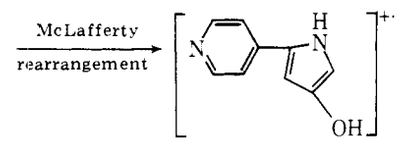


7a, *m/e* 104.0386 ($C_6H_4N_2$)
b, *m/e* 104
c, *m/e* 104.0379 ($C_6H_4N_2$)

ketenes (**7a–c**) as the major ions.[10] However, **2d** presumably undergoes a rearrangement preceding electron-impact-induced fragmentation transposing the exocyclic double bond to the energetically more favorable endocyclic position of the cyclohexyl moiety to first give **8**. A McLafferty-type fragmentation of **8** subsequently leads to the formation of cation radical **9** (or radical ion tautomer of **6**).

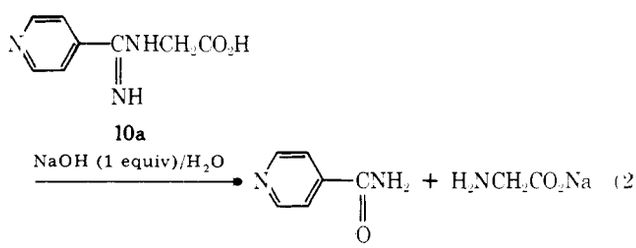


8
m/e 241.1208 ($C_{14}H_{15}N_3O$)



9
m/e 161.0592 ($C_8H_7N_3O$)

In sharp contrast to the reactivity of *N*-iminoglycyl peptides, simpler *N*-iminoglycines undergo a cleavage of –CN– bond to produce glycine and the corresponding amide (eq 2)



10a

as the major products. Although a detailed mechanistic probe of the latter reaction was not undertaken, the intramolecular participation of carboxyl group appears to be a reasonable process (Scheme II) in this hydrolysis.[11]

Experimental Section[12]

***N*-(Pyridylimino)glycines.** The preparation of **1** is illustrative of the general procedure. A mixture of glycyl-R-2-phenylglycine[13] (40 g, 192 mmol), sodium hydroxide (7.7 g, 192 mmol), and methanol (200 mL) was stirred for 15 min at 25 °C. To the resulting clear solution, methyl isonicotinimidate[14] (28.7 g, 211 mmol) was added and the stirring continued for 2 h. Hydrobromic acid (48%, 22.2 mL) was then added and the product filtered after granulation to give 52.8 g (80%) of *N*-(4-pyridylimino)glycyl-R-2-phenylglycine (**2**) as its methanol solvate: mp 172–176 °C dec; $[\alpha]^{25}_D$ −145.1 (1 N HCl, *c* 1); NMR (Me_2SO-d_6) δ 3.4 (s, 3 H), 4.20 (br s, 2 H), 5.15 (d, 1 H, *J* = 7 Hz), 7.25 (m, 5 H), 7.66 (d, 2 H, *J* = 6 Hz), 8.3 (d, 2 H, *J* = 6 Hz).

Anal. Calcd for $C_{16}H_{16}N_4O_3 \cdot CH_3OH$: C, 59.30; H, 5.81; N, 16.27. Found: C, 59.24; H, 5.66, N, 16.34; Br, 0.11.

***N*-(4-Pyridylimino)glycine (10a)** was similarly obtained in 87% yield: mp 215–220 °C dec; NMR (Me_2SO-d_6) δ 4.15 (s, 2 H), 8.0 (d, 2 H, *J* = 6 Hz), 8.63 (d, 2 H, *J* = 6 Hz); mass spectrum[15] *m/e* 179.0684 ($C_8H_9N_3O_2$), 134.0716 ($C_7H_8N_3$), 133.0642 ($C_7H_7N_3$), 106.0503 ($C_6H_6N_2$), 105.0447 ($C_6H_5N_2$), 104.0370 ($C_6H_4N_2$), 79.0411 (C_5H_5N), 78.0346 (C_5H_4N), 76.0192 (C_5H_2N).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.02; N, 23.46. Found: C, 53.89; H, 4.95; N, 23.08.

***N*-(2-Pyridylimino)glycine (10b)** was obtained in 83% yield by evaporation of the solvent from the reaction mixture (after the addition of 48% HBr, see preparation of **1**) to an oil and then granulation with acetone: mp 210–215 °C dec; NMR (CF_3CO_2D) δ 4.75 (s, 2 H), 8.13–9.26 (m, 4 H); mass spectrum[15] *m/e* 179.0707 ($C_8H_9N_3O_2$), 161.0589 ($C_8H_7N_3O$), 134.0718 ($C_7H_8N_3$), 106.0502 ($C_6H_6N_2$), 104.0369 ($C_6H_4N_2$), 79.0419 (C_5H_5N), 78.0342 (C_5H_4N), 76.0192 (C_5H_2N).

Anal. Calcd for $C_8H_9N_3O_2 \cdot H_2O$: C, 48.73; H, 5.58; N, 20.31. Found: C, 48.29; H, 5.50; N, 20.63.

***N*-(4-Pyridylimino)-R-2-phenylglycine (10c)** was obtained in 98% yield, based on recovered (33%) R-2-phenylglycine, by the procedure used for **10b.** The product was recrystallized from methanol–water as white cubes: mp 280–285 °C dec; $[\alpha]^{25}_D$ −112.8 (CH_3OH, *c* 1); NMR (CF_3CO_2D) δ 6.01 (s, 1 H), 7.6 (s, 5 H), 8.7 (d, 2 H, *J* = 6 Hz), 9.33 (d, 2 H, *J* = 6 Hz); mass spectrum[15] *m/e* 237.0890 ($C_{14}H_{11}N_3O$), 211.1114 ($C_{13}H_{13}N_3$), 210.1044 ($C_{13}H_{12}N_3$), 194.0869 ($C_{13}H_{10}N_2$), 105.0465 ($C_6H_5N_2$), 104.0469 (C_7H_6N), 91.0523 (C_7H_7), 78.0374 (C_5H_4N), 65.0411 (C_5H_5).

Anal. Calcd for $C_{14}H_{13}N_3O_2 \cdot H_2O$: C, 61.53; H, 5.49; N, 15.38. Found: C, 61.14; H, 5.52; N, 15.42.

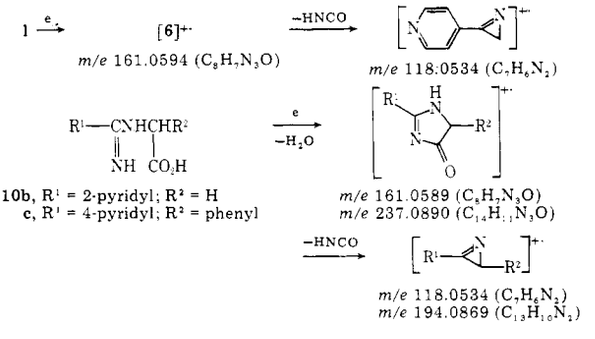
1,5-Dihydro-2-(4-pyridyl)-5-(alkyl- or arylmethylene)-4*H*-imidazol-4-ones (2). The preparation of **2a** is exemplified here. A mixture of **1** (62.4 g, 181 mmol), benzaldehyde (20 mL), water (200 mL), and sodium hydroxide (7.24 g, 181 mmol) was stirred at 25 °C for 24 h. 1,5-Dihydro-2-(4-pyridyl)-5-(phenylmethylene)-4*H*-imidazol-4-one (**2a**) was obtained as a light green crystalline material, yield 7.1 g (15.7%). The analysis of the filtrate (TLC, LC) showed the presence of 2-phenylglycine.

Compounds **2b–d** (Table I) were obtained in an analogous manner in 10–25% yields, which were not optimized.

Registry No.—**1**, 65566-05-4; **6**, 67722-44-5; **10a**, 64263-60-1; **10b**, 67722-48-9; **10c**, 67722-49-0; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; acetone, 67-64-1; cyclohexanone, 108-94-1.

References and Notes

(1) Part 6. S. K. Gupta, *Synthesis*, 39 (1977).
(2) G. Tacconi, L. D. Maggi, P. Righetti, G. Desimoni, O. Azzolina, and V. Ghislandi, *J. Chem. Soc., Perkin Trans. 2*, 150 (1976); G. Desimoni, A. Gamba, M. Monticelli, M. Nicola, and G. Tacconi, *J. Am. Chem. Soc.*, **98**, 2947 (1976); Y. S. Rao, *J. Org. Chem.*, **41**, 722 (1976).
(3) ^{13}C assignments were in fair agreement with the values reported for appropriate model systems; e.g., cinnamic acid moiety: C. J. Kelley, R. C. Harruff, and M. Carmack, *J. Org. Chem.*, **41**, 449 (1976); pyridine moiety: T. Drakenberg, *J. Chem. Soc., Perkin Trans. 2*, 147 (1976); benzene moiety: G. A. Olah and S. H. Yu, *J. Org. Chem.*, **41**, 717 (1976); J. Bromilow, R. T. C. Brownlee, R. D. Topsom, and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 2020 (1976).
(4) Attempts to isolate **6** from the reaction mixtures (reactions carried out with or without the addition of carboyl compound) by TLC and LC techniques were not successful; reactions in the absence of carbonyl compound gave a complex mixture from which only unreacted **1** was isolated. The formation of **6** as its cation radical was, however, detected in the electron-impact-induced fragmentation of **1** and other model *N*-iminoglycines:



(5) 2-Arylimidazol-4-ones analogous to **6** have been shown to be reactive intermediates in the following reports: (a) A. Kjaer, *Acta Chem. Scand.*, **7**, 1030 (1953); (b) T. Wieland and H. Biener, *Tetrahedron*, **15**, 1 (1961); (c) W. Ried and W. von der Emden, *Justus Liebigs Ann. Chem.*, **661**, 76 (1963); (d) I. Kh. Fel'dman, Yu. Ya. Usaevich, and E. I. Boksiner, *Zh. Obshch. Khim.*, **37**, 1246 (1967); (e) T. Wang, *J. Org. Chem.*, **39**, 3591 (1974).

(6) A related cyclization of *N*-acetylglycyl peptides to give oxazoles has recently been reported: R. G. Harrison, M. R. J. Jolley, and J. C. Saunders, *Tetrahedron Lett.*, 293 (1976).

(7) The synthesis of compounds analogous to **2** via an alternate route has recently been reported: G. M. Devasia, *Tetrahedron Lett.*, 571 (1976). The stereochemistry of the compounds obtained was, however, not reported.

(8) The calculated[9] values are: *Z* stereoisomer = δ 6.83; *E* stereoisomer = δ 6.17. Experimentally determined values are: **2a** = δ 6.96; **2b** = δ 7.11. See also A. Maquestiau, Y. Van Haverbeke, and R. N. Muller, *Bull. Soc. Chim. Belg.*, **83**, 259 (1974); *Chem. Abstr.*, **82**, 42895u (1975).

(9) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon, New York, 1969, p 184.

(10) For an earlier mass spectral study of imidazolones, see J. A. Ballantine and R. G. Fenwick, *Org. Mass. Spectrom.*, **5**, 615 (1971).

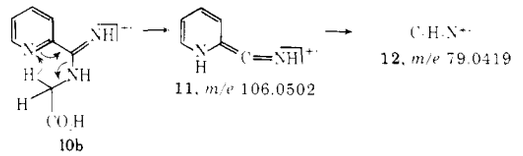
(11) For an analogous participation by carboxyl group, see J. H. Smith, *J. Am. Chem. Soc.*, **98**, 3598 (1976); M. K. Priebat and L. Chauffe, *J. Org. Chem.*, **41**, 3914 (1976).

(12) For details regarding instrumentation used, see S. K. Gupta, *J. Org. Chem.*, **41**, 2642 (1976).

(13) Glycyl-R-2-phenylglycine was obtained by reacting chloroacetyl chloride with R-2-phenylglycine in water (pH 11.5–12.5) followed by acidification to first give *N*-(2-chloroacetyl)-R-2-phenylglycine (85%), mp 99–101 °C, $[\alpha]^{25}_D$ −178 (CH_3OH, *c* 1). The aminolysis of the latter with NH_4OH gave the desired compound (80%), mp 235–237 °C $[\alpha]^{25}_D$ −189 (1 N HCl, *c* 1).

(14) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. III, Academic Press, New York, 1972, p 268. The base-catalyzed addition of methanol to 2- and 4-cyanopyridines was effected in the present study with an anion-exchange resin (Rexyn-201, HO-form, 2–10% w/w). The filtration of the catalyst followed by displacement of excess methanol with hexane gave the desired imidates in 90–95% yield.

(15) The ionization of **10b** to give ions **11** and **12** was indeed observed.[16]



Although **10c** and **1** did not give ion **11**, the formation of *m/e* 106.0503 ($C_6H_6N_2$) ion in the case of **10a** and *m/e* 106.0547 ($C_6H_6N_2$, **11**) ion in the case of **2d** was unexpected.[16]

(16) P. H. Chen, *J. Org. Chem.*, **41**, 2973 (1976).

New Synthesis of Azaserine

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There has been a recent resurgence of interest in the antibiotic azaserine [*O*-(diazoacetyl)-L-serine, **4**]. Rats receiving repeated doses of this cytotoxic amino acid develop a high incidence of tumors of the exocrine pancreas, thus providing one of the first useful animal models of pancreatic cancer.[1,2] Moreover, interest in azaserine as an antitumor agent has been continuous since the late 1950's,[3] and two phase I clinical trials of this drug have been recently completed.[4,5] When studies in our laboratory of the mechanism of azaserine carcinogenesis required radiochemically labeled compound, we were prompted to reexamine the synthesis of azaserine, with the results reported in this note.

Published syntheses of azaserine converge on the same penultimate intermediate, *O*-(glycyl)-L-serine, which is converted by nitrous acid to the final product.[6–8] The yield in the nitrosation step is low, and azaserine must be isolated from the reaction mixture by carbon column chromatography. Attempts by Buchanan and co-workers to prepare ^{14}C-labeled azaserine by these procedures led to a 6% yield of material with only 50% radiochemical purity.[9] Neither the overall yield nor purity of this product was judged satisfactory for the synthesis of the large amount of pure radiochemical necessary for our work. Our attempts to improve the yield in the nitrosation step by varying reaction time, stoichiometry, pH, and temperature were without issue. In all cases yields of azaserine, as determined by TLC and by NMR spectroscopy, were uniformly low. Reasoning that the low yields in this step might arise from competing reaction of the serine amino group with nitrous acid, a new synthesis was sought in which a suitable blocking group would prevent the offending amino nitrogen from reacting. The sensitivity of azaserine toward light, heat, and extremes of pH[10,11] placed rather stringent requirements on the blocking group. It would have to be stable enough to survive several synthetic operations, yet be removable under very mild conditions. These requirements suggested the use of a group removable by enzymatic means, with trifluoroacetyl as a promising candidate. Trifluoroacetylamides are stable to a number of different reaction conditions, while those derived from α-amino acids undergo very rapid hydrolysis catalyzed by acylase I at neutral pH.[12] From these considerations a new synthesis of azaserine, shown in Scheme I, was developed.

Scheme I

$$\underset{\mathbf{1}}{HOCH_2CH(NHCOCF_3)CO_2CH_2Ph} \xrightarrow[4\text{-DMAP}]{ZNHCH_2CO_2COCMe_3} \underset{\mathbf{2}}{ZNHCH_2CO_2CH_2CH(NHCOCF_3)CO_2CH_2Ph}$$

$$\xrightarrow[\text{aq MeOAc}]{H_2\text{-Pd/C}} \underset{\mathbf{3}}{H_3N^+CH_2CO_2CH_2CH(NHCOCF_3)CO_2^-}$$

$$\xrightarrow[2.\ \text{acylase I}]{1.\ LiNO_2,\ ClCH_2CO_2H} \underset{\mathbf{4}}{N_2CHCO_2CH_2CH(NH_3^+)CO_2^-}$$

The serine component for the synthesis, *N*-(trifluoroacetyl)-L-serine benzyl ester (**1**), was prepared from *N*-(trifluoroacetyl)-L-serine, triethylamine, and benzyl bromide in DMF. Esterification of **1** by benzyloxycarbonylglycine was best accomplished by allowing the protected serine derivative to react in the presence of 4-dimethylaminopyridine[13] with the mixed anhydride formed from benzyloxycarbonylglycine, pivaloyl chloride, and *N*-methylmorpholine. Other coupling procedures such as the use of *N,N'*-dicyclohexylcarbodiimide with various additives, benzenesulfonyl chloride in the presence of pyridine, and carbonate mixed anhydrides proved less effective. Although previous workers have synthesized azaserine from serine components with free carboxyl groups,[6–8] we found it advantageous to block this group as the benzyl ester, hence our choice of **1** as a starting material. The yield in the coupling step appeared to improve, and the ester **2**, as the only neutral product, was more readily isolated from the reaction mixture. Hydrogenolysis of **2** to form the amino acid **3** was best conducted over a palladium on charcoal catalyst using aqueous methyl acetate as solvent. This unconventional choice of solvent was made to facilitate isolation of the hydrolytically labile product **3**. After filtration of the hydrogenation reaction mixture to remove catalyst, methyl acetate was removed in vacuo at room temperature, and the resulting aqueous solution lyophilized to give **3**.

The last two steps of the synthesis were carried out without isolating the intermediate diazoacetyl compound. Exposure of **3** to aqueous lithium nitrite in the presence of a catalytic amount of chloroacetic acid smoothly coverted the *O*-glycyl residue to diazoacetyl.[14] After adjusting the pH to 7.3 with Tris buffer, acylase I was added to catalyze hydrolysis of the intermediate trifluoroacetylamide. Azaserine was isolated from the lyophilized reaction mixture by trituration with alcohol and recrystallization of the insoluble fraction from aqueous alcohol. No chromatography was necessary. Although intermediates **2** and **3** are solids which may be recrystallized, if desired, the whole synthetic sequence may advantageously be conducted with only minimal purification of intermediates.

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