mixture was cooled to 0 °C and washed four times with 15 mL of dry ether to yield 2.0 g (72%) of colorless crystals: mp 163–164 °C (from benzene–cyclohexane); IR (Nujol) 3180 cm^{-1} (N-H); UV λ_{max} (log ϵ) ($CHCl_3$) 273 (4.12), 277 (4.15), 281 (4.17), 288 (4.02), 294 (3.90), 305 nm (3.59); ^1H NMR ($CDCl_3$) δ 3.56 (s, 2), 7.2–8.3 (m, 8); ^{13}C NMR ($CDCl_3$) δ 136.22, 134.53, 133.68, 132.54, 130.98, 127.76 (12 C, aromatic) 41.88 (2 C, CHNH); MS (relative intensity) *m/e* 193 (M^+, 100), 192 (11.6), 178 (34.0), 176 (9.6), 165 (74.0), 152 (6.4), 151 (3.6), 150 (3.2), 139 (6.4), 127 (5.2), 89 (5.2), 76 (6.0). Anal. Calcd for $C_{14}H_{11}N$: C, 87.0; H, 5.7; N, 7.3. Found: C, 87.3; H, 5.9; N, 7.0.

B. A solution of 0.942 g (2 mmol) of **12** in 100 mL of CH_2Cl_2 was refluxed for 15 min. The solvent was distilled, and most of the triphenylphosphine oxide was removed by extraction with ether (3 × 25 mL). The residue was dissolved in 2 mL of CH_2Cl_2 and purified by two dimensional PLC on alumina (5:1 hexane–ether eluent). In the best run we obtained 0.234 g of **13** (85% purity). Further purification by PLC and by recrystallization was associated with significant losses.

Conversion of 13 into 9-Aminophenanthrene (14). A mixture of 50 mg of the previous imine and 2 mL of 15% aqueous HCl was refluxed for 10 min. After cooling, 5 mL of benzene was added and the acid was neutralized with NaOH. The organic layer was dried and concentrated. The residue proved to be pure **14**, which was identical with an authentic sample prepared according to Schmidt and Heinle.[19]

Deamination of 13. A mixture of 0.97 g (5 mmol) of **13**, 6.4 g (50 mmol) of isoamyl nitrite, and 1.5 mL of triethylamine was stirred for 45 min at room temperature. Extraction with benzene and column chromatography on alumina afforded 0.63 g (71%) of phenanthrene.

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Registry No.—**2**, 67364-41-9; **3**, 1499-00-9; **4**, 1689-71-0; **5**, 1439-07-2; **6**, 67464-42-0; **7**, 67464-43-1; **8**, 1605-06-7; **9**, 25125-72-8; **10**, 585-08-0; **11**, 53581-32-1; **12** (uncharged), 67464-44-2; **12** (charged), 67464-45-3; **13**, 67464-46-4; **14**, 947-73-9.

References and Notes

(1) Department of Organic Chemistry.
(2) The Casali Institute of Applied Chemistry.
(3) Y. Ittah, I. Shahak, and J. Blum, *J. Org. Chem.*, **43**, 397 (1978).
(4) See, e.g., D. Avnir and J. Blum, *J. Heterocycl. Chem.*, **13**, 619 (1976), and ref 1 and 2 therein.
(5) W. E. McEwen, W. E. Conrad, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **74**, 1168 (1952).
(6) K. Shudo and T. Okamoto, *Chem. Pharm. Bull.*, **24**, 1013 (1976).
(7) For the stereochemical course of epoxide cleavage by sodium azide, see, e.g., C. A. VanderWerf, R. Y. Heisler, and W. E. McEwen, *J. Am. Chem. Soc.*, **76**, 1231 (1954).
(8) A. Hassner and J. E. Galle, *J. Am. Chem. Soc.*, **92**, 3733 (1970).
(9) For a discussion on benzene imine–azepine valence tautomerism, see, e.g., L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, **10**, 11 (1971).
(10) J. H. D. Eland and C. T. Danby, *J. Chem. Soc.*, 5935 (1965).
(11) J. Blum, Y. Ittah, and I. Shahak, *Tetrahedron Lett.*, 4607 (1975).
(12) M. S. Newman and S. Blum, *J. Am. Chem. Soc.*, **86**, 5598 (1964).
(13) R. M. Carlson and S. Y. Lee, *Tetrahedron Lett.*, 4001 (1969).
(14) H. Staudinger and M. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(15) See, e.g., G. L'abbé, *Ind. Chim. Belge*, **34**, 519 (1968).
(16) S. J. Boris, *J. Org. Chem.*, **27**, 3532 (1962).
(17) A. Hassner, G. J. Matthews, and F. W. Fowley, *J. Am. Chem. Soc.*, **91**, 5046 (1969).
(18) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).
(19) J. Schmidt and E. Heinle, *Ber.*, **44**, 1488 (1911).

2-Chloroacrylonitrile as a Cyclodipolarophile in 1,3-Cycloadditions. 3-Cyanopyrroles

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The reaction of 2-chloroacrylonitrile with *N*-acyl-α-amino acids in acetic anhydride gave 3-cyanopyrroles, through an oxazolium 5-oxide (**2**) intermediate, with an overall yield of about 70%. Representative 3-cyanopyrroles, 7-cyano-2,3-dihydro-1*H*-pyrrolizines, and 1-cyano-5,6,7,8-tetrahydroindolizines were synthesized. Regiospecificity was achieved in some cases.

The 1,3-cycloaddition of oxazolium 5-oxides (**2**) with dipolarophiles has recently been utilized in the synthesis of a variety of heterocyclic systems,[1–3] the reaction pathway involving a cycloaddition to an azomethine ylide to give a N-bridged intermediate that loses carbon dioxide and forms a heterocycle.[4] This note describes the reaction between oxazolium 5-oxides and 2-chloroacrylonitrile to give 3-cyanopyrrole derivatives in a single pot operation starting from α-amino acids or their *N*-acyl derivatives.

The overall reaction is represented by the following sequence: N-acylation of the amino acid (**1**), oxazolium 5-oxide (**2**) formation, 1,3-cycloaddition to give a N-bridged intermediate (**3**), carbon dioxide elimination to give an unstable chlorocyanopyrroline (**4**), and elimination of hydrochloric acid[5] to give a 3-cyanopyrrole (**5**). When a cyclic α-amino acid (proline or pipecolic acid) was used, the corresponding 7-cyano-2,3-dihydro-1*H*-pyrrolizines (**14** and **15**) or 1-cyano-5,6,7,8-tetrahydroindolizines (**16** and **18**) were obtained.

This reaction can be carried out using aromatic, halogenated, or aprotic solvents or an excess of acetic anhydride at temperatures ranging between 20 and 100 °C. It represents a useful synthetic route to 3-cyanopyrroles with the same substituents in positions 2 and 5 (**6** and **12**) or when the reaction is regiospecific, giving only one isomer, as in the cycloaddition to the azomethine ylide system derived from *N*-formyl-*C*-phenylglycine, *N*-acylproline, or *N*-acylpipecolic acid (compounds **9** and **14–21**). As expected, a mixture of pyrroles is obtained when the reaction is not regiospecific, as with L-leucine, which gives compounds **7** and **8**. The same mixture of pyrroles **10** and **11** is obtained starting from either DL-α-phenylglycine or *N*-benzoylalanine. From this mixture, compound **11** was isolated. Both mixtures were hydrolyzed to the corresponding mixture of acids, which were decarboxylated to a single pyrrole **13**.

The presence of a substituent in position 4 in the oxazolium 5-oxide intermediate **2** seems to be necessary since no reaction was obtained with *N*-formylglycine, *N*-acetylglycine, or hippuric acid under experimental conditions described for the preparation of **9**. The oxazolone derived from hippuric acid (**2**; R = C_6H_5, R_1 = H) was isolated and does not react with 2-chloroacrylonitrile in the conditions described in this note. Anyhow, the desired compound **9** could be obtained using

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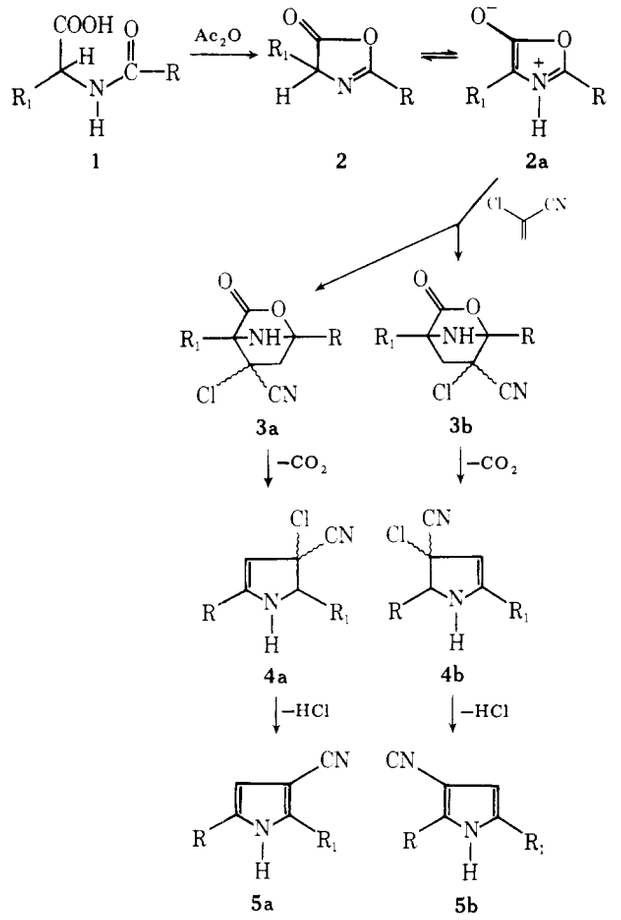
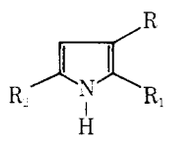


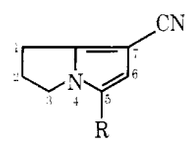
N-formyl-*C*-phenylglycine as starting material.

In spite of the interest in the pyrrole nucleus, only a few simple 3-cyanopyrroles have been previously prepared, usually by the use of ring synthesis, due to the difficulties associated with the selective substitution in the 3 position.[6]

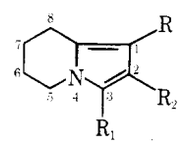
The regiospecificity found in some of these reactions was also found using ethyl propiolate[2,3] as a cyclodipolarophile and is caused by asymmetry of the dipole frontier orbitals produced by the substituents as calculated by Houk et al.[7] The NMR spectra of compounds **14, 16,** and **17** showed the presence of an AB quartet with $\Delta\nu$ values of 10, 7, and 10 Hz, respectively. Compound **16** was hydrolyzed to **17** and compared with an authentic sample.[8]



6, R = CN; R_1 = CH_3; R_2 = CH_3
7, R = CN; R_1 = CH_3; R_2 = $CH_2CH(CH_3)_2$
8, R = CN; R_1 = $CH_2CH(CH_3)_2$; R_2 = CH_3
9, R = CN; R_1 = C_6H_5; R_2 = H
10, R = CN; R_1 = CH_3; R_2 = C_6H_5
11, R = CN; R_1 = C_6H_5; R_2 = CH_3
12, R = CN; R_1 = C_6H_5; R_2 = C_6H_5
13, R = H; R_1 = C_6H_5; R_2 = CH_3



14, R = H
15, R = CH_3



16, R = CN; R_1 = H; R_2 = H
17, R = COOH; R_1 = H; R_2 = H
18, R = CN; R_1 = CH_3; R_2 = H
19, R = CN; R_1 = H; R_2 = Ac
20, R = CN; R_1 = CH_3; R_2 = Ac
21, R = CN; R_1 = CH_3; R_2 = COOH

During the preparation of compounds **16** and **18**, a small amount of 1-cyano-2-acetyl-5,6,7,8-tetrahydroindolizine (**19**) and 1-cyano-2-acetyl-3-methyl-5,6,7,8-tetrahydroindolizine (**20**), respectively, was isolated. Characterization of both **19** and **20** as 2-acetyl derivatives was made by their spectral data. The deshielding of the proton on C_3 in **19** and of the protons of the methyl on C_3 in **20** is due to the anisotropy of the carbonyl group. Furthermore, reaction of **20** with sodium hypoiodite gave iodoform and 1-cyano-2-carboxy-3-methyl-5,6,7,8-tetrahydroindolizine (**21**). Decarboxylation of **21** gave **18** in high yield.

The yield of 1-cyano-2-acetyl-5,6,7,8-tetrahydroindolizines (**19** and **20**) obtained is related to the concentration of acetic acid in the reaction media. When formation of the oxazolium 5-oxide is the only source of acetic acid, the concentration is low and the 2-acetyl derivatives are isolated in small yields, but if acetic acid is added to the media (see Experimental Section) compounds **19** and **20** become the major products of the reaction, emphasizing the importance of the purity of the acetic anhydride. Formation of **19** and **20** could not be detected after heating **16** or **18** with acetic anhydride pure or in mixtures with acetic acid;[9] therefore, the 2-acetyl derivatives must be produced during the reaction and not subsequently.

Experimental Section

Caution: *Hydrogen cyanide is evolved in small quantities during this reaction; it should be carried out with proper precautions.* Melting points were measured on a Kofler micro hot stage apparatus. Infrared spectra were recorded using a Perkin-Elmer 735 B spectrometer. NMR spectra were recorded on a Perkin-Elmer R 12 spectrometer. Microanalyses were performed by Mrs. Martha I. C. de Cassanello of this university. TLC and preparative thick-layer chromatography were performed on silica gel GF-254. Acetic anhydride was distilled before use. Mass spectra were obtained with an Atlas CH-7 spectrometer operating at an ionization potential of 70 eV.

2,5-Dimethyl-3-cyanopyrrole (6). A mixture of DL-alanine (178 mg, 2 mmol), 4 mL of acetic anhydride, and 1.8 mL (1.74 g, 20 mmol) of 2-chloroacrylonitrile was heated on a steam bath for 3 h. The excess reagents were evaporated in vacuo, and the residue was chromatographed through a silica gel column. The fraction eluted with methylene chloride gave 168 mg (70%) of **6**: mp 69–72 °C; IR ($CHCl_3$) 3400, 3250, 2900, 2200 cm^{-1}; NMR ($CDCl_3$) δ 5.98 (broad s, 1, proton on C_4, 2.32 and 2.18 (2s, 6, CH_3).

Anal. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.83; H, 6.61; N, 23.25.

2-Phenyl-3-cyanopyrrole (9). To a suspension of *N*-formyl-*C*-phenylglycine (358 mg, 2 mmol), prepared by us according to Shapiro and Newton,[10] in 4 mL of acetic anhydride was added 1.8 mL (1.74 g, 20 mmol) of 2-chloroacrylonitrile. The stirred suspension was heated at 90 °C (bath temperature) for 1.5 h. Solvent and excess dipolarophile were removed in vacuo, and the residue was chromatographed on 15 g of silica gel. The fraction eluted with chloroform gave 213 mg (64%) of **9**: mp 152–154 °C subl; IR (KBr) 3250, 2230, 1500, 1460, 760, 700 cm^{-1}; NMR ($CDCl_3$) δ 9.40–8.80 (s, 1, NH), 7.80–7.30 (m, 5, aromatic protons), 6.80 (m, 1, proton on C_5), 6.50 (m, 1, proton on C_4); NMR after D_2O exchange, 24 h) δ 7.80–7.30 (m, 5, aromatic protons), 6.80 (d, 1, J = 3 Hz, proton on C_5), 6.50 (d, 1, J = 3 Hz, proton on C_4).

Anal. Calcd for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.67. Found: C, 78.50; H, 4.63; N, 16.65.

2-Methyl-5-phenyl-3-cyanopyrrole (10) and 2-Phenyl-5-methyl-3-cyanopyrrole (11). A solution of DL-α-phenylglycine (302 mg, 2 mmol), 2-chloroacrylonitrile (1.8 mL, 1.74 g, 20 mmol), and 4 mL of acetic anhydride was stirred and heated (80 °C) for 1 h. The solution was evaporated in vacuo, and the residue was purifed by a silica gel column. The fraction eluted with dichloromethane yielded 286 mg (80%) of a mixture of **10** and **11**: NMR ($CDCl_3$) δ 9.60–9.10 (s, 1, NH), 7.90–7.20 (m, aromatic protons). **10**: NMR 6.55 (d, 1, proton on C_4), 2.45 (s, 3, $-CCH_3$). **11**: NMR δ 6.20 (m, 1, proton on C_4), 2.30 (s, 3, $-CCH_3$). The isomer ratio of **10** to **11** was 1:2. From this mixture compound **11** was isolated: mp 149–150 °C; IR (KBr) 3400–2800 (broad), 2225, 1400 (strong) cm^{-1}.

Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.12; H, 5.50; N, 15.38. Found: C, 78.95; H, 5.55; N, 15.30.

2-Methyl-5-phenyl-3-cyanopyrrole (10) and 2-Phenyl-5-methyl-3-cyanopyrrole (11) from *N*-Benzoylalanine. A mixture of **10** and **11** was obtained from *N*-benzoylalanine[11] under the same conditions described above for its preparation from DL-α-phenyl glycine (yield 70%).

2,5-Diphenyl-3-cyanopyrrole (12). Procedure A. A solution of α-benzamidophenylacetic acid[4] (225 mg, 1 mmol) in 0.16 mL of acetic anhydride, 2 mL of benzene, and 0.18 mL (174 mg, 2 mmol) of 2-chloroacrylonitrile was refluxed for 1.5 h. The solution was evaporated to dryness and the residue crystallized from benzene to give 190 mg (78%) of **12:** mp 228–230 °C (at 190 °C there is a change in the crystalline form) (lit.[12] mp 218.5–219.6 °C); IR (KBr) 3225, 3027, 2220, 1610, 1585, 1500, 800, 760, 680 cm^{-1}; NMR [$(CD_3)_2CO$] δ 8.60–8.25 (s, 1, NH), 7.90–7.20 (m, 10, aromatic protons), 6.90 (d, 1, proton on C_4).

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.50. Found: C, 83.20; H, 5.24; N, 11.35.

2,5-Diphenyl-3-cyanopyrrole (12). Procedure B. A solution of 2,4-diphenyl-Δ^2-oxazolin-5-one (237 mg, 1 mmol), prepared as described in the literature,[4] in 0.6 mL of xylene and 0.9 mL (880 mg, 10 mmol) of 2-chloroacrylonitrile was stirred for 45 min at a bath temperature at 100 °C. After cooling, 170 mg (70%) of **12** separated, mp 228–230 °C. The same reaction was carried out replacing xylene by 2 mL of benzene (80 °C, 1.5 h; 55% yield) or by 1.2 mL of DMF (45 °C, 1.5 h; 35% yield).

2-Phenyl-5-methylpyrrole (13). The crude mixture of **10** and **11** (150 mg) was saponified in 8 mL of boiling 40% NaOH solution in ethanol–water (1:1) for 24 h. The solution was diluted with water (10 mL), acidified with tartaric acid, and extracted with ether (3 × 10 mL). The ethereal extract was concentrated in vacuo and the residue sublimated at 60 °C (bath temperature), 0.08 torr, to give **13** in low yield. The melting point and mixture melting point with an authentic sample were 102–103 °C subl (lit.[13] 101 °C); IR (KBr) 3150, 3030, 1400 cm^{-1}.

7-Cyano-2,3-dihydro-1*H*-pyrrolizine (14). To a well-stirred solution of 190 mg (1.32 mmol) of *N*-formyl-L-proline[2] in 4 mL of acetic anhydride was added 0.45 mL (435 mg, 5 mmol) of 2-chloroacrylonitrile. The solution was heated at 80 °C for 24 h and evaporated, and the residue was chromatographed on 10 g of silica gel. The fraction eluted with chloroform gave 121 mg (70%) of **14:** mp 46–50 °C (methanol); IR (CCl_4) 3200 (broad), 2225 cm^{-1}; NMR ($CDCl_3$) δ 2.31–3.1 (m, 4, protons on C_1 and C_2), 3.95 (t, 2, C_3), 6.45 (AB quartet, 2, $\Delta\nu$ = 10 Hz, J = 3 Hz, olefinic protons).

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.51; H, 5.90; N, 20.95.

5-Methyl-7-cyano-2,3-dihydro-1*H*-pyrrolizine (15). A solution of L-proline (115 mg, 1 mmol) in 4 mL of acetic anhydride and 0.9 mL (880 mg, 10 mmol) of 2-chloroacrylonitrile was heated at 80 °C for 24 h. Excess reagents were evaporated in vacuo, and the residue was chromatographed through a silica gel column. The fraction eluted with methylene chloride gave 95 mg (65%) of **15:** mp 58–62 °C; IR (CCl_4) 3200 (broad), 2225 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3, $-CCH_3$), 2.29–3.15 (m, 4, protons on C_1 and C_2), 3.87 (t, 2, protons on C_3), 6.10 (s, 1, olefinic proton).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.85; H, 6.42; N, 18.92.

1-Cyano-5,6,7,8-tetrahydroindolizine (16) and 1-Cyano-2-acetyl-5,6,7,8-tetrahydroindolizine (19). A solution of *N*-formylpipecolic acid[3] (314 mg, 2 mmol) in 3 mL of acetic anhydride and 0.9 mL (880 mg, 10 mmol) of 2-chloroacrylonitrile was heated at 80 °C for 3 h. Excess reagents were evaporated in vacuo, and the residue was chromatographed on silica gel. The fraction eluted with benzene gave 224 mg (77%) of **16:** IR (CCl_4) 3100, 2990, 2225, 1565 cm^{-1}; NMR ($CDCl_3$) Δ 6.45 (AB quartet, 2, $\Delta\nu$ = 7 Hz, J = 3 Hz, olefinic protons), 3.95 (broad t, 2, protons on C_8), 2.90 (broad t, 2, protons on C_5), 1.90 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.60; H, 7.20; N, 19.30.

The fraction eluted with benzene–chloroform (19:1) gave 54 mg (14%) of **19:** mp 105–106.5 °C; IR (KBr) 3100, 2950, 2925, 2225, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (s, 1, olefinic proton), 4.35 (broad t, 2, protons on C_8), 2.91 (broad t, 2, protons on C_5), 2.37 (s, 3, CCH_3), 1.89 (m, 4, protons on C_6 and C_7); mass spectrum, m/e 188 (M^+).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.35; H, 6.61; N, 14.95.

1-Cyano-5,6,7,8-tetrahydroindolizine (16). The same reaction was carried out with a solution of *N*-formylpipecolic acid (314 mg, 2 mmol), acetic anhydride (3 mmol), 2-chloroacrylonitrile (1.8 mL, 1.74 g, 20 mmol), and 10 mL of methylene chloride stirred for 24 h at room temperature. Workup of the solution as previously described afforded 240 mg (82%) of **16** and a small quantity of **19** (detected by TLC).

5,6,7,8-Tetrahydroindolizine-1-carboxylic Acid (17). Alkaline Hydrolysis of 16. A 144-mg (1 mmol) sample of **16** in 4 mL of 1 N KOH solution in 2:1 methanol–water was heated for 4 h at reflux. Methanol was evaporated in vacuo and the solution acidified with HCl to pH 1. The precipitate was filtered and dried, giving 40 mg (25%) of **17.** The melting point and mixture melting point with an authentic sample were 151–153 °C dec (lit.[8] 151–153 °C); IR (KBr) 3600–3200 (broad), 2950, 1640 cm^{-1}; NMR ($CDCl_3$) δ 11.00 (broad s, 1, exchangeable with D_2O, –COOH), 6.68 (AB quartet, 2, $\Delta\nu$ = 10 Hz, J = 3 Hz, olefinic protons), 4.08 (broad t, 2, protons on C_8), 3.23 (broad t, 2, protons on C_5), 1.85 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.66; N, 8.48. Found: C, 65.30; H, 6.64; N, 8.40.

1-Cyano-3-methyl-5,6,7,8-tetrahydroindolizine (18) and 1-Cyano-2-acetyl-3-methyl-5,6,7,8-tetrahydroindolizine (20). A solution of pipecolic acid (387 mg, 3 mmol), 1.35 mL (1.3 g, 15 mmol) of 2-chloroacrylonitrile, and 4 mL of acetic anhydride was refluxed and stirred for 2 h. Excess reagents were evaporated in vacuo, and the residue was dissolved in benzene and chromatographed on 20 g of silica gel. The fraction eluted with benzene–chloroform (1:1) gave 334 mg (70%) of **18:** mp 61–65 °C: IR (KBr) 3100, 2910, 2225, 1530 cm^{-1}; NMR ($CDCl_3$) δ 6.00 (s, 1, olefinic proton), 3.72 (broad t, 2, protons on C_8), 2.85 (broad t, 2, protons on C_5), 2.10 (s, 3, CCH_3), 1.85 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.00; H, 7.50; N, 17.50. Found: C, 75.40; H, 7.94; N, 17.35.

The fraction eluted with benzene–chloroform (1:2) gave 30 mg (5%) of **20:** mp 166–169 °C; IR (KBr) 3100, 2950, 2925, 1660, 1540 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (broad t, 2, protons on C_8), 2.90 (broad t, 2, protons on C_5), 2.55 and 2.45 (2s, 3, CCH_3), 1.95 (m, 4, protons on C_6 and C_7); mass spectrum m/e 202 (M^+).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.35; H, 7.03; N, 13.50.

Preparation of 18 and 20 with Acetic Acid. The reaction was carried out as above, with the addition of 1 mL of acetic acid. The fraction eluted with benzene–chloroform (1:1) gave 150 mg (31%) of **18** and that eluted with benzene–chloroform (1:2) gave 280 mg (46%) of **20.**

1-Cyano-2-carboxy-3-methyl-5,6,7,8-tetrahydroindolizine (21). To a solution of **20** (74 mg, 0.37 mmol) in 2 mL of *p*-dioxane was added 4 mL of a 32% NaOH solution, and a iodine–iodide solution (316 mg of I_2, 632 mg of KI, 2.6 mL of water) was added dropwise with stirring. Water (10 mL) was added, the precipitated iodoform was centrifuged, and the solution was extracted (2 × 5 mL) with ether. After acidification (6 N HCl), the iodine was reduced with sodium bisulfite. The acid was extracted with ether (3 × 5 mL) and the ether evaporated to give 64 mg (84%) of **21:** mp 220–224 °C dec; IR (KBr) 3300 (broad), 2950, 2225, 1650, 1580, 1540 cm^{-1}; NMR (NaDO in D_2O) δ 4.2 (broad t, 2, protons on C_8), 3.30 (broad t, 2, protons on C_5) 2.60 (s, 3, $-CCH_3$), 2.15 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_{11}H_{12}N_2O_2$:C, 64.69; H, 5.92; N, 13.72. Found: C, 64.30; H, 6.25; N, 13.60.

Preparation of 18 from 21. The acid **21** was heated at 230 °C (bath temperature), 16 torr, giving **18** in 80% yield.

2-Phenyloxazolium 5-Oxide (2; R = C_6H_5, R_1 = H). A solution of 179 mg (1 mmol) of hippuric acid in 3 mL of acetic anhydride was refluxed for 30 min. The solution was evaporated to dryness, and the residue was chromatographed on 10 g of silica gel. The fraction eluted with chloroform gave 50 mg of **2** (R = C_6H_5, R_1 = H): NMR ($CDCl_3$) δ 8.00 (m, 2 H, protons on C_2' and C_6'), 7.45 (m, 3, protons on C_3', C_4' and C_5'), 4.40 (s, 2, protons on C_4). This compound is unstable and cannot be analyzed. By treating the oil with water, hippuric acid was isolated.

Registry No.—**2,** 30216-01-4; **6,** 26187-29-1; **9,** 52179-70-1; **10,** 67421-64-1; **11,** 67421-65-2; **12,** 67421-66-3; **13,** 3042-21-5; **14,** 67421-67-4; **15,** 67421-68-5; **16,** 67421-69-6; **17,** 61009-82-3; **18,** 67421-70-9; **19,** 67421-71-0; **20,** 67421-72-1; **21,** 67421-73-2; DL-alanine, 302-72-7; 2-chloroacrylonitrile, 920-37-6; *N*-formyl-*C*-phenylglycine, 67421-74-3; DL-α-phenylglycine, 2835-06-5; α-benzamidophenylacetic acid, 29670-63-1; 2,4-diphenyl-Δ^2-oxazolin-5-one, 28687-81-2; *N*-formyl-L-proline, 13200-83-4; L-proline, 147-85-3; *N*-formylpipecolic acid, 54966-20-0; pipecolic acid, 535-75-1; hippuric acid, 495-69-2.

References and Notes

(1) (a) H. Gotthardt and R. Huisgen, *Chem. Ber.*, **103,** 2625 (1970); (b) H. Gotthardt, R. Huisgen, and F. C. Schaefer, *Tetrahedron Lett.*, 487 (1964).

(2) M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).
(3) M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **42**, 909 (1977).
(4) H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).
(5) A referee has suggested the possibility of a competing loss of HCN to give chloropyrroles as coproducts. They have not been detected; however, this possibility cannot be ruled out because halopyrroles are unstable: G. A. Cordell, *J. Org. Chem.*, **40**, 3161 (1975).
(6) C. E. Loader and H. J. Anderson, *Tetrahedron*, **25**, 3879 (1969).
(7) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, **95**, 7301 (1973).
(8) M. T. Pizzorno, Thesis, Buenos Aires University, Buenos Aires, Argent., 1977.
(9) A. G. Anderson, Jr., and M. M. Exner, *J. Org. Chem.*, **42**, 3952 (1977).
(10) E. Shapiro and R. F. Newton, *J. Am. Chem. Soc.*, **65**, 777 (1943).
(11) O. Grahl-Nielsen and E. Solheim, *Anal. Chem.*, **47**, 333 (1975).
(12) R. H. Henze and J. H. Shown, Jr., *J. Am. Chem. Soc.*, **69**, 1662 (1947).
(13) C. Paal, *Ber.*, **18**, 367 (1885).
(14) This investigation was partially supported by grants from the Consejo Nacional de Investigaciones (Argent.).

Synthesis of 2-Aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles

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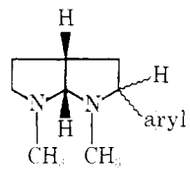
The synthesis of a series of 2-aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles (**1**) via the reductive cyclization of 3-(2-aryl-2-aminoethyl)-1-methyl-2-pyrrolidones (**4**) using diisobutylaluminum hydride is described. The diastereomers of **1** were separated and structures assigned on the basis of NMR spectra. The products resulting from the reductive trapping of the ring opened iminium species **7** with sodium cyanoborohydride generated from **1** in acid solution are also identified.

In our search for new bioactive structures, the octahydropyrrolo[2,3-*b*]pyrrole ring system bearing an aryl substituent in the 2 position (**1**) appeared as a promising candidate. This



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relatively simple ring system has not previously been reported, although it does occur fused to an aromatic ring in the physostigmine-type alkaloids.

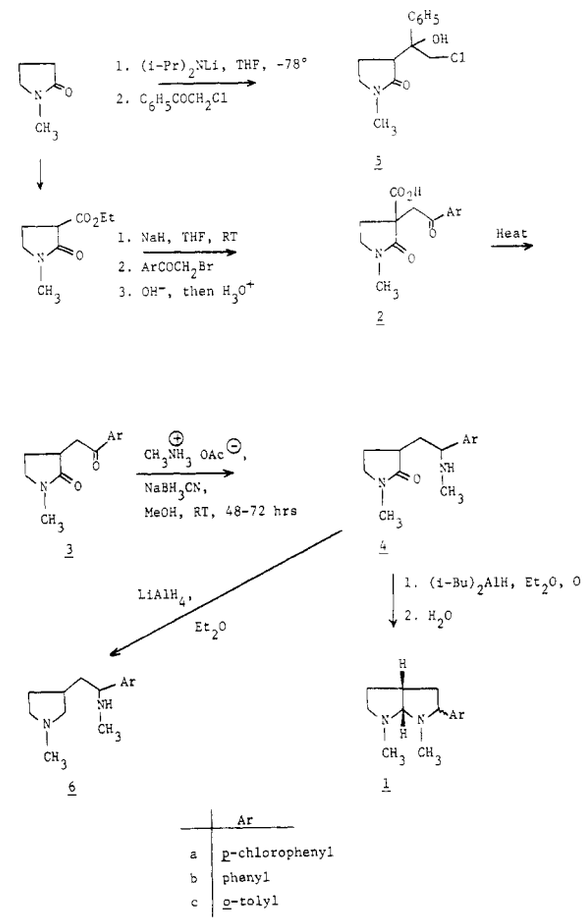
N-Methyl-2-pyrrolidone was chosen as the starting material for the synthesis of **1** since it was hoped that anion formation followed by alkylation with a phenacyl halide would lead to ketone **2**. Surprisingly, the only product which could be isolated from the alkylation reaction was the chloro alcohol **5** in 20–25% yield.

We then decided to alkylate the enolate of *N*-methyl-3-carbethoxy-2-pyrolidinone[1] since it was felt that this anion would be less reactive with respect to carbonyl addition. In the event, the desired alkylation proceeded cleanly and was followed by hydrolysis to afford the carboxylic acids **2**. Decarboxylation then gave the ketolactam **3**. The ketolactam **3** was then aminated using sodium cyanoborohydride[2] and methylammonium acetate to afford good yields of **4**.

Although the literature of the physostigmine alkaloids reports ring closures of the desired type (**4** to **1**) using lithium aluminum hydride,[3] in our hands this reagent gave only poor yields of **1**. The primary product from this reaction was the mixture of diastereomers **6**. Changing the order of addition, temperature, or using clarified solutions of lithium aluminum hydride in place of a suspension had little or no effect on the results. However, the use of diisobutylaluminum hydride, which has found utility in the generation of enamines from lactams,[4] afforded **1** in good yield accompanied by small amounts of **6** (Scheme I).

Chromatography of the reaction mixture on alumina cleanly separated the C-2 epimers of **1**. Table I lists examples of

Scheme I



compounds prepared by this route. The yields are believed to represent the distribution of products from the reaction mixture since the epimers of **1** were found to be stable to base and to rechromatography on alumina. However, the dissolution of either isomer in acid and reisolation gave the same mixture of isomers observed in the reaction before chromatography, determined in both cases by NMR spectrometry.

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