Synthesis of Ring-Fused Pyrroles. I. 1,3-Dipolar Cycloaddition Reactions of Munchnone Derivatives Obtained from Tetrahydro-β-carboline-3- and -1-carboxylic Acids

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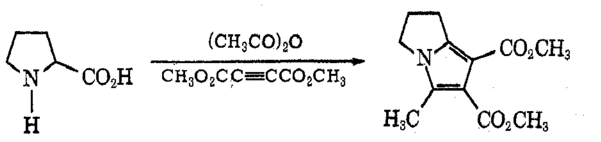
The reaction of various tetrahydro-β-carboline-3-carboxylic acids, **2a–c**, with dimethyl acetylenedicarboxylate in acetic anhydride directly afforded the corresponding indolizino[6,7-*b*]indoles **4a–c**, in moderate yields. Likewise, treatment of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid, **5**, in acetic anhydride, with a variety of acetylenic dipolarophiles and less successfully with olefinic dipolarophiles furnished the corresponding indolizino[8,7-*b*]indole derivatives. These reactions involve a 1,3-dipolar cycloaddition of the respective munchnone intermediates (**3** and **6**), respectively, formed *in situ*, with the dipolarophilic substrates.

Huisgen and coworkers have recently reported a general synthesis of pyrroles[1] and pyrrolines[2] using mesoionic Δ^2-oxazolium-5-olates (munchnones). These reactions involved a 1,3-dipolar cycloaddition of the munchnone, behaving like a cyclic azomethine ylide,[3] to the corresponding acetylenic or olefinic dipolarophile, followed by CO_2 evolution, and aromatization or tautomerization.[4] Most examples of the application of this reaction, to date, have involved the use of acyclic, *N*-acyl α-amino acids as the starting material,[5-8] although Huisgen has converted L-proline to the pyrrolizine derivative, **1**, in 76% yield by reaction with dimethyl acetylenedicarboxylate in acetic anhydride.[1]



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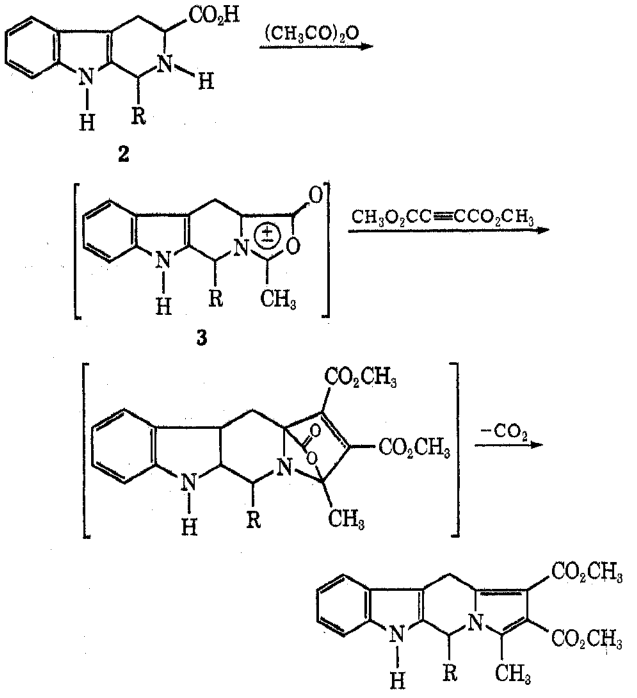
This paper will describe the transformation of another group of "cyclic" α-amino acids, namely, the tetrahydro-β-carboline-3- and -1-carboxylic acids (**2** and **5**), respectively, into the corresponding pyrrole derivatives *via* munchnone intermediates.

The conversion of the three tetrahydro-β-carboline-3-carboxylic acids **2a–c**, to the 5,6-dihydro-11*H*-indolizino[6,7-*b*]indoles, **4a–c**, involved treatment with dimethyl acetylenedicarboxylate in acetic anhydride at 70–120° (Scheme I). No attempt was made to isolate the intermediate munchnones (**3a–c**), since Huisgen has shown the oxazolium-5-olate system to be extremely reactive.[9] The progress of these reactions, and those described below, was monitored by CO_2 evolution. Work-up procedures generally involved the simple evaporation of solvents (acetic acid and acetic anhydride) *in vacuo* and subsequent recrystallization of the product. Only **4b** required the use of column chromatography in the work-up.

SCHEME I



4a, R = H
b, R = $C_6H_5CH_2$
c, R = *p*-$CH_3OC_6H_4$

The facility by which three steps, namely, acetylation, 1,3-dipolar cycloaddition, and aromatization, could be achieved in a single operation, prompted the examination of this reaction with the isomeric tetrahydro-β-carboline-1-carboxylic acid, **5**.

Whereas attempts to nitrosate **5** with sodium nitrite in cold concentrated hydrochloric acid, followed by formation of the sydnone derivative with acetic anhydride, failed,[10] the reaction of **5** with dimethyl acetylenedicarboxylate in acetic anhydride at 115° furnished methyl 3-methyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (**7a**) in 75% yield (Scheme II). Once again, no attempt was made to isolate the intermediate munchnone **6**. Compound **5** reacted in similar manner with propionic anhydride and dimethyl acetylenedicarboxylate, yielding the 3-ethylindolizino[8,7-*b*]indole derivative **7b**; however, attempts to

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[1] R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.*, **103**, 2611 (1970).

[2] H. Gotthardt and R. Huisgen, *ibid.*, **103**, 2625 (1970).

[3] For a classification of 1,3 dipoles, see R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

[4] H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Amer. Chem. Soc.*, **92**, 4340 (1970).

[5] A. Padwa and L. Hamilton, *J. Heterocycl. Chem.*, **4**, 118 (1967).

[6] K. T. Potts and U. P. Singh, *Chem. Commun.*, 66 (1969).

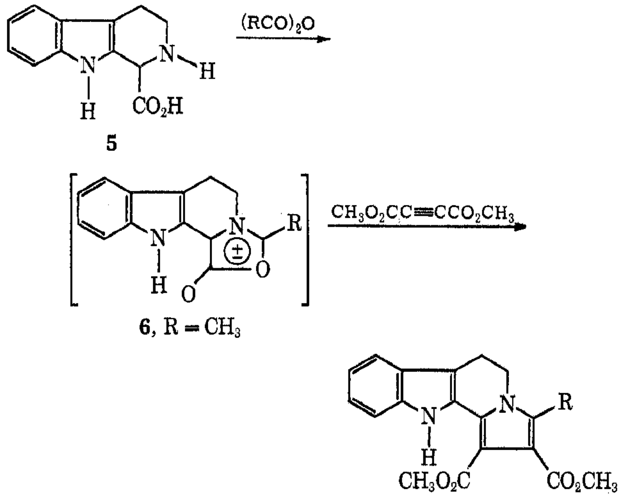
[7] H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.*, **33**, 1097 (1968).

[8] D. F. McLean, *Org. Prep. Proc.*, **2**, 145 (1970).

[9] Isolation of munchnones have been possible when aromatic substituents are present at the 2 and 4 positions of the oxazolium-5-olate ring, *i.e.*, 2,4-diphenyl- and 2-(*p*-nitrophenyl)-4-phenyloxazolium-5-olates: ref 4; G. Kille and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 4636 (1968); H. O. Bayer, R. Huisgen, R. Knorr, and F. C. Schaefer, *Chem. Ber.*, **103**, 2581 (1970).

[10] H. A. Wagner, G. D. Searle & Co., personal communication.

Scheme II



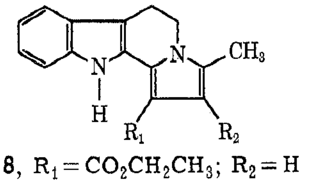
5

6, R = CH_3

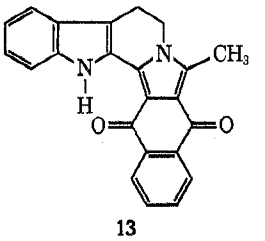
7a, R = CH_3
b, R = CH_3CH_2
c, R = CF_3

employ trifluoroacetic anhydride failed to provide the desired trifluoromethyl analog, **7c**. Instead, decarboxylation of **5** in the presence of the strong acid, trifluoroacetic acid, occurred prior to munchnone formation.[11,12]

In addition to using dimethyl acetylenedicarboxylate, several other acetylenic and olefinic dipolarophiles were employed. Ethyl propiolate provided the two isomeric monoesters, **8** and **9**, in 51 and 11% yields, respectively. The isomers were easily separated by fractional crystallization and identification of each isomer was made on the basis of their respective nmr spectra. Particular attention was given to the chemical shifts and coupling constants of the pyrrole ring protons. In **8**, the pyrrole ring proton appeared as a quartet at δ 6.31 with long-range coupling to the adjacent ring methyl group (J_{H,CH_3} = 1.0 Hz). The ring proton in **9**, however, appeared as a singlet at δ 6.73. This deshielding of H-1 in **9** *vs.* H-2 in **8** is undoubtedly due to the anisotropic effect of the indole ring.



8, $R_1 = CO_2CH_2CH_3$; $R_2 = H$
9, $R_1 = H$; $R_2 = CO_2CH_2CH_3$
10, $R_1 = C_6H_5$; $R_2 = H$
11, $R_1 = H$; $R_2 = C_6H_5$
12, $R_1 = R_2 = H$



13

Treatment of **5** with phenylacetylene in acetic anhydride at 115° furnished a single product, **10**, in 34% yield. Careful examination of the reaction mixture failed to provide any evidence for the formation of the isomeric product, **11**. The nmr spectrum of **10**, once again, showed the pyrrole ring proton to be a quartet at δ 6.00 with long-range coupling to the adjacent ring methyl protons (J_{H,CH_3} = 0.8 Hz). The apparent regiospecificity of the reaction of phenylacetylene with munchnones has been reported,[1] and the isolation of **10** as the only product here is consistent with the arguments previously presented.

The reaction of **5** with olefinic dipolarophiles in acetic anhydride was generally less successful. While vinyl acetate or excess 1,4-naphthoquinone afforded the corresponding pyrrole derivatives **12** and **13**, reactions involving the use of acenaphthylene, isopropenyl acetate, *N*-*p*-methoxyphenylmaleimide, 2-cyclohexen-1-one, or methyl acrylate furnished complex, inseparable mixtures of products. These mixtures generally consisted of pyrrolines and dimeric products.[2]

Experimental Section[13]

Methyl 3-Methyl-5,6-dihydro-11*H*-indolizino[6,7-*b*]indole-1,2-dicarboxylate (4a).—A mixture consisting of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[14] (**2a**, 7.0 g, 0.03 mol), dimethyl acetylenedicarboxylate (6.4 g, 0.045 mol), and acetic anhydride (100 ml) was stirred and heated to 80°. Carbon dioxide evolution ensued and the reaction mixture warmed to 115°. This temperature was maintained until the CO_2 evolution had ceased (~15 min). The brown solution that remained was then cooled and a light yellow powder (6.50 g, 64% yield), mp 255–260°, was collected: ir (KBr disk) NH at 3360, C=O at 1725 and 1690 cm^{-1}; nmr (DMSO-d_6) CH_3 at δ 2.41 (s), two OCH_3 at 3.75 (s), CH_2 at 4.08 (m), CH_2 at 5.15 (m).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.08; H, 5.37; N, 8.03.

Methyl 3-Methyl-5-benzyl-5,6-dihydro-11*H*-indolizino[6,7-*b*]-indole-1,2-dicarboxylate (4b).—A mixture of 1-benzyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[15] (**2b**, 9.2 g, 0.03 mol), dimethyl acetylenedicarboxylate (6.4 g, 0.045 mol), and acetic anhydride (100 ml) was stirred and heated to 80–90° for 45 min. The reaction mixture was then cooled to room temperature and evaporated to dryness *in vacuo*. The brown gum that remained was washed several times with petroleum ether, 60–90°, and the resultant brown, amorphous solid that formed was dissolved in benzene and chromatographed on a column of silica gel (800 g) in benzene. Elution with 10% ethyl acetate–90% benzene afforded a light brown solid (5.6 g). Recrystallization from ethanol yielded a yellow crystalline solid (3.5 g, 27% yield): mp 199–200.5°; ir ($CHCl_3$) NH at 3465, C=O at 1705 and 1695 cm^{-1}; nmr ($CDCl_3$) CH_3 at δ 2.54 (s), CH_2 at 3.15 (m), CH at 3.20 (d of d), OCH_3 at 3.80 (s), OCH_3 at 3.85 (s), CH at 4.13 (d of d), CH at 5.52 (m).

Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.72; H, 5.90; N, 6.18.

Methyl 3-Methyl-5-(*p*-methoxyphenyl)-5,6-dihydro-11*H*-indolizino[6,7-*b*]indole-1,2-dicarboxylate (4c).—Dimethyl acetylenedicarboxylate (6.4 g, 0.045 mol) was added to a stirred suspension of 1-(*p*-methoxyphenyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid[15] (**2c**, 9.65 g, 0.03 mol) in acetic anhydride (150 ml), and the reaction mixture was heated to 100° for 1 hr. After cooling and evaporation to dryness *in vacuo*, the residual oil was triturated with warm cyclohexane. The cyclohexane supernatant was decanted and the syrupy residue dissolved in warm ethanol. The ethanolic solution was cooled and an orange solid

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[11] G. Hahn and K. Stiehl, *Chem. Ber.*, **69**, 2627 (1936).

[12] R. A. Abramovitch and I. D. Spenser, *Advan. Heterocycl. Chem.*, **3**, 79 (1964).

[13] Melting points were determined in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. The author wishes to thank Dr. J. W. Ahlberg and staff for the analyses and spectra reported. Ir spectra were obtained in a 3% $CHCl_3$ solution or in KBr disks on an IR-12 spectrometer, Beckman Instruments, and are reported in reciprocal centimeters. Nmr spectra were determined in $CDCl_3$ or DMSO-d_6 solutions on a Model A-60 or HA-100 spectrometer, Varian Associates, Inc., using tetramethylsilane as an internal standard. Chemical shifts for aliphatic and aromatic pyrrole protons are reported in parts per million (δ). Aromatic (benzenoid) protons, in all cases studied, appeared as multiplets in the region of δ 6.66–8.33.

[14] D. G. Harvey, E. J. Miller, and W. Robson, *J. Chem. Soc.*, 153 (1941).

[15] H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmerter, and E. C. Spaeth, *J. Amer. Chem. Soc.*, **70**, 219 (1948).

(10.15 g, 75%), mp 202–205°, collected. Recrystallization from 2-propanol furnished a light yellow powder (6.55 g, 49%): mp 207–208°; ir (KBr) NH at 3320 C═O at 1725 and 1695 cm^{-1}; nmr (DMSO-d_6) CH_3 at δ 2.49 (s), CH_2 at 3.67 (m), OCH_3 at 4.00, 4.03, and 4.11 (s), CH at 4.68 (m).

Anal. Calcd for $C_{26}H_{24}N_2O_5$: C, 70.25; H, 5.44; N, 6.30. Found: C, 69.96; H, 5.69; N, 5.80.

Methyl 3-Methyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (7a).—A stirred mixture consisting of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid[16] (**5**, 14.0 g, 0.065 mol), dimethyl acetylenedicarboxylate (12.8 g, 0.09 mol), and acetic anhydride (150 ml) was heated to 115° for 45 min. The reaction mixture was cooled, filtered, and evaporated to dryness *in vacuo*. The amorphous residue was triturated with cold methanol and then recrystallized from methanol yielding light tan prisms (16.50 g, 75%): mp 172–174°; ir ($CHCl_3$) NH at 3400, C═O at 1720 and 1695 cm^{-1}; nmr ($CDCl_3$) CH_3 at δ 2.35 (s), CH_2 at 3.10 (t), two OCH_3 at 3.86 (s), CH_2 at 3.93 (t).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.74; H, 5.36; N, 8.28. Found: C, 67.34; H, 5.55; N, 8.06.

Methyl 3-Ethyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (7b).—A similar reaction as described above for **7a** was carried out using propionic anhydride (150 ml) in place of acetic anhydride. Recrystallization of the crude product from methanol furnished a light yellow crystalline solid in 69% yield: mp 168–169°; ir ($CHCl_3$) NH at 3370, C═O at 1705 and 1685 cm^{-1}; nmr ($CDCl_3$) CH_3 at δ 1.21 (t), CH_2 at 2.81 (q), CH_2 at 3.13 (t), two OCH_3 at 3.88 (s), CH_2 at 4.03 (t).

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.07; H, 5.85; N, 7.86.

Reaction of 5 with Ethyl Propiolate in Acetic Anhydride.—Ethyl propiolate (4.4 g, 0.045 mol) was added to a mixture of **5** (6.5 g, 0.03 mol) in acetic anhydride (100 ml). After heating to 110° for 1 hr, the reaction mixture was cooled to room temperature and filtered. The solid collected was washed with cold methanol leaving a light beige powder (0.95 g, 11%), mp 285–289°, which was identified as **ethyl 3-methyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole-2-carboxylate (9)**: ir (KBr) NH at 3320, C═O at 1665 cm^{-1}; nmr (DMSO-d_6) CH_3 at δ 1.30 (t), CH_3 at 2.55 (s), CH_2 at 3.06 (t), CH_2 at 4.10 (t), CH_2 at 4.21 (q), pyrrole CH at 6.73 (s).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.24; H, 6.35; N, 9.37.

The acetic anhydride filtrate of **9** was evaporated to dryness *in vacuo* and the residue was recrystallized from methanol. **Ethyl 3-methyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole-1-carboxylate** (**8**, 4.5 g, 51%), mp 104–105°, was thus obtained as light tan plates: ir ($CHCl_3$) NH at 3370, C═O at 1680 cm^{-1}; nmr (DMSO-d_6) CH_3 at δ 1.33 (t), CH_3 at 2.25 (d), CH_2 at 3.11 (t), CH_2 at 4.08 (t), CH_2 at 4.33 (q), pyrrole CH at 6.31 (q).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.21; H, 6.15; N, 9.45.

1-Phenyl-3-methyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole (10).—A stirred mixture consisting of **5** (6.5 g, 0.03 mol), phenylacetylene (4.6 g, 0.045 mol), and acetic anhydride (100 ml) was heated to 115° for 30 min, then cooled to room temperature, and evaporated to dryness *in vacuo*. The residue was washed, first with petroleum ether (bp 60–90°) and then with cold methanol. Recrystallization of the remaining residue from methanol furnished a light tan crystalline solid (3.10 g, 34%): mp 156–158°; ir ($CHCl_3$) NH at 3470 cm^{-1}; nmr ($CDCl_3$) CH_3 at δ 2.30 (d), CH_2 at 3.11 (t), CH_2 at 4.00 (t), pyrrole CH at 6.00 (q).

Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.03; N, 9.39. Found: C, 84.67; H, 6.46; N, 9.17.

Combination of the mother liquor and washings of **10**, followed by evaporation, and column chromatographic work-up of the residue failed to provide the isomeric indolizino[8,7-*b*]indole (**11**).

3-Methyl-5,6-dihydro-11*H*-indolizino[8,7-*b*]indole (12).—A mixture of **5** (6.5 g, 0.03 mol), vinyl acetate (3.9 g, 0.045 mol), and acetic anhydride (150 ml) was heated to 110° for 1 hr. The reaction mixture was cooled and evaporated to dryness *in vacuo*, and the residue was recrystallized from ethanol, yielding a light tan powder (3.55 g, 53%): mp 209.5–212°; ir ($CHCl_3$) NH at 3480 cm^{-1}; nmr ($CDCl_3$) CH_3 at δ 2.26 (d), CH_2 at 3.06 (t), CH_2 at 3.98 (t), pyrrole CH (H-2) at 5.93 (d of d), pyrrole CH (H-1) at 6.18 (d).

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.10, H, 6.27; N, 12.46.

5,14-Dioxo-13-methyl-5,11,12,14-tetrahydro-6*H*-naphth[2′,3′:1,2]indolizino[8,7-*b*]indole (13).—A similar reaction as described above for **12** was carried out using 1,4-naphthoquinone (9.5 g, 0.06 mol) in place of vinyl acetate. The reaction mixture, on cooling to room temperature, furnished **13**, as a red-brown solid (9.0 g, 85%), mp 241–244°. Recrystallization from DMF yielded a red-brown solid: mp 244–245°; ir ($CHCl_3$) NH 3330, C═O at 1660 cm^{-1}; nmr ($CDCl_3$) CH_3 at δ 2.60 (s), CH_2 at 3.21 (t), CH_2 at 4.08 (t).

Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.28; H, 4.55; N, 7.82.

Registry No.—**4a,** 35105-58-9; **4b,** 35105-59-0; **4c,** 35105-60-3; **7a,** 35105-61-4; **7b,** 35105-62-5; **8,** 35105-63-6; **9,** 35105-64-7; **10,** 35105-65-8; **12,** 35105-66-9; **13,** 35105-67-0.

Acknowledgments.—The author wishes to thank Dr. Hans A. Wagner for many valuable discussions and Mr. Paul Langerman for technical assistance.

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[16] G. de Stevens, H. Lukaszewski, M. Sklar, A. Halamandaris, and H. M. Blatter, *J. Org. Chem.*, **27**, 2457 (1962).