g), polyphosphoric acid (4 g), and acetic acid (10 mL) was stirred and heated at 100 °C for 1 h and then poured on ice. Extraction with chloroform gave a solid which was chromatographed on silica gel. Elution with 20% ether–pentane furnished 3-acetamidothiophen-2(5*H*)-one (**15**) (0.4 g, 64%): mp 153–155 °C; IR ν_{max} 3380 (NH), 1705 (amide C=O), and 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.21 (3 H, s), 4.03 (2 H, d, J = 3.1 Hz), and 7.87 (1 H, t, J = 3.1 Hz); mass spectrum, *m/e* 157 [M^+], 115, 86. Anal. Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.92; S, 20.39. Found: C, 45.90; H, 4.50; N, 8.89; S, 20.30.

Thermal Decomposition of 3-Azidothiophene (1) in Acetic Anhydride. A solution of 3-azidothiophenone (0.4 g) in 6 mL of acetic anhydride was refluxed for 6 h (until TLC showed that no starting material was left). The reaction mixture was poured into water and extracted with chloroform. The combined extracts were washed with water, dried, and evaporated to give an oily residue which was chromatographed on silica gel. Elution with pentane afforded 3-diacetylamino-2-acetoxythiophene (**16**) (0.4 g, 52%) as a yellow oil: bp 118–120 °C (1 mm); IR ν_{max} 1780 (ester C=O) and 1720 cm^{-1} (amide C=O); NMR δ 2.20 (6 H, s), 2.24 (3 H, s), 6.47 and 6.77 (AB q, J = 5.6 Hz); mass spectrum, *m/e* 241 [M^+], 199, 157, 139. Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.80; H, 4.56; N, 5.80; S, 13.27. Found: C, 49.85; H, 4.54; N, 5.86; S, 13.21.

The same compound (**16**) was obtained in quantitative yield from 3-acetamidothiophene-2(5*H*)-one (**15**) in refluxing acetic anhydride.

Thermal Decomposition of 3-Azidobenzo[*b*]thiophene in Acetic Anhydride and in an Acetic Acid–Polyphosphoric Acid Mixture. Decomposition of 3-azidobenzo[*b*]thiophene (**10**) (0.5 g) in boiling acetic anhydride (10 mL) as described above for 3-azidothiophene led, after column chromatography, to (i) trace amounts of an unidentified yellow oil, (ii) 3-diacetylamino-2-acetoxybenzo[*b*]thiophene (**17**) (0.15 g, 18%) as white plates, and (iii) a solid material (**18**) (0.25 g). **17** had: mp 117–118 °C; IR ($CHCl_3$) ν_{max} 1775 (ester C=O) and 1720 cm^{-1} (amide C=O); NMR δ 2.4 (9 H, s), 7.4 (4 H, m); mass spectrum, *m/e* 291 [M^+], 249, 207, 189, 165. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.00. Found: C, 57.78; H, 4.48; N, 4.89; S, 10.93. **18** had: mp 148–152 °C; IR ($CHCl_3$) ν_{max} 3410 (NH), 1775 (ester C=O), and 1690 cm^{-1} (amide C=O); NMR 2.1 (3 H, s), 2.28 (3 H, s), 7.3 (4 H, m); mass spectrum, *m/e* 249 [M^+], 207, 165, 164, 136, 86, 84.

A satisfactory elemental analysis could not be obtained for **18**.

Thermolysis of azide **10** (0.5 g) in a mixture of polyphosphoric acid (4 g) and acetic acid (10 mL) at 100 °C gave, after chromatography: (a) a solid material (0.1 g), mp 140–150 °C, whose spectral analysis showed it to be a mixture of products, the major component being compound (**18**); and (b) a complex mixture of unidentifiable products (0.3 g).

Acknowledgment. The authors thank C.N.R. for a research grant.

Registry No.—**11,** 66768-66-9; **12,** 66768-67-0; **13,** 66768-68-1; **14,** 66768-69-2; **15,** 66768-70-5; **16,** 66768-71-6; **17,** 66768-72-7; **18,** 66768-73-8; 2-bromothiophene, 1003-09-4; 3-bromothiophene, 872-31-1; 2-formyl-3-bromothiophene ethylene acetal, 56857-02-4; 3-formyl-4-iodothiophene ethylene acetal, 66768-74-9; 3-bromo-4-methylthiothiophene, 58414-59-8; 3-bromo-2-methylthiothiophene, 66768-75-0; 3-bromobenzo[*b*]thiophene, 7342-82-7; 2-bromobenzo[*b*]thiophene, 5394-13-8; tosylazide, 941-55-9; acetylene, 74-86-2; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Full NMR and mass spectral data for compounds 1–10 (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) S. Patai, Ed., "The Chemistry of the Azido Group", Interscience, New York, N.Y. 1971.
(2) P. A. S. Smith in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., pp 142–158.
(3) S. Gronowitz, C. Westerlund, and A. B. Hornfeldt, *Acta Chem. Scand., Ser B,* **29,** 224 (1975).
(4) Fragmentation of the magnesium salts to 1-aryl-3-*p*-toluenesulfonyltriazenes with sodium pyrophosphate to give aryl azides has been reported.[5]
(5) P. A. S. Smith, C. D. Rowe, and L. B. Bruner, *J. Org. Chem.,* **34,** 3430 (1969); S. Ito, *Bull. Chem. Soc. Jpn.,* **39,** 635 (1966).
(6) An attempt to prepare 2-azido-3-formylthiophene ethylene acetal by the same general procedure was unsuccessful, a mixture of colored products being obtained after fragmentation of the corresponding triazene salt. The failure in isolating any azide in this case and the low yields obtained with 2-azidothiophene (**2**) and 2-azidobenzo[*b*]thiophene (**9**) might be attributed to unfavorable fragmentation of the triazene–lithium salts; the observed instability of the 2-azido derivatives most probably plays an important role in affecting the nature of the reaction products. This point is being under investigation.
(7) R. K. Smalley and H. Suschitzky, *J. Chem. Soc.,* 5571 (1963).
(8) R. C. Elderfield, Ed. "Heterocyclic Compounds", Vol. 5, Wiley, New York, N.Y., 1957, pp 420–424.
(9) Thermolysis of aryl azides in a mixture of polyphosphoric acid and alyphatic carboxylic acid can represent a convenient route to benzooxazoles;[10a,b] this procedure has been recently extended to the preparation of some thienobenzoxazoles.[10c]
(10) (a) R. Gardner, E. B. Mullock, and H. Suschitzky, *J. Chem. Soc. C,* 1980 (1966); (b) E. B. Mullock and H. Suschitzky, *ibid.,* 1937 (1968); (c) B. Iddon, H. Suschitzky, D. S. Taylor, and M. W. Pickering, *J. Chem. Soc., Perkin Trans. 1,* 575 (1974).
(11) S. O. Lawesson, *Ark. Kemi,* **11,** 373 (1957).
(12) R. D. Schuetz, F. M. Gruen, D. R. Byrne, and R. L. Brennan, *J. Heterocycl. Chem.,* **3,** 184 (1966).
(13) S. Gronowitz, *Ark. Kemi,* **21,** 265 (1963).
(14) L. Lunazzi, A. Mangini, G. Placucci, M. Tiecco, and P. Spagnolo, *J. Chem. Soc., Perkin Trans. 2,* 192 (1972).
(15) R. A. Hoffman and S. Gronowitz, *Ark. Kemi,* **16,** 501 (1960).
(16) W. H. Cherry, W. Davies, B. C. Ennis, and Q. Porter, *Aust. J. Chem.,* **20,** 313 (1967).
(17) W. Von E. Doering and C. H. De Puy, *J. Am. Chem. Soc.,* **75,** 5955 (1953).

Syntheses of Indoles and Carbolines via Aminoacetaldehyde Acetals[1]

J. M. Bobbitt,* C. L. Kulkarni, C. P. Dutta, Hans Kofod and Kaolin Ng Chiong

Department of Chemistry, University of Connecticut, Storrs, Connecticut 06268

Received March 7, 1978

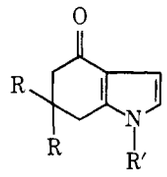
Aminoacetaldehyde dimethyl acetal has been condensed with 1,3-cyclohexanediones and cyclized with acid to 4-oxo-4,5,6,7-tetrahydroindoles. These oxoindoles have, in turn, been condensed with formaldehyde and methylaminoacetaldehyde dimethyl acetal and cyclized with acid to octahydro-β-carboline derivatives. Indole has been condensed with formaldehyde and methylaminoacetaldehyde dimethyl acetal and cyclized with acid to a tetrahydro-γ-carboline derivative.

For several years, we have used aminoacetaldehyde acetals in the synthesis of isoquinoline derivatives.[2] In this paper, we would like to present a modified experimental procedure for the use of these versatile acetals for the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles[3] and to extend the work to β- and γ-carboline systems.

4-Oxo-4,5,6,7-tetrahydroindoles, prepared by an alternate route,[4] have been developed[5,6] as synthetic intermediates. In a preliminary communication,[3] we described the preparation of these compounds (**1** → **3,** Scheme I) by an extremely simple process. The synthesis involves a remarkably stable enamine **2,** which undergoes an intramolecular condensation to yield

0022-3263/78/1943-3541$01.00/0 © 1978 American Chemical Society

Table I. 4-Oxo-4,5,6,7-tetrahydroindoles



3

Compd	Registry no.	R	R′	Yield, %	Mp, °C
3a	13754-86-4	H	H	33	184–186[a]
3b	20955-75-3	CH_3	H	33	182–183[b]
3c	13671-74-4	H	$C_6H_5CH_2$	61	81–82[c]
3d	66842-60-2	CH_3	$C_6H_5CH_2$	57	Viscous liquid
3e	51471-08-0	H	CH_3	60	84–86[d]
3f	20955-76-4	CH_3	CH_3	65	109–110[b]

[a] Lit.[12] mp 188–190 °C. [b] Analytical data were within ±0.3% for C, H, N. [c] Lit.[4] mp 80–81.5 °C. [d] Lit.[12] mp 85–86 °C.

the 4-oxotetrahydroindole **3.** The synthesis is similar to one described by Gomez Sanchez and co-workers,[7,8] involving the reactions between D-glucosamine (as the aminoaldehyde) and 1,3-diketones. The compounds prepared are described in Table I. The proton NMR spectra of these indoles showed characteristic peaks at δ 6.7 (t, J = 3 Hz, 1, H-2) and 6.5 (t, J = 3 Hz, 1, H-3) for **3a,** and similar peaks were observed for **3b.** For compounds **3c, 3d, 3e,** and **3f** these protons (H-2 and H-3) appear as single peaks in the region of δ 6.5–6.7.

The precise experimental procedures for the preparation of **3a, 3b, 3c,** and **3d** have been changed from the original publication[3] (see ref 9). In more recent papers, similar ring closures of enamine acids[10] and methylaminovinyl compounds[11] have been described.

Scheme I

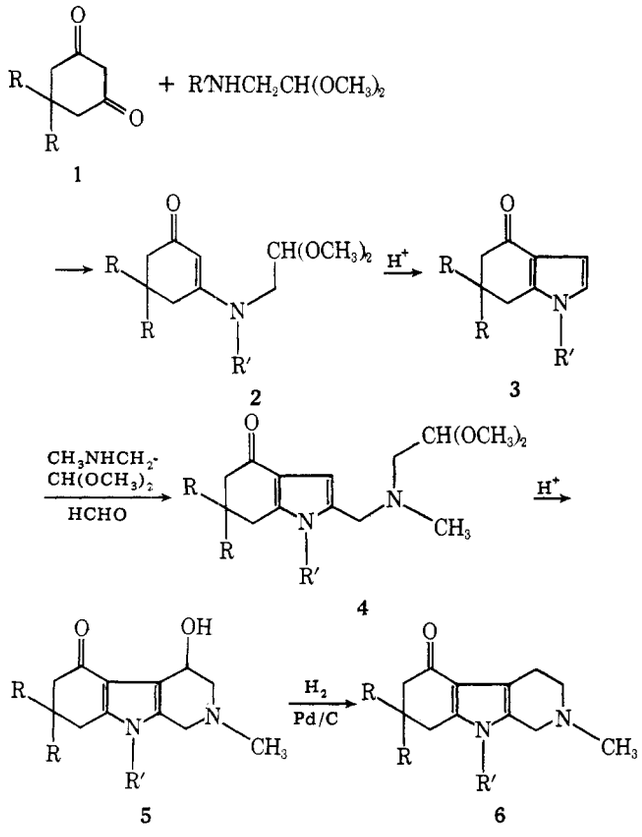
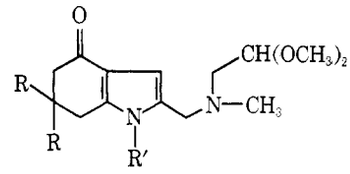


Table II. Condensation Products from 3, Methylaminoacetaldehyde Dimethyl Acetal, and Formaldehyde



4

Compd	Registry no.	R	R′	Yield, %
4a	66842-61-3	H	H	59
4b	66842-62-4	CH_3	H	88
4c	66842-63-5	H	$C_6H_5CH_2$	73 (crude)
4d	66842-64-6	CH_3	$C_6H_5CH_2$	34 (45 crude)
4e	66842-65-7	H	CH_3	61 (92 crude)
4f[a]	66842-66-8	CH_3	CH_3	65

[a] This compound was crystalline and melted at 71–72 °C. The others were viscous oils.

The general method involving Mannich reactions with aminoacetals[13] was applied to the oxoindoles **3** and indole itself to yield β-carboline derivatives (Scheme I) and a γ-carboline derivative (Scheme II), respectively. The oxoindoles **3** described in Table I were allowed to react with formaldehyde and methylaminoacetaldehyde dimethyl acetal in glacial acetic acid[14] to yield the condensation products **4** listed in Table II. These materials were mostly viscous liquids and were not completely characterized. Their NMR spectra exhibited the expected peaks. Evidence for the fact that the Mannich reaction takes place at C-2 rather than C-3 of the oxoindoles is derived from the ^{13}C NMR spectra of the products **4.** Carbons 2 and 3 of **3f** were shown to appear at 124.3 and 105.7 ppm (downfield from Me_4Si), respectively, by correlation with known spectra of pyrrole[15] and indole[16] and their derivatives. After the addition of the side chain (as shown in **4f**), these carbons appeared at 132.4 and 103.4 ppm, a shift of +8.1 for carbon 2 and −2.3 for carbon 3. For pyrrole[15] these shifts are +9.4 and −1.9, respectively. For indole they are +10.5 and −2.2.[16] Indole gave the corresponding Mannich base **7** as anticipated.[14]

Ring closure of the Mannich bases **4a–f** and **7** to the corresponding hydroxy compounds was carried out by treatment with dilute HCl.[17,18] 4-Hydroxy-*N*-methyl-1,2,3,4-tetrahydro-γ-carboline (**8**) was obtained in 62% yield. The products

Scheme II

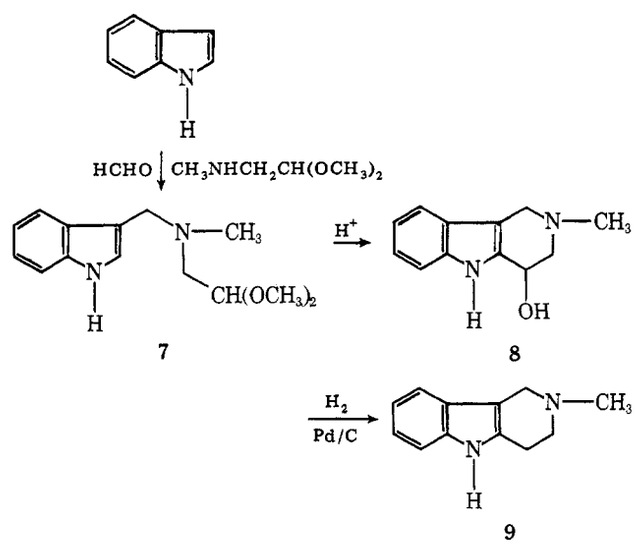
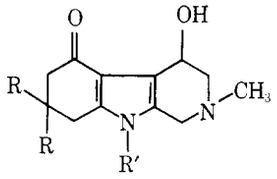


Table III. 2-Methyl-4-hydroxy-5-oxo-1,2,3,4,5,6,7,8-octahydro-β-carbolines[a]

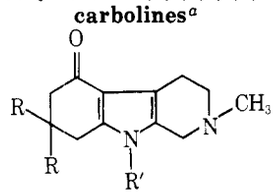


5

Compd	Registry no.	R	R′	Yield, %	Mp, °C
5a	66842-67-9	H	H	20	173–175
5b	66842-68-0	CH_3	H	56	178–180
5c	66842-69-1	H	$C_6H_5CH_2$	86	154–156
5d	66842-70-4	CH_3	$C_6H_5CH_2$	57	135–136
5e	66842-71-5	H	CH_3	63	157–159
5f	66842-72-6	CH_3	CH_3	77	159–160

[a] Analytical data were within ±0.4% for C, H, N.

Table IV. 2-Methyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-β-carbolines[a]



6

Compd	Registry no.	R	R′	Yield, %	Mp, °C
6a	66842-73-7	H	H	59	193–195
6b	66842-74-8	CH_3	H	57	227–229
6c	66842-75-9	H	$C_6H_5CH_2$	55	124–125
6d	66842-76-0	CH_3	$C_6H_5CH_2$	50	131–133
6e	66842-77-1	H	CH_3	45	166–168
6f	66842-78-2	CH_3	CH_3	74	130–131

[a] Analytical data were within ±0.35% for C, H, N for all new compounds in the table except for **6a**, where they were C, +0.75, H, +0.60, and N, −0.35.

derived from **4a–f** are described as **5a–f** in Table III. The proton NMR spectra of these compounds showed a characteristic broad triplet (J = 4–6 Hz) for H-4 in the δ 4.75–5.1 region. However, this proton (H-4) was buried beneath the benzyl protons in compounds **5c** and **5d**.

The hydrogenolysis of the various hydroxy compounds, **5a–f** and **8**, was accomplished with some difficulty over palladium on carbon.[19] The time and temperature of the hydrogenolysis were varied to accomplish the desired results. In no case was an N-benzyl group removed by hydrogenolysis. The known compound N-methyl-1,2,3,4-tetrahydro-γ-carboline (**9**)[20] was obtained in 66% yield. The various β-carboline derivatives (**6a–f**) are described in Table IV.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus or on a Reichert hot stage apparatus and are uncorrected. Proton NMR spectra were determined in $CDCl_3$ with a Me_4Si standard on a Varian A-60 instrument. The proton noise-decoupled ^{13}C NMR spectra were measured in $CDCl_3$ on a Bruker WP-60 FT spectrometer with 8K computer memory using a 10 mm sample tube. Spectra were recorded on a 4000 Hz sweep width at 15.08 MHz using the fast Fourier transform technique. All solvent evaporations were carried out on a Büchi rotary vacuum evaporator. Analyses were carried out by Baron Consulting Co., Orange, Conn.

4-Oxo-4,5,6,7-tetrahydroindoles 3a, 3b, 3e, and 3f. A mixture of 4.48 g (0.04 mol) of 1,3-cyclohexanedione, 6.4 g (0.06 mol) of aminoacetaldehyde dimethyl acetal, and 0.2 g of p-toluenesulfonic acid in 150 mL of benzene was heated to reflux for 24 h with continuous removal of H_2O through a Dean-Stark tube. The benzene was evaporated, and the orange residue was treated with an ice-cold mixture of 60 mL of 3 N HCl and 50 mL of $CHCl_3$. The mixture was stirred for a few minutes at room temperature, and the aqueous acidic layer was separated and transferred to a continuous extraction apparatus designed for extraction with heavier-than-H_2O liquids. The mixture was extracted with $CHCl_3$ overnight or until no more material was extracted. A few chips of $CaCO_3$ were placed in the $CHCl_3$ reservoir to neutralize any acid which might be extracted.[21] After removal of the solvent from the extract, the residue was dissolved in 10 mL of benzene/acetone (4:1) and placed on top of a short column (2.4 × 11 cm) of silica gel[22] and eluted with benzene/acetone (4:1). Fractions of 75 mL were taken. The product, **3a** (1.8 g), obtained from fractions 2, 3, and 4, was crystallized from benzene/hexane. Compounds **3b, 3e,** and **3f** were prepared in the same manner. Compound **3f** had the following spectral properties: ^1H NMR ($CDCl_3$) δ 6.57 (s, 2, H-2 and H-3); ^{13}C NMR ($CDCl_3$) (downfield from Me_4Si) 124.3 (C-2) and 105.7 (C-3) ppm.

4-Oxo-4,5,6,7-tetrahydroindoles 3c and 3d. A mixture of 2.24 g (0.02 mol) of 1,3-cyclohexanedione, 5.85 g (0.03 mol) of N-benzylaminoacetaldehyde dimethyl acetal, 70 mL of benzene, and 0.1 g of p-toluenesulfonic acid was heated to reflux for 24 h with continuous removal of H_2O with a Dean-Stark tube. The benzene was removed, and the residue was heated to 45–50 °C with 30 mL of 3 N HCl for 4 h. A gummy material separated. The mixture, gum and all, was extracted with $CHCl_3$, washed (H_2O), dried (Na_2SO_4), and concentrated to give 3.75 g of dark red viscous material. This was dissolved in 10 mL of benzene/acetone (4:1) and chromatographed over silica gel as described for **3a** to give 2.75 g of **3c** which was crystallized from benzene/hexane. Compound **3d** was prepared in the same manner.

Mannich Bases Derived from Compounds 3. A solution of 0.01 mol of the 4-oxo-4,5,6,7-tetrahydroindole in 5 mL of acetic acid was treated with 0.012 mol of methylaminoacetaldehyde dimethyl acetal. The mixture was heated to 70–75 °C for 2 h, cooled, diluted with about 50 mL of H_2O, and extracted with ether to remove any nonbasic material. The aqueous acidic layer was basified (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), concentrated to a residue, dissolved in 15 mL of benzene/acetone (4:1), and chromatographed over a silica gel column as described for **3a.** The eluents were concentrated to give the Mannich bases which, except for **4f,** were viscous oils. Compound **4f** melted at 71–72 °C and had the following spectral properties: ^1H NMR ($CDCl_3$) δ 6.5 (s, 1, H-3) and 4.54 (t, 1, $-CH(OCH_3)_2$); ^{13}C NMR ($CDCl_3$) (downfield from Me_4Si) 132.4 (C-2) and 103.4 (C-3) ppm.

4-Hydroxy-1,2,3,4,5,6,7,8-octahydro-5-oxo-β-carbolines 5. General Procedure. A solution of the appropriate Mannich base **4** (0.005 mol) in 15 mL of 8 N HCl was warmed to 60–70 °C for 5 min. After cooling, the mixture was washed ($CHCl_3$), basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), concentrated to a residue, and crystallized to yield the product (**5a** from chloroform/hexane; **5b** from acetone/hexane; and **5c, 5d, 5e,** and **5f** from benzene/hexane).

5-Oxo-1,2,3,4,5,6,7,8-octahydro-β-carbolines 6. A mixture of the hydroxycarboline **5** and an equal weight of 5% Pd/C, 8 N HCl (5 mL per 0.1 g of carboline), and ethanol (5 mL per 0.1 g of carboline) was hydrogenated in a Paar apparatus at 16 psi until no more hydrogen was absorbed. The hydrogenations of **5a, 5b, 5e,** and **5f** were carried out at room temperature, and those of **5c** and **5d** were carried out at 60–65 °C. The catalyst was removed by filtration, and the filtrate was concentrated to a small volume, basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), and concentrated to a residue which was crystallized to give the product (**6a** from ether; **6b** and **6e** from chloroform/hexane; and **6c, 6d,** and **6f** from benzene/hexane).

Mannich Base 7. This compound was prepared from indole by a method identical with that described above for **3** except that the formaldehyde was added dropwise and the solution was not heated but was allowed to stir for 1 h. The product, 4 g (80%), was obtained by triturating the crude final residue (see procedure for **4**) with hexane. The compound melted at 79–80 °C. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.97; H, 8.05; N, 11.22.

4-Hydroxy-2-methyl-1,2,3,4-tetrahydro-γ-carboline (8). Compound **7** (2 g, 0.01 mol) was added to 60 mL of 6 N HCl which had been previously cooled to 0 °C. The solution was stirred at 0 °C for 1 h and at room temperature for 3.5 h and then basified (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried

(Na_2SO_4), and evaporated to give 1 g (62%) of **8** which was recrystallized from $CHCl_3$ to give the product, mp 205–207 °C. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.76; H, 6.98; N, 13.85. Found: C, 70.99; H, 6.89; N, 13.87.

2-Methyl-1,2,3,4-tetrahydro-γ-carboline (9). A mixture of 0.202 g of **8**, 0.2 g of 5% Pd/C, 10 mL of 6 N HCl, and 10 mL of ethanol was hydrogenated at 17 psi for 16 h at room temperature. The product was isolated as described above for **6**. The final residue was triturated with benzene to give 0.123 g (66%) of crystalline **9** with mp 163–165 °C. After recrystallization from acetone/benzene, the compound melted at 172–173 °C (lit.[20] mp 171–172 °C).

Acknowledgment. In addition to the financial support previously mentioned, we would like to thank Professor A. Makriyannis of the College of Pharmacy of the University of Connecticut for measuring the ^{13}C NMR spectra.

Registry No.—**1a**, 504-02-9; **1b**, 126-81-8; **7**, 66842-79-3; **8**, 66842-80-6; **9**, 5094-12-2; $H_2NCH_2CH(OMe)_2$, 22483-09-6; $PhCH_2NHCH_2CH(OMe)_2$, 54879-88-8; $MeNHCH_2CH(OMe)_2$, 122-07-6; indole, 120-72-9; formaldehyde, 50-00-0.

References and Notes

(1) This work was sponsored in part by Contract DA-49-193-MD-2948 from the U.S. Army Medical Research and Development Command, publication 1500 from the Army Research Program on Maleria, and in part by Research Grant CA-10494 from the Cancer Institute of the National Institutes of Health.
(2) J. M. Bobbitt and S. Shibuya, *J. Org. Chem.*, **35**, 1181 (1970), and preceding papers of the series.
(3) The synthesis of 4-oxo-4,5,6,7-tetrahydroindoles was published as a preliminary communication: J. M. Bobbitt and C. P. Dutta, *Chem. Commun.*, 1429 (1968).
(4) W. A. Remers and M. J. Weiss, *J. Am. Chem. Soc.*, **87**, 5262 (1965).
(5) W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971); D. B. Repke, W. J. Ferguson, and D. K. Bates, *J. Heterocycl. Chem.*, **14**, 71 (1977).
(6) W. A. Remers and M. J. Weiss, *J. Org. Chem.*, **36**, 1241 (1971).
(7) F. Garcia Gonzalez, A. Gomez Sanchez, and M. I. Goni de Rey, *Carbohydr. Res.*, **1**, 261 (1965).
(8) A. Gomez Sanchez, M. Gomez Guillen, and V. Scheidegger, *Carbohydr. Res.*, **3**, 486 (1967).
(9) Dr. J. A. Joule of the University of Manchester in England has informed us that he was unable to repeat our original procedure[3] for the preparation of **3a**. We have been able to repeat it, but the extraction procedure described in this paper is more reliable. A third procedure has been described to us in a private communication by Dr. James Cook of the University of Wisconsin in Milwaukee, Wis.
(10) R. J. Friary, R. W. Franck, and J. F. Tobin, *J. Chem. Soc. D*, 283 (1970).
(11) A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 593 (1976).
(12) P. Crabbé, B. Halpern, and E. Santos, *Tetrahedron*, **24**, 4299 (1968).
(13) J. M. Bobbitt and C. P. Dutta, *J. Org. Chem.*, **34**, 2001 (1969).
(14) W. J. Brehm and H. G. Lindwall, *J. Org. Chem.*, **15**, 685 (1950).
(15) T. F. Page, Jr., T. Alger, and D. M. Grant, *J. Am. Chem. Soc.*, **87**, 5333 (1965).
(16) R. G. Parker and J. D. Roberts, *J. Org. Chem.*, **35**, 996 (1970).
(17) J. M. Bobbitt and J. C. Sih, *J. Org. Chem.*, **33**, 856 (1968).
(18) J. M. Bobbitt, *Adv. Heterocycl. Chem.*, **15**, 99 (1973).
(19) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).
(20) V. Boekelheide and C. Ainsworth, *J. Am. Chem. Soc.*, **72**, 2132 (1950).
(21) The basis of this procedure is that the Schiff base **2** is basic and soluble in dilute HCl, whereas the product **3** is no longer basic and is extracted as it is formed.
(22) Silica gel M was obtained from Herrmann Brothers, Cologne, Ger.

Azaindolizines. 5. Nucleophilic Substitution on Chloro-6- and -8-azaindolizines

Robert Buchan, Martin Fraser,* and Charles Shand

Department of Chemistry, Robert Gordon's Institute of Technology, Aberdeen, Scotland.

Received November 8, 1977

Cyclization of the products of reaction between phenacyl bromide and 4,6-dimethyl-2-pyrimidone and 2-methyl-4-pyrimidone gave the 6- and 8-azaindolizinones **7** and **9**, which on reaction with phosphoryl chloride gave the corresponding 5- and 7-chloro-6- and -8-azaindolizines **2** and **5**, respectively. The substitution of chlorine from **2** and **5** by hydroxide, methoxide, and amide was investigated; displacement of chlorine by all these nucleophiles occurred with the 5-chloro-6-azaindolizine **2**, whereas only methoxylation occurred with the 7-chloro-8-azainolizine **5**. Reaction of **2** with phosphoryl chloride gave the peri condensed structure **13**. Formylation of the product of ammonolysis of **2** gave the 1,7-diazacyclo[3.2.2]azine **16**.

Both 6- and 8-azaindolizines can be formally classified as π-excessive[1] heteroaromatic systems and as such would be expected to show a propensity toward electrophilic rather than nucleophilic substitution processes. Electrophilic substitution of both 6- and 8-azaindolizines has been shown[2,3] to occur preferentially at C-3 and then at C-1, findings which are broadly in agreement with theoretical MO calculations.[4,5] Although the 6- and 8-azaindolizines are π excessive, the MO calculations indicate both systems to have sites of considerable electron deficiency. The sites of minimum electron density, as might be expected, occur within the pyrimidine moiety specifically at C-5 and C-7, the C-5 site being the most deficient for the 6-aza- and the C-7 site for the 8-azaindolizine system.

Although nucleophilic displacement from pyrimide and other π-deficient[1] heteroaromatic systems is common, even hydride ion displacement being possible,[6] no instances of successful nucleophilic displacement from the indolizine nucleus have been reported, and of the seven possible azaindolizines only the 1-azaindolizine system has been shown to undergo nucleophilic displacement of chlorine.[7–9] In this paper we describe the reactivity of the chlorine in 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) and 7-chloro-2-phenyl-8-azaindolizine (**5**). Attempts to effect direct nucleophilic subtitution on 7-methyl-2-phenyl-6-azaindolizine (**1**) by treatment with sodamide or sodium methoxide at temperatures up to 180 °C merely resulted in decomposition or at lower temperatures in the recovery of starting material.

The chloro-6- and 8-azaindolizines **2** and **5** were prepared by heating the corresponding 6- and 8-azaindolizinones **7** and **9** with phosphoryl chloride. 7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (**7**) and 2-phenyl-8-azaindolizine-7(8*H*)-one (**9**) were each obtained by reacting 4,6-dimethyl-2-pyrimidone and 2-methyl-4-pyrimidone, respectively, with phenacyl bromide. In each reaction the minor product was the corresponding azaindolizinone **7** and **9** and the major product the corresponding *N*-phenacylpyrimidones **11** and **12** which were readily cyclized to the 6- and 8-azaindolizinones **7** and **9** by heating at 180 °C. While the reaction of 4,6-dimethyl-2-pyrimidone with phenacyl bromide can only lead, on cyclization, to the 6-azaindolizin-5(6*H*)-one **7**, 2-methyl-4-pyrimidone could give either the 2-phenyl-8-azaindolizin-7(8*H*)-one **9** or

0022-3263/78/1943-3544$01.00/0 © 1978 American Chemical Society