Methyleneindolines, indolenines, and indoleniniums. 19. A new entry into the hexahydropyrrolidino[2,3-d]carbazole system

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or CF_3CO_2H-d_1 (Merck), and 1K to 2K transients were collected. Chemical shifts from tetramethylsilane were referenced internally to Me_2SO-d_6 (39.5 ppm) and CF_3CO_2H-d_1 (116.6 ppm). Spectra were run at either 30 °C or 50 °C as indicated.

Registry No. 2, 115-43-5; 3, 25860-24-6; 4, 25860-23-5; 6, 91159-05-6; 7, 91159-06-7.

Methyleneindolines, Indolenines, and Indoleniniums. 19.[1] A New Entry into the Hexahydropyrrolidino[2,3-*d*]carbazole System

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The pyrrolidino[2,3-*d*]carbazole system is part of many important indole alkaloids of the Aspidosperma and Strychnos families inter alia, and it has been the object of several recent synthetic efforts[3]. We report herein a novel approach to this system, exemplified by a three-step synthesis of **1**.

Tetrahydro-β-carbolines **2** and **3** are obtained in high yield (Scheme I) through Pictet–Spengler condensation of N_b-ethyltryptamine[4] with aldehydes **4** and **5**, the Michael addition products of acrolein with ethyl and methyl malonate, respectively.[5] Treatment of **2** with *t*-BuOCl[6] gives a quantitative yield of the chloroindolenines **6a,b** in a 1:1 ratio. When treated with NaH in THF, **6a,b** is transformed into a mixture containing the rearranged **1** (48%) and unaffected **6a** (18%). Similar treatment of **3** affords two chloroindolenines **7a,b**, which are separated before being subjected to the rearrangement conditions. While the less polar isomer **7a** is recovered unchanged, **7b** is cleanly transformed by NaH into the α-methyleneindoline **8** (75%).

Compounds **1** and **8** display the typical UV spectra of β-anilinoacrylate esters (λ_{max}^{MeOH} 226, 298, 328 nm) and give intense blue TLC spots upon spraying with Ce(IV). Their mass spectra are dominated by the retro-Diels–Alder fragmentation of ring C, accompanied by the rupture of the tryptamine chain α and β to N_b.[7] Final structural proof for **1** and **8** was obtained by an independent synthesis according to a literature procedure.[3d]

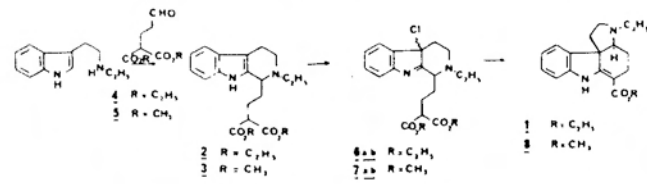
Although several pathways may explain the transformation **6** → **1**, we favor a mechanism in which the initially formed malonate anion intramolecularly attacks C-2 of the indole (Scheme II). C-ring contraction with chloride expulsion is followed by Krapcho-like decarbalkoxylation of intermediate B, which occurs under extremely mild conditions because of the triactivated nature of the ester-bearing carbon.[8] Repetition of the experiment with enantiomerically enriched **3** ($[\alpha]_D$ + 18° (*c* 0.8, EtOH)) leads to optically active **8** ($[\alpha]_D$ + 72° (*c* 0.5, EtOH)); this rules out mechanisms in which achiral intermediates are produced. The unreactivity of chloroindolenines **6a** and **7a** is probably due to the wrong relative stereochemistry of the side chain and the chlorine atom. Fortunately, the unreacted chloroindolenine can be reduced back to the parent indoles **2** and **3** with thiophenol.[9]

Additions of carbon nucleophiles at C-2 of chloroindolenines are rare, and one of the few examples reported is Kuehne's addition of diethyl thalliomalonate to the chloroindolenine of tetrahydrocarbazole.[10] Use of the thallium counterion was found to be essential; sodiomalonate led only to reduction to tetrahydrocarbazole, probably by attack at chlorine rather than at carbon. In our case, the length of the chain between the indole nucleus and the nucleophile does not favor attack at chlorine.

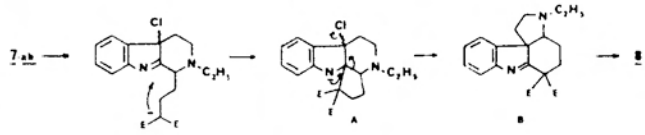
Brief exploration of the scope of the rearrangement led us to examine the behavior of the more reactive aldehydo ester **9** (which exists mainly in the carbinolamine form **10**). Surprisingly, its treatment with *t*-BuOCl (Scheme III) leads directly to α-methyleneindoline **11**. Rearrangement of the (undetected) intermediate chloroindolenine is probably catalyzed by triethylamine.

The availability of synthons such as **9** by direct formylation[11] of esters renders this approach attractive, and application of these rearrangements to the synthesis of pentacyclic natural alkaloids is currently being explored. The production of diversely substituted indolo[2,3-*d*]-indoles opens the way to the synthesis of the corresponding vindoline adducts[3d] and benzofurans.[12]

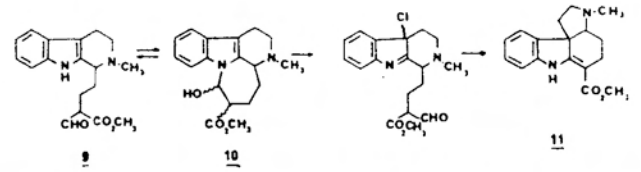
Scheme I



Scheme II



Scheme III



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Experimental Section

General Methods. All melting points were determined on a Koffler apparatus and are corrected; the IR spectra were recorded on a Beckmann Acculab 2 spectrometer and the UV spectra on a LERES-SPILA S28 photometer; ^{1}H NMR spectra were measured on a Perkin-Elmer R12B spectrometer (60 MHz) or on an IEF 400, a prototype built at the University of Orsay (401 MHz). Mass spectra were recorded on a JEOL D300 spectrometer. Elemental analyses were performed by Microanalysis Department of the Faculty of Sciences of Reims.

Preparation of Carboline 2. To a solution of N_b-ethyltryptamine (862 mg, 4.5 mmol) in 20 mL of boiling toluene was added aldehyde **4** (1.1 g, 1.15 equiv). After 30 min, 2 mL of glacial AcOH was added, and the mixture was refluxed for 6 h. After evaporation of toluene, the residue was partitioned between ether and 0.5 N aqueous NaOH. The organic layer was dried and evaporated, leaving 1.65 g (95%) of a solid, homogeneous by TLC. An analytical sample was prepared by crystallization of the camphosulfonate salt of **2** (mp 204 °C): MS, m/z (relative intensity) 386 ($M^{+\cdot}$, 12), 385 (10), 341 (40), 238 (30), 199 (100); IR 3410, 1750, 1730 cm^{-1}; ^{1}H NMR (base, 60 MHz, $CDCl_3$) δ 8.2 (s, 1 H), 4.2 (q, J = 7 Hz, 4 H), 1.25 (t, J = 7 Hz, 6 H), 1.1 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{31}H_{46}N_2O_8S$: C, 61.3; H, 7.6; N, 4.6. Found: C, 61.5; H, 7.4; N, 4.7.

Preparation of Carboline 3. To a solution of N_b-ethyltryptamine (4.5 g, 23.9 mmol) in 30 mL of refluxing benzene was added aldehyde **5** (5 g, then 1 h later 2 g, total 1.5 equiv). After being refluxed for 24 h, the solvent was evaporated and the residue chromatographed on 120 g of silica gel. Elution with a mixture of CH_2Cl_2 and MeOH (99:1) yielded 5.8 g (68%) of an oil, homogeneous by TLC: MS, m/z (relative intensity) 358 ($M^{+\cdot}$, 18), 238 (10), 212 (17), 199 (100); IR 3400, 1750, 1720 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.0 (s, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.5 (t, J = 7 Hz, 1 H), 1.1 (t, J = 7 Hz, 3 H).

Chlorination of 2 (6a,b). To a solution of **2** (1.5 g, 3.9 mmol) in 10 mL of CH_2Cl_2 was added Et_3N (810 μL, 588 mg, 5.8 mmol, 1.5 equiv) and then t-BuOCl (500 μL, 510 mg, 4.6 mmol, 1.2 equiv). After 10 min at room temperature, the solution was washed twice with water and evaporated in vacuo, leaving 1.7 g (96%) of a solid showing two spots on TLC: colors on TLC (Ce(IV) spray) **6a** colorless, **6b** orange; UV (mixture) λ_{max}^{MeOH} 227, 263, 292 (sh); MS m/z (relative intensity) 422 ($M^{+\cdot}$, 0.5), 420 ($M^{+\cdot}$, 1), 419 (1.5), 385 (30), 235 (10), (35), 212 (25), 199 (100), 197 (25); IR 1745, 1730, 1580 cm^{-1}.

Chlorination of 3 (7a,b). **3** (1.7 g) was treated with Et_3N and t-BuOCl as described for **2** to yield 1.67 g of solid, which was purified on a Merck Lobar column. In addition to fractions containing a mixture of **7a** and **7b**, pure **7a** (405 mg, 28%) and **7b** (455 mg, 31%) were obtained. Compound **7a**: TLC (Ce(IV)) colorless; UV λ_{max}^{MeOH} 230, 265, 303 nm; IR 1750, 1735, 1580 cm^{-1}; MS m/z (relative intensity) 394 ($M^{+\cdot}$, 0.5), 392 ($M^{+\cdot}$, 1.5), 357 (35), 235 (32), 233 (100), 199 (80), 197 (30), 178 (20); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.7–7.2 (m, 4 H), 3.8 (s, 6 H), 1.05 (t, 3 H, 7 Hz). Compound **7b**: TLC (Ce(IV)) orange; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.7–7.3 (m, 4 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 1.05 (t, 3 H, 7 Hz); MS and UV same as **7a**; IR are superimposable except for fingerprint area.

Rearrangement of 6a,b (1). A mixture of compounds **6a,b** (800 mg, 1.9 mmol) was dissolved in 10 mL of dry THF (Na, benzophenone), and 50% NaH suspension in oil (100 mg, 1.1 equiv) was added. After 18 h at room temperature, the reaction mixture was partitioned between ether and water. The usual workup yielded 657 mg of a mixture, which was purified on 100 g of silica gel. Elution with $CHCl_3$ yielded **6a** (120 mg) followed by **1** (320 mg, 48%): UV 227, 298, 328 nm; MS, m/z (relative intensity) 312 ($M^{+\cdot}$, 20) [analyzed for $C_{19}H_{24}N_2O_2$ 312.1793, calcd 312.1836)], 241 (241.1091, $C_{15}H_{15}NO$; calcd 241.1101), 199, 166, 84 (100); IR 3370, 1670, 1610 cm^{-1}; ^{1}H NMR (401 MHz, $CDCl_3$) δ 9.09 (s, 1 H), 4.32(q, J = 7 Hz, 2 H), 3.23 (d, J = 5 Hz, 1 H), 3.04 and 2.83 (dq, J = 14 Hz, 7 Hz, 2 × 1 H), 1.43 (t, J = 7 Hz, 3 H), 1.33 (t, J = 7 Hz, 3 H).

Rearrangement of 7b (8). Pure chloroindolenine **7b** (400 mg, 1 mmol) was treated with NaH (50 mg) in 5 mL of dry THF. After 4 h at room temperature and 8 h at reflux, the usual workup gave a mixture which was purified by column chromatography to yield 230 mg (75%) of **8**: UV 226, 298, 328 nm; MS, m/z (relative intensity) 298 ($M^{+\cdot}$, 35) [$C_{18}H_{22}N_2O_2$, found 298.1628; calcd 298.1670], 267 (10), 239 (16), 227 (100), 214 (15), 168 (18), 167 (17), 84 (100); IR 3390, 1670, 1610 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) 9.0 (s, 1 H), 3.75 (s, 3 H), 1.2 (t, J = 7 Hz, 3 H).

Rearrangement of 10. To compound **10**[2] (40 mg, 0.12 mmol, mixture of isomers) dissolved in 2 mL of CH_2Cl_2 were added Et_3N (26 μL, 1.5 equiv) and then t-BuOCl (17 μL, 1.2 equiv). After 20 min, the suspension was poured into 10 mL of saturated aqueous NH_4Cl. The usual workup followed by column chromatography of the residue gave 18 mg of pure **11**, in all regards identical with compound **1** of ref 3d.

Registry No. **1**, 91085-29-9; **2**, 75622-29-6; **3**, 91085-30-2; **4**, 19515-61-8; **5**, 72473-15-5; **6** (isomer 1), 91085-31-3; **6** (isomer 2), 91085-32-4; **7** (isomer 1), 91085-33-5; **7** (isomer 2), 91085-34-6; **8**, 91085-35-7; **10**, 91085-36-8; **11**, 91176-85-1; N-ethyltryptamine, 61-53-0.

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Stereochemistry of Nucleophilic Substitution Reaction of 16-Bromo-17-oxo Steroids with Thiols

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Recent studies[1] on the reaction of 16-bromo-17-oxo steroids with nucleophiles, hydroxide ion, and morpholine, demonstrated that equilibration between the 16α- and 16β-bromo ketones precedes the displacement of bromine with nucleophiles, in which the true intermediate is the 16β-bromo isomer and not the 16α-isomer, and that 16α-substituted 17-oxo derivatives are formed by the direct S_N2 displacement of the 16β-bromine. 16α-Morpholino derivative initially produced is, then, almost completely epimerized to the thermodynamically stable 16β-epimer[2] in the presence of heated basic morpholine, while a 16α-hydroxy 17-one is quantitatively obtained under controlled conditions[1,3] (Scheme I).

However, the reaction of the bromo ketones with a sulfur nucleophile is somewhat complicated and its reaction mechanism remains to be unclear. Takeda et al.[4] reported that both 16α- and 16β-bromo 17-ketones gave the same product, the 16β-thio ether derivative A (Scheme II), in the reaction with thioacetate. On the other hand, Pelc and Holmes[5] reported the conversion of 16α- and 16β-bromo ketones **1** and **2** with thioglycolic acid to the corresponding (carboxymethyl)thio derivatives **6** and **7** with retention of configuration at the C-16 position, respectively (Chart I).

In our continuing interest in the chemistry of 16-bromo 17-ketones, we found that direct S_N2 displacement of bromine by sulfur nucleophiles is possible in the α-bromo ketones without prior epimerization of the bromo ketones.

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