Synthesis of Vinca Alkaloids and Related Compounds. 37.[1] Some New Reactions of (±)-*C*-Norquebrachamine and Its Derivatives

György Kalaus,[†] Numan Malkieh,[†] Mária Kajtár-Peredy,[‡] János Brlik,[†] Lajos Szabó,[†] and Csaba Szántay*[‡]

Department of Organic Chemistry and MS Laboratory of the Institute for General and Analytical Chemistry, Technical University, Budapest, Gellért tér 4, H-1521 Budapest, Hungary, and Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest, Pusztaszeri ut 59-67, H-1525 Budapest, Hungary

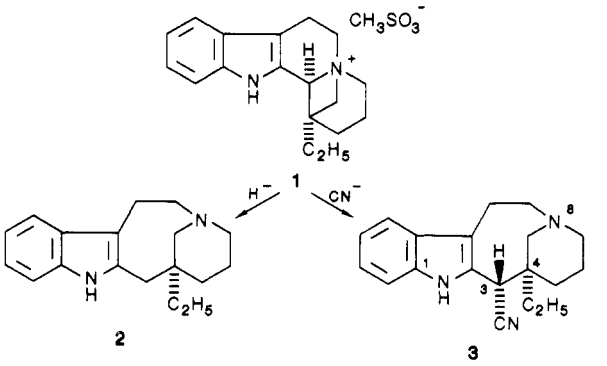
Received April 23, 1987

Oxidation of (±)-*C*-norquebrachamine (**2**) with chromyl acetate ($CrO_3/(CH_3CO)_2O$) in dichloromethane/acetic acid resulted, by ring cleavage, in the macrocyclic compound **17**. Similar oxidation of **3** and **4** gave **7** + **8** and **16b**, respectively.

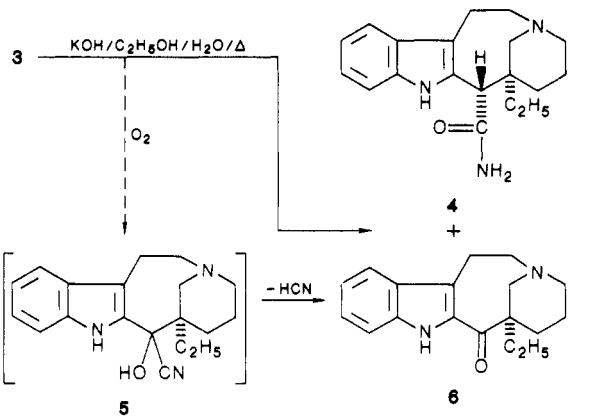
Previously we have reported[2] that the mesylate obtained from 1α-ethyl-1β-(hydroxymethyl)-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine immediately formed a quaternary salt (**1**). The behavior of **1** toward nucleophiles was investigated, and it was established that with hydride ion (±)-*C*-norquebrachamine (**2**) was obtained exclusively; with cyanide ion both in protic and in dipolar aprotic solvents, (±)-3α-cyano-*C*-norquebrachamine (**3**) proved to be the main product (Scheme I). In the present paper we describe further transformations of these compounds. At first we wished to transform the cyano group of **3** into a methoxycarbonyl function in order to obtain (±)-*C*-norvincadine and/or its C3 epimer.[3] In CH_3OH/HCl[4] or in CH_3OH/H_2SO_4[5], **3** remained unchanged, while treatment with KOH in ethylene glycol[6,7] resulted in no definite product. However, on boiling of **3** in KOH/EtOH for several days, two products were isolated. The main product was the amide **4**, which resisted further hydrolysis in acidic medium. As a minor product, (±)-3-oxo-*C*-norquebrachamine (**6**) was separated. Compound **6** was presumably formed via **5**, which can be derived from **3** as a result of oxidation by air (Scheme II). This latter observation prompted us to study the behavior of the ring system on oxidation. When **3** was reacted with common oxidizing agents (such as $Hg(AcO)_2$[8] and $KMnO_4$[9]) or the Polonovsky reaction[10] was applied, either no reaction was observed or undefined products were formed. Oxidation with chromyl acetate[11] was, however, successful. Compound **3** was dissolved in a mixture of CH_2Cl_2 and AcOH and then oxidized with a solution of CrO_3 in Ac_2O at −60 to −30 °C. As reaction products, **7** and **8** were obtained. It is worth mentioning that higher temperature and longer reaction time favors the formation of **8** (Scheme III). Structures **7** and **8** were inferred from NMR observations. The absence of the indole NH signal in the proton spectrum of **7**, on the one hand, and the number as well as the chemical shift values of the sp^2 carbon resonances, on the other, indicated that this product contained an indolenine moiety. An additional quaternary sp^3 carbon resonance at 84.18 ppm was assignable to C13b substituted by a hydroxyl group. The carbon-13 spectrum of **8** indicated the presence of two carbonyl functions in the molecule (206.58 and 162.92 ppm); their location (C4 and C13) within the product followed from the chemical shift changes of neighboring carbon atoms.

The (±)-*C*-norrhazidigenine[12] derivative **7** proved to be the intermediate of **8**. Compound **8** was obtained by starting from **7** under the mentioned reaction conditions. Similar observations have also been reported by Japanese authors[13] on oxidation of 2,3-disubstituted indole derivatives. In order to convert the cyano group of **7** into an ester function, it was dissolved in MeOH/HCl and kept at room

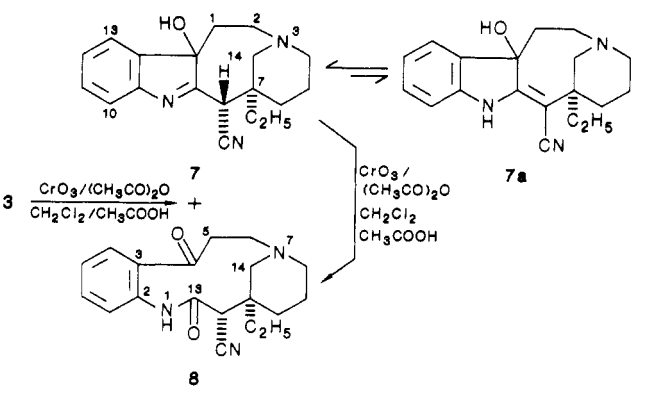
Scheme I



Scheme II



Scheme III

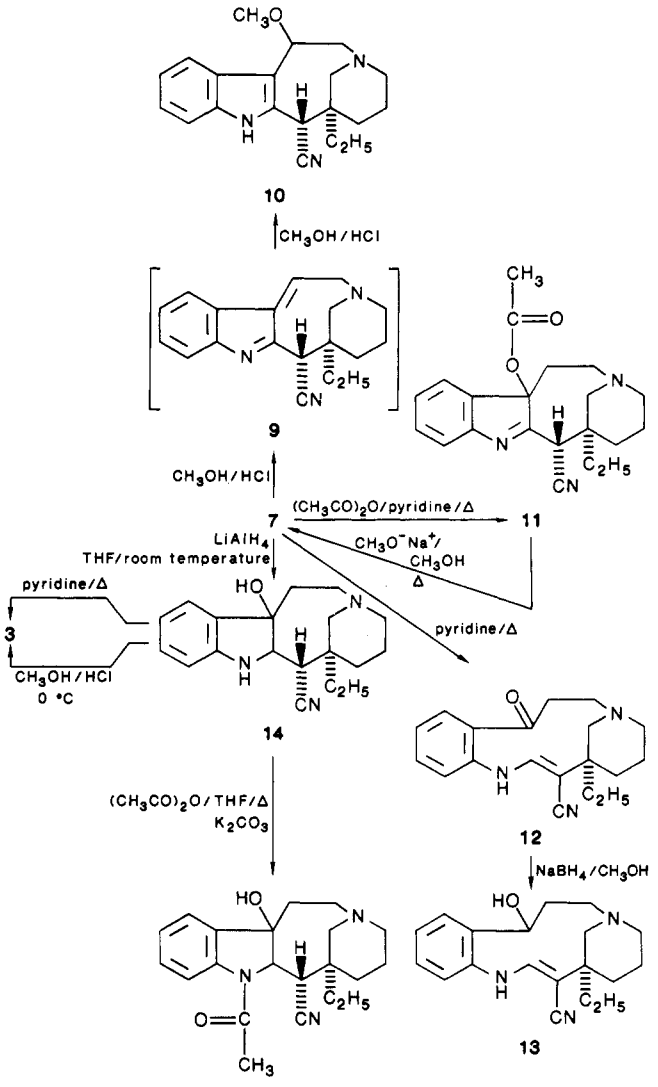


[†] Technical University, Budapest.
[‡] Hungarian Academy of Sciences, Budapest.

(1) Part 36: Kalaus, Gy.; Galambos, J.; Kajtár-Peredy, M.; Tamás, J.; Szabó, L.; Sápi, J.; Szántay, Cs. *Liebigs Ann. Chem.* **1987**, 745.

0022-3263/88/1953-0042$01.50/0

Scheme IV



temperature. After about 0.5 h, the starting material disappeared, and a well-defined product (**10**) was formed, presumably by elimination–addition[14] via **9** (Scheme IV).

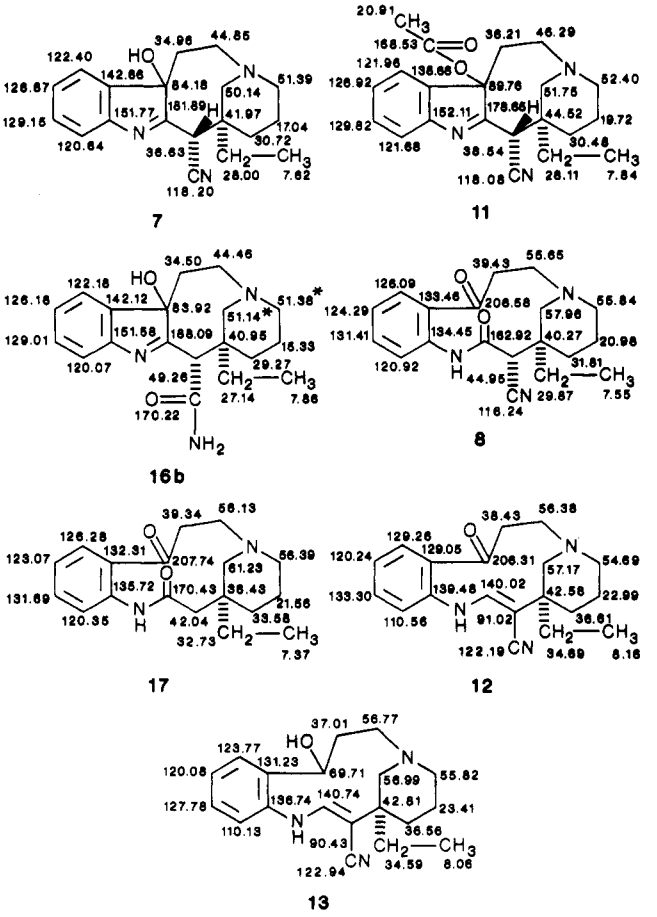
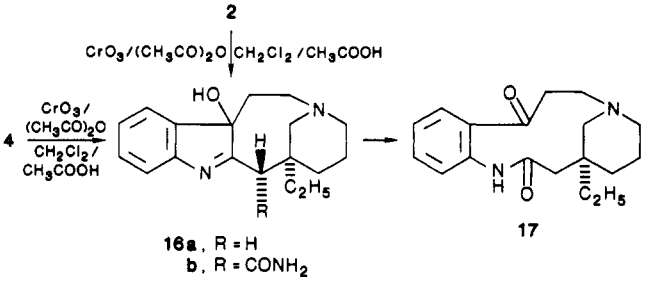


Figure 1. ^{13}C chemical shifts of **7**, **11**, **16b**, **8**, **17**, **12**, and **13**, δ (ppm). * may be interchanged.

Scheme V



The ^1H and ^{13}C NMR data of the product **10** attested to the presence of an indole moiety. The occurrence of a three-proton singlet at 3.55 ppm and a carbon resonance at 56.93 ppm disclosed the presence of a methoxyl group in the molecule. The position of this substituent followed from the replacement of the C10 methylene signal of **3** (26.46 ppm) by a methine carbon resonance (77.68 ppm) in the spectrum of **10**. The hydroxyl group of the tertiary alcohol in **7** was acylated in pyridine with Ac_2O, and the product (**11**) was easily desacylated by $CH_3OH/NaOCH_3$. On prolonged treatment of **7** with pyridine, **12** was formed, likely through the tautomeric intermediate (**7a**) by proton abstraction from OH and subsequent ring opening. Reduction of **12** with $NaBH_4$ yielded **13**. The C=N double bond of indolenine **7** can be reduced by $LiAlH_4$ at room temperature to the hydroxyindoline **14**. The latter can be dehydrated to **3** either by MeOH/HCl or by boiling in

(2) Kalaus, Gy.; Malkieh, N.; Katona, I.; Kajtár-Peredy, M.; Koritsánszky, T.; Kálmán, A.; Szabó, L.; Szántay, Cs. *J. Org. Chem.* **1985**, *50*, 3760.
(3) Zsadon, B.; Tamás, J. *Chem. Ind. (London)* **1972**, 32.
(4) Atta-Ur-Rahman; Beilser, J. A.; Harley-Masson, J. *Tetrahedron* **1980**, *36*, 1063.
(5) Kalaus, Gy.; Szabó, L.; Györy, P.; Szentirmay, É.; Szántay, Cs. *Acta Chim. Acad. Sci. Hung.* **1979**, *101*, 387.
(6) Kutney, J. P.; Chan, K. K.; Failli, A.; Formson, J. M.; Gletsos, C.; Nelson, V. R. *J. Am. Chem. Soc.* **1968**, *90*, 3891.
(7) Kutney, J. P.; Chan, K. K.; Failli, A.; Formson, J. M.; Gletsos, C.; Leutwiler, A.; Nelson, V. R.; de Souza, J. P. *Helv. Chim. Acta* **1975**, *58*, 1648.
(8) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708.
(9) Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1147.
(10) Kalaus, Gy.; Kiss, M.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *Heterocycles* **1985**, *23*, 2783.
(11) (a) Jovanovics, K. U.S. Patent 3 899 493; *Chem. Abstr.* **1975**, *83*, 179360*f*. (b) Jovanovics, K. U.S. Patent 4 310 582; *Chem. Abstr.* **1982**, *96*, 181492*n*.
(12) (a) Kny, H.; Witkop, B. *J. Org. Chem.* **1960**, *25*, 635. (b) Markey, S.; Biemann, K.; Witkop, B. *Tetrahedron Lett.* **1967**, 157.
(13) Hino, T.; Yamaguchi, H.; Matsuki, K.; Nakano, K.; Sodeoka, M.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 141 and references cited therein.
(14) Incze, M.; Sóti, F.; Kardos-Balogh, Zs.; Kajtár-Peredy, M.; Szántay, Cs. *Heterocycles* **1985**, *23*, 671.

pyridine. Acetylation of **14** furnished **15**.

The chromyl acetate oxidation was performed on compounds **2** and **4** as well (Scheme V). Compound **17** was obtained by starting from **2**, presumably through intermediate **16a**, while **4** furnished **16b** (Figure 1).

Experimental Section

General Procedures. The IR spectra were measured with a Spectromom 2000 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 Fourier transform spectrometer operating at 100.1 and 25.16 MHz, respectively. Chemical shifts (in parts per million) are relative to internal Me_4Si. Mass spectra were determined by using a JEOL-JMS-01-SG-2 instrument. All melting points are uncorrected. Thin-layer chromatography separations were carried out on silica gel (Kieselgel 60 $PF_{254+366}$), developed by C_6H_6–MeOH, 10:1.4, and eluted by CH_2Cl_2–MeOH, 10:1. The organic layers were dried over $MgSO_4$.

3α-Carbamoyl-*C*(4)-norquebrachamine (5α) (4) and 3-Oxo-*C*(4)-norquebrachamine (5α) (6). A solution of **3**[2] (1.5 g, 5.1 mmol) and KOH (11.5 g, 205 mmol) in EtOH (200 mL) was stirred at reflux for 6 days. The solvent was removed under reduced pressure, and the residue was diluted with H_2O (70 mL) and then extracted with CH_2Cl_2 (100 mL). The organic layer was dried and evaporated in vacuo. The residue was treated with cold MeOH (10 mL) to give **4** (0.91 g, 57.2%): mp 215–218 °C (CH_3CN–EtOH); IR (KBr) ν 3350 (indole NH), 1660 cm^{-1} (amide C=O); MS, *m/z* (relative intensity) 311 (39), 267 (3), 181 (19), 125 (50), *124* (100), 110 (26), 96 (35); ^1H NMR ($CDCl_3$ + DMSO-d_6, 2:1) δ 0.69 (3 H, t, J = 7.5 Hz, CH_2CH_3), 4.60 (1 H, s, C3-H), 6.2 and 6.7 (2 H, br s, $CONH_2$), 6.95–7.55 (4 H, m, Ar), 9.90 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 1:1) δ 7.98 (C20), 17.85 (C6), 25.56 (C10), 28.60 (C19), 31.95 (C5), 39.91 (C4), 44.85 (C3), 50.80* (C9), 51.40* (C7), 53.95 (C18), 109.94 (C11), 111.03 (C16), 117.15 (C13), 118.26 (C14), 120.30 (C15), 127.72 (C12), 131.46 (C2), 134.44 (C17), 173.82 ($CONH_2$) [* may be interchanged]. Anal. Calcd (found) for $C_{19}H_{25}N_3O$: C, 73.28 (73.14); H, 8.09 (7.99); N, 13.49 (13.26). The mother liquor was concentrated and then separated by TLC. The faster running fraction was evaporated and crystallized from MeOH to give **6** (0.16 g, 11.1%) as white crystals: mp 258–262 °C (MeOH); IR (KBr) ν 1645 cm^{-1} (C=O); MS, *m/z* (relative intensity) 282 (45), 254 (22), 225 (11), 199 (31), 143 (69), *124* (100), 112 (25), 110 (24); ^1H NMR ($CDCl_3$) δ 0.74 (3 H, t, J = 7.4 Hz, CH_2CH_3), 2.78 (1 H, d, J_{AB} = 15 Hz, C18-H_AH_B), 3.97 (1 H, dd, C18-H_AH_B), 7.05–7.70 (4 H, m, Ar), 8.51 (1 H, br s, NH); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 2:1) δ 7.24 (C20), 16.24 (C6), 24.42 (C10), 30.79 (C19), 32.86 (C5), 48.28 (C4), 50.74* (C9), 51.74* (C7), 53.28 (C18), 111.94 (C16), 119.21 (C11), 119.31 (C13), 119.54 (C14), 123.79 (C15), 127.14 (C12), 131.78 (C2), 135.87 (C17), 203.21 (C=O) [* may be interchanged].

Oxidation of 3. A solution of **3** (1.00 g, 3.40 mmol) in CH_2Cl_2 (100 mL) and AcOH (50 mL) was cooled to −70 °C, and then CrO_3 (1.0 g, 10.0 mmol) in Ac_2O (100 mL) was added in small portions at −60 °C. The reaction mixture was stirred at −60 to −30 °C for 2 h and then poured into a mixture of concentrated NH_4OH (400 mL) and ice (400 g). The organic layer was separated, and the inorganic part was extracted with CH_2Cl_2 (400 mL). The combined extracts were dried and evaporated in vacuo, and the residue was treated with MeOH to afford **7** (0.55 g, 52.2%): mp 212–214 °C (EtOH); IR (KBr) ν 2300 (CN), 1590 cm^{-1} (indolenine C=N); UV (CH_3OH) λ_{max} (log ϵ) 223 (4.4349), 266 (3.7905), 284 nm (3.7557); MS, *m/z* (relative intensity) *309* (100), 292 (35), 280 (8), 125 (64), 124 (40), 110 (69), 96 (22); ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.5 Hz, CH_2CH_3), 4.67 (1 H, s, C8-H), 7.0–7.5 (4 H, m, Ar); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 2:1) see Figure 1. The mother liquor was concentrated and then separated by TLC to afford **7** (0.10 g, 9.5%) and **8** (30 mg, 2.7%) as white crystals: mp 198–200 °C (MeOH); IR (KBr) ν 3300 (indole NH), 2300 (CN), 1688 cm^{-1} (C=O); MS, *m/z* (relative intensity) *325* (100), 296 (15), 165 (16), 164 (16), 147 (72), 146 (52), 135 (40), 124 (51), 123 (24), 120 (14), 92 (11); ^1H NMR ($CDCl_3$) δ 0.98 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.2–2.6 (10 H, m), 2.9–3.5 (4 H, m), 4.20 (1 H, s, C12-H), 7.15 (1 H, ddd, ΣJ = 6.4 + 7.5 + 1.0 Hz, C2c-H), 7.22 (1 H, ddd, ΣJ = 7.5 + 2.8 + 0.6 Hz, C2d-H), 7.46 (1 H, ddd, ΣJ = 8.2 + 6.4 + 2.8 Hz, C2b-H), 8.28 (1 H, ddd, ΣJ = 8.2 + 1.0 + 0.6 Hz, C2a-H), 9.76 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 2:1) see Figure 1.

Further Oxidation of 7. CrO_3 (0.10 g, 1.0 mmol) in Ac_2O (10 mL) was added to a solution of **7** (100 mg, 0.32 mmol) in a mixture of CH_2Cl_2 (20 mL) and AcOH (5 mL). The reaction mixture was stirred at room temperature for 24 h and then treated with concentrated NH_4OH at 0 °C. The organic layer was separated, and the inorganic part was extracted with CH_2Cl_2 (40 mL). The combined extracts were dried and evaporated, and the residue was separated by TLC to afford **8** (10 mg, 9.5%).

3α-Cyano-10-methoxy-*C*(4)-norquebrachamine (5α) (10). Compound **7** (0.55 g, 1.78 mmol) was dissolved in MeOH (60 mL) saturated with HCl at 0 °C. The solution was allowed to stand at 0 °C for 1.5 h, then treated with concentrated NH_4OH, and extracted with CH_2Cl_2 (100 mL). The organic layer was dried and evaporated in vacuo. The residue was separated by TLC to give **10** (0.27 g, 47%) as white crystals: change in modification 180–200 °C; mp 206–210 °C (MeOH); IR (KBr) ν 3350 (indole NH), 2320 cm^{-1} (CN); MS, *m/z* (relative intensity) 323 (25), 292 (6), 198 (5), *125* (100), 110 (50), 96 (33); ^1H NMr ($CDCl_3$) δ 0.79 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.60 (1 H, d, J_{AB} = 14 Hz, C18-H_AH_B), 2.70 (1 H, d, C18-H_AH_B), 3.00 (2 H, m, C7-H_2), 3.27 (2 H, m, C9-H_2), 3.55 (3 H, s, OCH_3), 4.61 (1 H, dd, ΣJ = 10 Hz, C10-H), 4.85 (1 H, s, C3-H), 7.0–7.8 (4 H, m, Ar), 8.31 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 7.82 (CH_2CH_3), 18.88 (C6), 29.15 (CH_2CH_3), 31.33 (C5), 35.76 (C3), 41.01 (C4), 51.33 (C7), 53.33 (C18), 54.11 (C9), 56.93 (OCH_3), 77.68 (C10), 110.94 (C16), 114.61 (C11), 118.63 (CN), 120.41* (C13), 120.44* (C14), 122.62 (C15), 125.04 (C12), 127.32 (C2), 135.30 (C17) [* may be interchanged]. Anal. Calcd (found) for $C_{20}H_{25}N_3O$: C, 74.27 (74.18); H, 7.79 (7.57); N, 12.99 (13.26).

13b-Acetoxy-8α-cyano-7α-ethyl-3,7-methano-1,2,4,5,6,7,8,13b-octahydroazecino[5,4-*b*]indole (11). Compound **7** (0.30 g, 0.97 mmol) was dissolved in a mixture of pyridine (15 mL) and Ac_2O (1 mL). The reaction mixture was refluxed for 1.5 h, and then the solvent was removed in vacuo (0.5 mbar) at room temperature. The residue was treated with 5% $NaHCO_3$ to give **11** (0.23 g, 76.5%) as white crystals: mp 143–145 °C (MeOH); IR (KBr) ν 2320 (CN), 1755 (C=O), 1590 cm^{-1} (indolenine C=N); MS, *m/z* (relative intensity) 351 (81), 308 (50), 292 (77), 291 (42), 262 (29), *125* (100), 124 (72), 110 (55), 96 (26); ^1H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.09 (3 H, s, CH_3COO), 4.61 (1 H, s, C8-H), 7.1–7.7 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) see Figure 1.

Desacetylation of 11. A solution of **11** (65 mg, 0.18 mmol) in MeOH (6 mL) was added to MeONa (22 mg, 0.4 mmol) in MeOH (10 mL). The reaction mixture was refluxed for 5 min, then poured into water, and extracted with CH_2Cl_2. The organic layer was dried and evaporated in vacuo. The residue was crystallized from MeOH to give **7** (45 mg, 78.6%).

Preparation of 12. A solution of **7** (0.20 g, 0.65 mmol) in pyridine (15 mL) was refluxed for 8 days and then evaporated in vacuo. The remaining oil was purified by TLC to afford **12** (0.11 g, 55%) as white crystals: mp 173–174 °C (MeOH); IR (KBr) ν 2240 (CN), 1704–1612 cm^{-1} (C=O, C=C); UV (CH_3OH) λ_{max} (log ϵ) 217 (4.5249), 260 (4.2817), 311 nm (4.5992); MS, *m/z* (relative intensity) *309* (100), 294 (9), 280 (32), 252 (16), 237 (13), 146 (41), 135 (7), 120 (11), 77 (18), 70 (20); ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.93 (1 H, d, J_{gem} = 12.5 Hz, C14-H_A), 3.45 (2 H, m, C6-H_2), 3.46 (1 H, d, C14-H_B), 6.90 (1 H, dd, J = 7.7, 7.1, and 1.1 Hz, C2c-H), 7.03 (1 H, ddd, J = 8.1, 1.1, and 0.5 Hz, C2a-H), 7.30 (1 H, ddd, J = 7.7, 1.9, and 0.5 Hz, C2d-H), 7.39 (1 H, ddd, J = 8.1, 7.1, and 1.9 Hz, C2b-H), 7.53 (1 H, d, J = 10.2 Hz, C13-H), 13.38 (1 H, br d, J = 10.2 Hz, NH); ^{13}C NMR ($CDCl_3$) see Figure 1.

Selective Reduction of 12. A solution of **12** (0.17 g, 0.55 mmol) in EtOH (17 mL) was cooled to 0 °C, and then $NaBH_4$ (0.17 g, 4.5 mmol) was added in small portions. The reaction mixture was stirred at 0–5 °C for 40 min, then poured into water (30 mL), and extracted with CH_2Cl_2. The organic layer was dried and evaporated to afford **13** (0.15 g, 87.7%) as white crystals: mp 167–169 °C (MeOH); IR (KBr) ν 3400 (OH), 1645 (C=C), 2210 cm^{-1} (CN); MS, *m/z* (relative intensity) 312 (48), *311* (100), 296 (10), 298 (30), 161 (10), 146 (13), 135 (11), 130 (25), 124 (15), 110 (11), 96 (15), 77 (22), 72 (34), 71 (19), 58 (19), 44 (43), 42 (37); ^1H NMR ($CDCl_3$) δ 0.84 (3 H, t, J = 7.2 Hz, CH_2CH_3), 1.90 (1 H, d,

J_{gem} = 12.2 Hz, C14-H_A), 3.22 (1 H, d, C14-H_B), 4.73 (1 H, br dd, ΣJ = 7 Hz, C4-H), 6.89 (1 H, m, C2a-H), 6.93 (1 H, m, C2c-H), 7.20 (1 H, m, C2b-H), 7.45 (1 H, d, J = 10.4 Hz, C13-H), 7.50 (1 H, m, C2d-H), 12.02 (1 H, br d, J = 10.4 Hz, NH); ^{13}C NMR ($CDCl_3$) see Figure 1.

Reduction of 7. A solution of **7** (0.50 g, 1.62 mmol) in THF (30 mL) was dropped to a suspension of $LiAlH_4$ (0.50 g, 13.2 mmol) in THF (20 mL) within 20 min. The reaction mixture was stirred at room temperature for 10 min, then cooled, and decomposed with 10% NaOH (5 mL). The organic layer was separated, and the inorganic part was extracted with THF (30 mL). The combined extracts were dried and evaporated in vacuo. The residue was treated with Et_2O to give **14** (0.32 g, 63.6%) as white powder: mp 195–198 °C dec; IR (KBr) ν 3280–3200 (OH, indole NH), 2300 cm^{-1} (CN); MS, m/z (relative intensity) *311* (100), 294 (29), 293 (42), 282 (13), 264 (29), 250 (24), 177 (40), 163 (42), 147 (37), 144 (17), 124 (59), 110 (35), 96 (46); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 2:1) δ 0.91 (3 H, t, J = 7.3 Hz, CH_2CH_3), 4.32 (1 H, br s, C8a-H), 4.78 (1 H, br s, NH), 6.5–7.3 (4 H, m, Ar); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 3:1) δ 7.63 (CH_2CH_3), 46.38 (C2), 50.92 (C4 + C14), 122.61 (C13), 128.60 (C11), 149.20 (C9a).

Dehydration of 14. (a) A solution of **14** (30 mg, 0.10 mmol) in pyridine (6 mL) was refluxed for 6 h and then evaporated in vacuo. The remaining oil was crystallized from MeOH to give **3** (26 mg, 92.0%).

(b) Compound **14** (100 mg, 0.32 mmol) was dissolved in MeOH (15 mL) saturated with HCl at 0 °C. The solution was allowed to stand at 0 °C for 30 min, then treated with 25% NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried and evaporated in vacuo. The residue was crystallized from MeOH to give **3** (90 mg, 95.5%).

Selective Acetylation of 14. To a solution of **14** (0.18 g, 0.58 mmol) in THF (25 mL) were added anhydrous K_2CO_3 (0.7 g) and Ac_2O (0.5 mL). The reaction mixture was stirred at reflux for 75 min, then cooled to room temperature, and filtered. The filtrate was evaporated, and the residue was treated with 5% $NaHCO_3$ to give **15** (0.11 g, 53.8%) as white powder: mp 208–210 °C (MeOH); IR (KBr) ν 3270 (OH), 2300 (CN), 1640 cm^{-1} (amide C=O); MS, m/z (relative intensity) *353* (100), 338 (85), 337 (25), 336 (24), 293 (16), 264 (21), 250 (22), 117 (38), 164 (35), 130 (26), 110 (38), 96 (52); ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 7.3 Hz, CH_2CH_3), 2.37 (3 H, s, $COCH_3$), 3.34 (2 H, s, C8-H + OH), 5.47 (1 H, br s, C8a-H), 7.0–7.45 (4 H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 7.15 (CH_2CH_3), 21.98 (C5), 23.99 ($COCH_3$), 28.68 (CH_2CH_3), 31.84 (C1 + C6), 40.54 (C7), 42.00 (C8), 46.33 (C2), 50.94* (C4), 51.50* (C14), 71.97 (C8a), 77.33 (C13b), 115.24 (C10), 118.45 (CN), 123.41† (C12), 124.47† (C13), 130.01 (C11), 137.60 (C13a), 140.58 (C9a), 168.73 ($COCH_3$) [*,† may be interchanged].

Oxidation of 2. CrO_3 (0.2 g, 2.0 mmol) in Ac_2O (20 mL) was dropped to a solution of **2**[2] (200 mg, 0.74 mmol) in a mixture of CH_2Cl_2 (40 mL) and AcOH (10 mL). The reaction mixture was stirred at room temperature for 3 h, then treated with concentrated NH_4OH (80 mL) at 0 °C, and extracted with CH_2Cl_2 (100 mL). The organic layer was dried and evaporated in vacuo. The remaining oil was purified by TLC to afford **17** (25 mg, 11.2%) as white crystals: mp 150–151 °C (MeOH); IR (KBr) ν 1690–1680 cm^{-1} (C=O); MS, m/z (relative intensity) *300* (100), 285 (12), 271 (4), 243 (7), 147 (15), 146 (18), 138 (8), 124 (44), 123 (55), 110 (16); ^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, t, J = 7.5 Hz, CH_2CH_3), 2.13 (1 H, d, J_{AB} = 13 Hz, C12-H_AH_B), 2.76 (1 H, d, C12-H_AH_B), 7.06 (1 H, ddd, ΣJ = 7.5 + 7.0 + 1.0 Hz, C2c-H), 7.18 (1 H, ddd, ΣJ = 7.5 + 2.1 + 0.6 Hz, C2d-H), 7.41 (1 H, ddd, ΣJ = 8.1 + 7.0 + 2.1 Hz, C2b-H), 8.26 (1 H, ddd, ΣJ = 8.1 + 1.0 + 0.6 Hz, C2a-H), 9.81 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) see Figure 1.

Oxidation of 4. A solution of CrO_3 (0.10 g, 1.0 mmol) in Ac_2O (10 mL) was dropped to a solution of **4** (100 mg, 0.32 mmol) in a mixture of CH_2Cl_2 (20 mL) and AcOH (5 mL). The reaction mixture was stirred at room temperature for 1 h, then treated with concentrated NH_4OH (40 mL) at 0 °C, and extracted with CH_2Cl_2 (100 mL). The organic layer was dried and evaporated in vacuo. The remaining oil was crystallized from MeOH to give **16b** (18 mg, 17.1%) as white powder: mp 219–222 °C dec; IR (KBr) ν 3300 (OH), 1645 cm^{-1} (amide C=O); MS, m/z (relative intensity) *327* (100), 310 (75), 283 (23), 251 (64), 125 (66), 124 (59), 110 (46); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 2:1) δ 0.86 (3 H, t, J = 7 Hz, CH_2CH_3), 4.30 (1 H, s, C8-H), 6.3 and 7.7 (2 H, br s, $CONH_2$), 7.1–7.5 (4 H, m, Ar); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 3:1) see Figure 1.

Acknowledgment. We express our sincere thanks to Dr. Péter György, Anna Korcsog-Kassa, and Magdolna Tóth for their valuable help. The financial support of the Richter Gedeon Pharmaceutical Co. and the Hungarian Academy of Sciences is gratefully acknowledged.

Registry No. (±)-**2**, 97720-63-3; (±)-**3**, 97720-62-2; (±)-**4**, 111324-81-3; (±)-**6**, 111324-82-4; **7**, 111324-83-5; (±)-**8**, 111324-84-6; **10**, 111324-85-7; **11**, 111324-86-8; (±)-**12**, 111324-87-9; **13**, 111324-88-0; **14**, 111324-89-1; **15**, 111324-90-4; **16b**, 111324-91-5; (±)-**17**, 111324-92-6.

Efficient Conjugate Alkylation of α,β-Unsaturated Nitro Olefins by Triorganoalanes

Angelo Pecunioso*† and Rita Menicagli†,‡

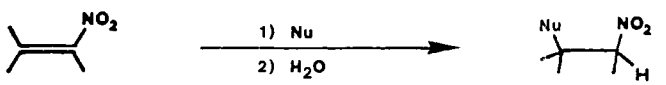
Dipartimento di Chimica e Chimica Industriale and Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, 56100 Pisa, Italy

Received April 2, 1987

Both trialkylaluminum (AlR_3; R = Et, *i*-Bu) and triorganoaluminum etherates (AlR_3·OEt_2; R = Et, *i*-Bu, Ph) rapidly react with α,β-unsaturated nitro olefins to give only 1,4-monoalkylated products in high yield. The natures of substrates, the reaction conditions as well as the reagents molar ratio, do not cause significant variations on the recovered products.

Reactions involving nitro compounds in carbon–carbon bond-forming processes are of increasing importance owing to the remarkable versatility of the nitro group.[1]

Scheme I



α-Nitro olefins are unique synthetic intermediates[2] because a wide class of nucleophiles adds, in a Michael-type

† Dipartimento di Chimica e Chimica Industriale.
‡ Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive.

0022-3263/88/1953-0045$01.50/0