Unusual Formation of a Novel Pyrrolo[1′,2′:1,2]pyrido[3,4-*b*]indole

Venkatachalam S. Giri*, Sankar K. Das and Parasuraman Jai Sankar

Indian Institute of Chemical Biology,
Calcutta-700 032, India

James N. Shoolery and Paul Keifer

Varian Associates, Palo Alto, CA 94303, USA

Received October 22, 1991

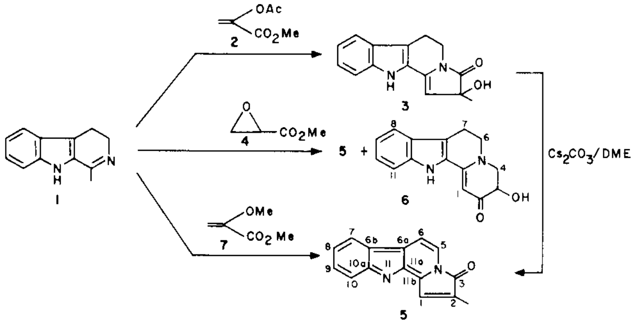
Reaction of 1-methyl-3,4-dihydro-β-carboline **1** with methyl glycidate **4** gave the novel tetracyclic conjugated γ-lactam, 2-methylpyrrolo[1′,2′:1,2]pyrido[3,4-*b*]indol-3-one **5**. The same compound **5** was obtained in higher yield when **1** was treated with methyl 2-methoxyacrylate **7**. Sodium borohydride treatment of **5** resulted in the cleavage of lactam to yield the unexpected alcohols **8** and **9**.

J. Heterocyclic Chem., **29**, 767 (1992).

Introduction.

The indole derivatives isolated from both marine and terrestrial sources have continued to draw the attention of synthetic organic chemists because of their interesting physiological properties as well as diverse structural features [1] [2]. In the course of our own efforts concerned with the synthesis of a key intermediate for aspidosperma type alkaloids we have earlier reported [3] that treatment of 1 equivalent of **1** with 3 equivalents of methyl 2-acetoxyacrylate **2** in methanol at room temperature resulted in the unexpected compound 2-hydroxy-2-methyl-5,6-dihydro-11*H*-pyrrolo[1′,2′:1,2]pyrido[3,4-*b*]indol-3[2*H*]-one **3** as the major product. We now report the interesting results of the reaction of **1** with methyl glycidate **4** [4] and methyl 2-methoxyacrylate **7** [5] (Scheme 1).

Scheme 1

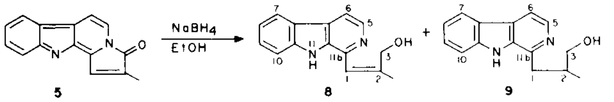


Results and Discussion.

Treatment of 1 equivalent of **1** with 1.5 equivalents of methyl glycidate **4** in refluxing acetonitrile gave surprisingly the conjugated γ-lactam **5**, mp 216-218°, apart from the expected 3-hydroxy-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizin-2-one **6**, mp 273-274° in 22 and 17% yield respectively. The formation of such anhydro-β-carboline system in one pot is not known in literature. As anticipated compound **5** was obtained in better yield (51%) when **1** was refluxed in acetonitrile with 1.5 equivalents of methyl 2-methoxyacrylate **7**. The ^{1}H nmr spectrum of **5** showed signals for seven protons in the region between δ 7.30 and δ 8.65 apart from a vinyl methyl signal at δ 2.30. Addition of a few drops of perdeuteriobenzene to the sample solution in deuteriochloroform altered (solvent effect) the chemical shifts of all the protons. The quartet at δ 7.67 due to 1-H proton clearly resolved from the doublet cluster (6-H) and appears at δ 7.98 (J = 1.5 Hz). Also, irradiation of the methyl protons at δ 2.30 results in an NOE difference spectrum (10%) which shows that the quartet is due to the 1-H proton as would be expected from coupling pattern. The doublets at δ 8.61 (J = 6.5 Hz) and δ 7.65 (J = 6.5 Hz) could be easily recognized from the coupling constant as well as the pattern and are assigned to the 5-H and 6-H protons respectively. The ^{13}C nmr spectrum of **5** exhibited signals for 15 carbons of which only one is in the aliphatic region at δ 17.97 for a methyl group, one in the lactam carbonyl region at δ 160.18 and the rest are in the aromatic region. The ^{1}H-^{13}C 2D HETCOR spectrum exhibited signals for the protons directly bonded to the carbons at C-1 (δ 135.72), C-5 (145.60), C-6 (115.23), C-7 (122.55), C-8 (125.44), C-9 (130.56), C-10 (117.16) and the methyl (17.97). Long range 2 and 3 bond ^{1}H-^{13}C 2D HETCOR experiment showed signals at δ 160.18 (C-3), 17.97 (Me) and 131.04 (C-11a) for the 1-H proton resonating at δ 7.67. It also showed signals at δ 136.40 (C-11b), 115.23 (C-6) and 129.49 (C-6a) for the 5-H proton at δ 8.61. The remaining are the four protons of the benzene portion of the indole moiety. Signals at δ 139.36 (C-10a), 129.49 (C-6a) and 130.56 (C-9) corresponding to the 7-H proton at δ 8.44 as well as the signals at δ 124.65 (C-6b) and 117.16 (C-10) for the 8-H proton at δ 7.36 unambiguously settles the structure of compound **5**. Further, it was also observed that reaction of **3** with cesium carbonate in refluxing dimethoxyethane results in the anhydro compound **5** in poor yield.

Sodium borohydride reduction of **5** in ethanol at room temperature yielded in 90% (1:1) two compounds **8**, mp 190-192° and **9**, mp 138-139° (Scheme 2). The mass spectrum of both **8** and **9** exhibited M$^+$ ions at m/z 238 and 240 with intense peaks at m/z 221 and 223 respectively for the loss of a OH group. This was further corroborated by ^{1}H nmr spectrum in DMSO-d$_6$ which exhibited signals for an additional exchangeable proton (other than the indole NH) at δ 5.92 and δ 4.52 for compounds **8** and **9** respectively. Acetylation also resulted in downfield shift of the 3-H$_2$ protons. The surprising feature in the ^{13}C nmr spectra is the absence of a lactam carbonyl in both **8** and **9**, instead there were peaks at δ 63.54 (t) and δ 66.73 (t) respectively suggesting reductive cleavage of the lactam resulting in α-substituted β-carbolines. This is further supported by the uv spectrum of compound **9** which is characteristic of a β-carboline system. The ^{1}H nmr spectra in deuteriochloroform further confirmed this with signals at δ 4.40 (br s) for C*H*$_2$OH of compound **8** and at δ 3.63 (dd) and δ 3.81 (dd) for HOC*H*$_2$CH(Me) of compound **9**. The presence of the double doublets as well the doublet at δ 1.22 (J = 7 Hz) for the Me group and the signals at δ 3.34 (dd), 3.44 (dd) suggests that compound **9** has resulted from both cleavage of lactam and reduction of double bond between C-1 and C-2. In addition, 2D experiments TOCSY, HMQC [6] and HMBC [7] of compounds **8** and **9** have further confirmed the assigned structures.

Scheme 2



EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were recorded on a Perkin Elmer 177 spectrometer in potassium bromide. Mass spectra were run on a Hitachi RMU-6L spectrometer at 70 eV. The uv spectra in methanol were taken on a Hitachi U-2000 spectrophotometer. High resolution 1D, 2D, NOE difference nmr spectra of compound **5** were carried out on a Varian XL GEMA 300 spectrometer equipped with a GEMINI-300 BB computer. The ^{1}H and ^{13}C nmr spectral data of compounds **8** and **9** were recorded on a Varian XL-500 spectrometer equipped with an APPLAB UNITY 500 computer. In both 300 and 500 MHz spectrometers, spectra were run with solutions of the samples in deuteriochloroform using TMS as the standard. The term petroleum ether refers to the fraction boiling in the range 60-80°.

2-Methylpyrrolo[1′,2′:1,2]pyrido[3,4-*b*]indol-3-one (**5**).

A solution of **1** (184 mg, 1 mmole) and **4** (153 mg, 1.5 mmoles) in dry acetonitrile (10 ml) and triethylamine (1 ml) was refluxed for 1 hour. The reaction mixture was then evaporated to dryness under reduced pressure and the residue subjected to column chromatography over silica gel. Elution with a chloroform-methanol mixture (98:2) afforded **5** which was recrystallized from petroleum ether-chloroform as colorless silky needles (52 mg, 22%), mp 216-218°; ir: ν 1668, 1636 cm^{-1}; uv: λ max 295 (log ϵ 3.64), 343 (3.65), 357 (3.89), 375 nm (3.89); ^{1}H nmr: δ 2.30 (d, J = 1.5 Hz, 3H, Me), 7.36 (td, J = 7.0, 1.5 Hz, 1H, H-8), 7.53 (td, J = 7.0, 1.5 Hz, 1H, H-9), 7.65 (d, J = 6.5 Hz, 1H, H-6), 7.67 (q, J = 1.5 Hz, 1H, H-1), 7.86 (d, J = 7.0 Hz, 1H, H-10), 8.44 (d, J = 7.0 Hz, 1H, H-7), 8.61 (d, J = 6.5 Hz, 1H, H-5); ^{13}C nmr: δ 17.97 (Me), 115.23 (C-6), 117.16 (C-10), 122.55 (C-7), 124.65 (C-6b), 125.44 (C-8), 129.49 (C-6a), 130.56 (C-9), 131.04 (C-11a), 135.72 (C-1), 136.40 (C-11b), 138.16 (C-2), 139.36 (C-10a), 145.60 (C-5), 160.18 (C-3); ms: m/z (relative intensity) 234 (M$^+$, 100), 219 (5), 206 (27), 205 (39), 178 (6), 104 (17), 43 (60).

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.99; H, 4.31; N, 11.97. Found: C, 76.90; H, 4.28; N, 12.01.

3-Hydroxy-2,3,4,6,7,12-hexahydroindolo[3,2-*a*]quinolizin-2-one (**6**).

Further elution with chloroform-methanol mixture (95:5) gave a solid which was recrystallized from petroleum ether-chloroform to afford **6** (44 mg, 17%), mp 273-274°; ir: ν 1685, 1660, 1620 cm^{-1}; uv: λ max 225 (log ϵ 2.5), 245 (1.9), 321 (2.1), 384 (1.8), 390 nm (1.96); ^{1}H nmr (100 MHz, DMSO-d$_6$): δ 3.04-3.18 (m, 2H, 7-H$_2$), 3.34-3.80 (m, 4H, 4-H$_2$ and 6-H$_2$), 4.32 (dd, 1H, J = 14, 6 Hz, C*H*OH), 4.40 (br s, 1H, OH), 5.75 (s, 1H, H-1), 7.00-7.50 (m, 4H, Ar-H), 11.04 (br s, 1H, NH); ^{13}C nmr (25 MHz, DMSO-d$_6$): δ 20.0 (t), 49.7 (t), 56.6 (t), 68.2 (d), 92.0 (d), 111.9 (d), 114.6 (s), 2 x 119 (d), 124.3 (d), 125.1 (s), 127.2 (s), 138.0 (s), 152.6 (s) and 191.6 (s); ms: m/z (relative intensity) 254 (M$^+$, 75), 236 (4), 225 (13), 210 (86), 209 (43), 181 (13), 180 (11), 154 (46), 43 (100).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.93; H, 5.66; N, 11.03. Found: C, 70.84; H, 5.57; N, 11.09.

Reaction of **1** with Methyl 2-Methoxyacrylate (**7**).

A solution of **1** (184 mg, 1 mmole) and **7** (174 mg, 1.5 mmoles) in dry acetonitrile (10 ml) and triethylamine (1 ml) was refluxed for 1 hour. The reaction mixture was then neutralized with 5% aqueous hydrochloric acid and extracted with dichloromethane. The extract was dried (sodium sulfate) and the solvent removed under reduced pressure. The residue was chromatographed over silica gel to yield a solid which was recrystallized from petroleum ether-chloroform to afford **5** (120 mg, 51%).

Reaction of **5** with Sodium Borohydride.

To a solution of **5** (234 mg, 1 mmole) in ethanol (20 ml), sodium borohydride (390 mg, 10 mmoles) was added in portions under stirring and the reaction mixture was further stirred at room temperature for 2 hours more. The mixture was then cooled and neutralized with 5% aqueous hydrochloric acid. The solution was concentrated under reduced pressure, basified with solid sodium bicarbonate and extracted with dichloromethane. The extract was dried (sodium sulfate), the solvent evaporated and the residue was chromatographed over silica gel. Petroleum ether-chloroform (1:1) eluates were combined and concentrated to afford 1-(2-methyl-3-hydroxy-1-propenyl)-β-carboline **8** (107 mg, 45%) which was recrystallized from petroleum ether-chloroform, mp 190-192°; ir: ν 3300-3100, 1645, 1620 cm^{-1}; uv: λ max 240 (log ϵ 4.6), 272 (4.4), 295 (4.3), 351 nm (4.0); ^{1}H nmr: δ 2.30 (d, J = 1.5 Hz, 3H, Me), 4.40 (s, 2H, H-3), 6.92 (m, 1H, H-1), 7.46 (td, J = 7.0, 1.5 Hz, 1H, H-8), 7.70 (m, 1H, H-9), 7.72 (m, 1H, H-10), 7.98 (d, J = 6.0 Hz, 1H, H-6), 8.27 (d, J = 7.0 Hz, 1H, H-7), 8.53 (d, J = 6.0 Hz, 1H, H-5), 8.89 (br s, 1H, NH); ^{13}C nmr: δ 25.53 (Me), 63.54 (C-3), 111.57 (C-10), 113.07 (C-6), 120.45 (C-8), 120.83 (C-1), 121.82 (C-7), 121.84 (C-2), 128.65 (C-9), 129.56 (C-6b), 133.89 (C-6a), 138.15 (C-5), 141.0 (C-11a), 141.5 (C-10a), 147.74 (C-11b); ms: m/z (relative intensity) 238 (M$^+$, 86), 221 (56), 209 (100), 195 (23), 186

(26), 182 (36), 169 (16), 168 (24), 129 (78), 43 (49).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.69; H, 5.93; N, 11.77. Found: C, 75.61; H, 5.98; N, 11.70.

Further elution with chloroform-methanol (99:1) afforded 1-(2-methyl-3-hydroxypropyl)-β-carboline **9** (108 mg, 45%) which was recrystallized from petroleum ether-chloroform, mp 138-139°; ir: ν 3125, 3075-3045, 1620 cm^{-1}; uv: λ max 235 (log ϵ 4.5), 288 (4.1), 337 (3.6), 350 nm (3.6); ^{1}H nmr: δ 1.22 (d, J = 7.0 Hz, 3H, Me), 2.50 (m, 1H, H-2), 3.34 (dd, J = 15.0, 6.0 Hz, 1H, H-1), 3.44 (dd, J = 15.0, 6.5 Hz, 1H, H-1), 3.63 (dd, J = 11.0, 6.5 Hz, 1H, H-3), 3.81 (dd, J = 11.0, 5.5 Hz, 1H, H-3), 7.43 (td, J = 7.0, 1.5 Hz, 1H, H-8), 7.66 (m, 1H, H-10), 7.67 (m, 1H, H-9), 7.98 (d, J = 6.0 Hz, 1H, H-6), 8.27 (d, J = 7.0 Hz, 1H, H-7), 8.50 (d, J = 6.0 Hz, 1H, H-5), 9.48 (br s, 1H, NH); ^{13}C nmr: δ 17.61 (Me), 35.64 (C-2), 37.72 (C-1), 66.73 (C-3), 111.71 (C-10), 113.04 (C-6), 119.98 (C-8), 121.76 (C-7), 121.93 (C-6b), 128.30 (C-9), 128.79 (C-6a), 135.16 (C-11a), 138.13 (C-5), 140.39 (C-10a), 144.18 (C-11b); ms: m/z (relative intensity) 240 (M$^+$, 40), 223 (41), 209 (46), 206 (25), 195 (26), 183 (81), 182 (100), 168 (24), 154 (44).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.06; H, 6.72; N, 11.67. Found: C, 74.97; H, 6.76; N, 11.61.

Reaction of **3** with Cesium Carbonate.

A mixture of **3** (25.4 mg, 0.1 mmole), cesium carbonate (32.5 mg, 0.1 mmole) and dimethoxyethane (2 ml) was refluxed for 6 hours. The reaction mixture was filtered and the solid washed with dichloromethane. The filtrate along with the washings were washed with water. The organic layer was separated, dried (sodium sulfate) and concentrated. Column chromatography of this residue over silica gel with petroleum ether-chloroform (1:1) as eluent yielded **5** (2.5 mg, 11%).

REFERENCES AND NOTES

[1] Y. Ban, Y. Murakami, Y. Iwasawa, M. Tsuchiya and N. Takano, *Med. Chem. Rev.*, **2**, 231 (1988).

[2] D. J. Faulkner, *Nat. Prod. Rep.*, 539 (1987).

[3] V. S. Giri, B. C. Maiti, S. B. Mondal and S. C. Pakrashi, *J. Chem. Res. (S)*, 342 (1988).

[4] U. Sequin, *Tetrahedron Letters*, 1833 (1979).

[5] N. Ogata, S. Nozakura and S. Murahashi, *Bull. Soc. Chim.*, **43**, 2987 (1970).

[6] L. Muller, *J. Am. Chem. Soc.*, **101**, 4481 (1979).

[7] A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, **108**, 2093 (1986).