Reaction of Methyl 2,3,5,6,11,11b-Hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-5-carboxylate and Its Derivatives with *N*-Bromosuccinimide

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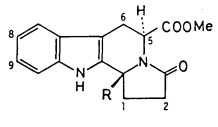
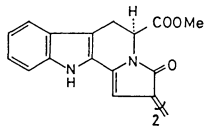
(Received April 13, 1989)

Synopsis. Methyl 2,3,5,6,11,11b-Hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-5-carboxylate was converted into the tetrahydro, dihydro, and dehydro esters using *N*-bromosuccinimide. On treatment with acetic acid, the 6a-bromo indolenine derivative bearing a substituent on C-11b gave a mixture of 8- and 9-bromo compounds by migration of the bromine to the benzene ring, while the corresponding 6a-chloro derivative afforded the oxindole.

In the preceding paper, we reported the isolation of 2,3,5,6,11,11b-hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]-indole-5-carboxylic acid and the 5,11b-dicarboxylic acid as the methyl esters **1** and **2** from *Clerodendron trichotomum* Thunb. The conversion of **1** into a blue pigment, trichotomine dimethyl ester (**3**), was achieved using *N*-bromosuccinimide (NBS) in *t*-BuOH, and the formation of **3** was suggested to proceed via the $\Delta^{1,11b}$-tetrahydro ester **4** derived from **5**.[1] The versatility of 3-halo-3*H*-indoles as intermediates in indole alkaloid synthesis is well documented in the literature.[2] This paper deals with the dehydrogenation of **1** by treatment with NBS and the reaction of 6a-halo derivatives **6a**, **b**, obtained from **2**, with acetic acid.



1 R=H
2 R=COOMe



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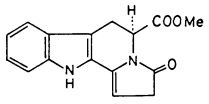

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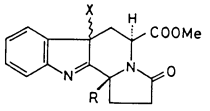


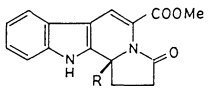
5 X=Br R=H
6a X=Br R=COOMe
6b X=Cl R=COOMe

Bromination of **1** with NBS in CH_2Cl_2 in the presence of K_2CO_3 followed by treatment with triethylamine (Et_3N) gave the $\Delta^{5,6}$-tetrahydro ester **7**. On the other hand, treatment of **1** with NBS in CH_2Cl_2 afforded **4**, from which Iwadare et al. synthesized **3** by autoxidation.[3] The formation of **4** from the initially formed **5** must be catalyzed by hydrogen bromide evolved and supports the intermediacy of **4** in the conversion of **1** into **3** with NBS in *t*-BuOH.

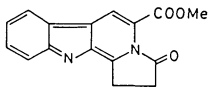
On heating with 5% palladium charcoal in toluene, **7** underwent dehydrogenation to the dihydro ester **8** (UV 329 nm, ε 10500), while on treatment with excess NBS in Et_3N–CH_2Cl_2 at 0 °C for 15 min, **7** was dehydrogenated to **8** and the dehydro ester **9** (UV 376 nm, ε 12800). In the latter reaction, a 6a-bromo derivative formed from **7** seems to undergo dehydrobromination to **8**, which might afford **9** by allylic bromination at C-1 followed by dehydrobromination. In the presence of MeOH, treatment of **7** with NBS in THF afforded the β-carboline **10** (UV 343 nm, ε 4000) presumably by methanolysis of the intermediate **8**. Compounds **8** and **9** were identical with those prepared in the following way. On heating with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in benzene, **1** underwent dehydrogenation to **9**, which gave **8** by catalytic reduction.

The properties of 6a-halo derivatives **6a**, **b** obtained from **2** were examined, since **6a**, **b** had a methoxycarbonyl group on C-11b and could not undergo such dehydrogenation reactions mentioned above.

Bromination of **2** with NBS gave **6a** as crystals (^{13}C NMR δ=56.5, C-6a). On treatment with Et_3N, **6a** gave the $\Delta^{5,6}$ diester **11**. On the other hand, treatment of **6a** with acetic acid afforded a separable mixture of bromo diesters **12** and **13** in a ratio of 2:5. The presence of bromine on C-8 of **12** and on C-9 of **13** was suggested from the ^1H NMR spectrum of **12** and **13**. The structure **13** was assigned to the major product, since the carbamate **14** formed from **13** with methyl chloroformate showed a singlet of C_{10}-proton at low field (δ=8.20) in the ^1H NMR spectrum. In 3-bromo-3*H*-indoles, migration of the bromine to the benzene ring was reported in the literature.[4] On further



7 R=H
11 R=COOMe



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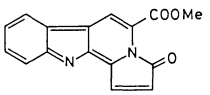

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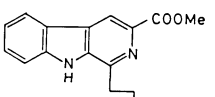

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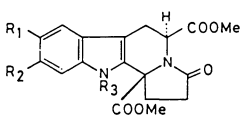
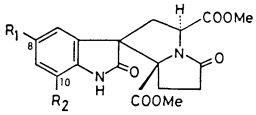


12 R_1=Br R_2=R_3=H
13 R_1=R_3=H R_2=Br
14 R_1=H R_2=Br R_3=COOMe
15 R_1=R_2=Br R_3=H



16 R_1=R_2=H
17 R_1=R_2=Cl
18 R_1=Cl R_2=H

treatment with NBS and then with acetic acid, the mixture of **12** and **13** yielded the 8,9-dibromo diester **15**.

After chlorination of **2** with *t*-butyl hypochlorite (*t*-BuOCl), the resulting **6b** was treated with acetic acid to afford the oxindole **16** (^{13}C NMR δ=58.9, C-6a). On treatment with *t*-BuOCl in EtOH–CH_2Cl_2, **2** gave the dichloroxindole **17**. The formation of **17** was rationalized by indole-oxindole rearrangement to **16** followed by chlorination of the benzene ring,[5] since **16** gave the chloroxindole **18** on treatment with *t*-BuOCl and then with EtOH, and **18** yielded **17** with *t*-BuOCl in EtOH–CH_2Cl_2.

Experimental[6]

Preparation of 7. To a stirred mixture of **1** (284 mg, 1.0 mmol), K_2CO_3 (0.50 g) and CH_2Cl_2 (30 ml) cooled to 0 °C was added dropwise a solution of NBS (214 mg, 1.2 mmol) in CH_2Cl_2 (10 ml). After stirring at 0 °C for 10 min, Et_3N (5 ml) was added. The mixture was stirred at room temperature for 7 h, and then filtered. The filtrate was concentrated under reduced pressure to leave a residue, which was dissolved in $CHCl_3$. The solution was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Separation of the residue by column chromatography (SiO_2–$CHCl_3$) gave **7** (163 mg, 68% based on reacted **1**) and **1** (42 mg). **7**: mp 253—256 °C (MeOH); ^{1}H NMR (CD_3COCD_3) δ=2.28—3.00 (4H, m), 3.76 (3H, s), 5.30 (1H, m), 7.13—7.77 (4H, m), 7.47 (1H, s), and 10.95 (1H, br s). Found: *m/z* 282.1027. Calcd for $C_{16}H_{14}N_2O_3$: M, 282.1004.

Preparation of 4. To a stirred solution of **1** (142 mg, 0.50 mmol) in CH_2Cl_2 (30 ml) cooled to 0 °C was added dropwise a solution of NBS (134 mg, 0.75 mmol) in CH_2Cl_2 (10 ml). After stirring at 22 °C for 1 h, the solution was washed successively with water, aqueous $NaHCO_3$, and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the products by column chromatography (SiO_2–$CHCl_3$) gave **4**[3] (62 mg, 44%).

Dehydrogenation of 7. A mixture of **7** (50 mg), 5% Pd-C (20 mg) and toluene (70 ml) was refluxed with stirring for 10 h, and then filtered. Evaporation of the solvent and separation of the products by column chromatography (SiO_2, 1 vol% MeOH–$CHCl_3$) gave **8** (27 mg, 54%): mp 257—259 °C ($CHCl_3$–hexane); UV 240 (ε 49200), 264 (21700), 283 (sh, 14600), 317 (8880), and 329 nm (10500); ^{1}H NMR δ=3.26 (2H, t, *J*=7.6 Hz), 3.60 (2H, t, *J*=7.6 Hz), 4.08 (3H, s), 7.51—8.57 (4H, m), and 8.67 (1H, s). Found: *m/z* 280.0864. Calcd for $C_{16}H_{12}N_2O_3$: M, 280.0847.

Reaction of 7 with NBS. To a stirred solution of **7** (28 mg, 0.10 mmol) in Et_3N–CH_2Cl_2 (0.2—20 ml) cooled to 0 °C was added NBS (71 mg, 0.40 mmol). The solution was stirred at 0 °C for 15 min, and worked up in the usual way. Separation of the products by PTLC (SiO_2, 3 vol% MeOH–$CHCl_3$) afforded **8** (1 mg, 4%) and **9** (8 mg, 30%). **8** was identical with that obtained above by ^{1}H NMR and TLC comparisons. **9**: mp 272—273 °C ($CHCl_3$–hexane); UV 214 (ε 28800), 246 (32000), 268 (20100), 305 (sh, 7020), 345 (sh, 8820), 359 (14000), and 376 nm (12800); ^{1}H NMR δ=4.13 (3H, s), 7.05 (1H, d, *J*=9.9 Hz), 7.57—8.70 (4H, m), 8.17 (1H, d, *J*=9.9 Hz), and 8.88 (1H, s); MS *m/z* 278 (M^+). Anal. ($C_{16}H_{10}N_2O_3$) C, H, N.

Preparation of 10. To a stirred solution of **7** (20 mg, 0.07 mmol) in MeOH–THF (2—10 ml) cooled to 0 °C was added NBS (15 mg, 0.08 mmol). The solution was stirred at 0 °C for 30 min, and diluted with AcOEt (100 ml). The solution was worked up in the usual way to give **10** (15 mg, 68%): mp 179—181 °C ($CHCl_3$–hexane); UV 219 (ε 17000), 237 (24100), 270 (35900), 303 (7360), 330 (4430), and 343 nm (4000); ^{1}H NMR δ=2.99 (2H, t, *J*=6.4 Hz), 3.53 (2H, t, *J*=6.4 Hz), 3.67 (3H, s), 4.05 (3H, s), 7.32—8.18 (4H, m), 8.78 (1H, s), and 9.61 (1H, br s). Found: *m/z* 312.1116. Calcd for $C_{17}H_{16}N_2O_4$: M, 312.1109.

Dehydrogenation of 1. A mixture of **1** (284 mg, 1 mmol), DDQ (0.91 g, 4.0 mmol) and benzene (300 ml) was refluxed with stirring for 5 h, and filtered. The filtrate was worked up in the usual way. Separation of the products by column chromatography (SiO_2, 1 vol% MeOH–$CHCl_3$) gave **9** (79 mg, 28%), which was found to be identical with that obtained above by IR and ^{1}H NMR comparisons.

Catalytic Reduction of 9. A mixture of **9** (150 mg, 0.54 mmol), PtO_2 (30 mg), and dioxane (220 ml) was stirred under hydrogen atmosphere at room temperature overnight, and filtered. Evaporation of the solvent and separation of the residue by column chromatography (SiO_2–$CHCl_3$) gave **8** (125 mg, 83%), which was identical with that obtained above by IR and ^{1}H NMR comparisons.

Preparation of 6a. To a solution of **2** (342 mg, 1.0 mmol) in $CHCl_3$ (30 ml) was added a solution of NBS (196 mg, 1.1 mmol) in $CHCl_3$ (30 ml). The solution was kept at room temperature for 15 min and worked up in the usual way. Crystallization from $CHCl_3$–hexane gave **6a** (395 mg, 94%): mp 130—132 °C (decomp); ^{13}C NMR δ=29.5 (t), 29.8 (t), 33.1 (t), 49.4 (d), 52.6 (q), 53.1 (q), 56.5 (s), 67.4 (s), 122.1 (d), 123.3 (d), 127.6 (d), 130.5 (d), 138.5 (s), 152.1 (s), 168.3 (s), 169.7 (s), 175.2 (s), and 178.4 (s). Without further purification, **6a** was subjected to the next experiment.

Preparation of 11. A solution of **6a** (43 mg) in Et_3N–CH_2Cl_2 (0.5—1 ml) was allowed to stand at room temperature for 2 d, and concentrated under reduced pressure. Separation of the residue by PTLC (SiO_2–AcOEt) gave **11** (10 mg, 29%) and **2** (20 mg, 57%). **11**: mp 231—233 °C ($CHCl_3$–hexane); ^{1}H NMR δ=2.39—3.03 (4H, m), 3.70 (3H, s), 3.89 (3H, s), 7.20—7.67 (4H, m), 7.50 (1H, s), and 8.97 (1H, br s). Found: *m/z* 340.1061. Calcd for $C_{18}H_{16}N_2O_5$: M, 340.1058.

Preparation of 12 and 13. A solution of **6a** (210 mg) in AcOH (10 ml) was kept at 20 °C for 22 h, and concentrated under reduced pressure to leave an oil, which was dissolved in $CHCl_3$. The solution was washed with aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which contained **12** and **13** in a ratio of 2:5 (determined by ^{1}H NMR). Separation of the products by column chromatography (SiO_2–$CHCl_3$) and PTLC (SiO_2, AcOEt–hexane, 2:1) gave **12** (26 mg, 12%) and **13** (89 mg, 42%). **12**: mp 186—188 °C ($CHCl_3$–hexane); ^{1}H NMR δ=2.17—2.98 (4H, m), 3.05 (1H, dd, *J*=16.0 and 7.0 Hz), 3.23 (1H, dd, *J*=16.0 and 1.8 Hz), 3.61 (3H, s), 3.85 (3H, s), 5.48 (1H, dd, *J*=7.0 and 1.8 Hz), 7.23 (C_{10}–H, d, *J*=8.6 Hz), 7.29 (C_9–H, dd, *J*=8.6 and 1.8 Hz), 7.62 (C_7–H, d, *J*=1.8 Hz), and 8.55 (1H, br s). Found: *m/z* 420.0320. Calcd for $C_{18}H_{17}N_2O_5Br$: M, 420.0320.

13: mp 176—178 °C (MeOH); ^{1}H NMR δ=2.17—2.98 (4H, m), 3.08 (1H, dd, *J*=16.1 and 7.3 Hz), 3.27 (1H, dd, *J*=16.1 and 1.2 Hz), 3.63 (3H, s), 3.86 (3H, s), 5.49 (1H, dd, *J*=7.3 and 1.2 Hz), 7.16 (C_8–H, dd, *J*=8.4 and 1.8 Hz), 7.32 (C_7–H, d, *J*=8.4 Hz), 7.37 (C_{10}–H, d, *J*=1.8 Hz), and 8.65 (1H, br s). Found: *m/z* 420.0300. Calcd for $C_{18}H_{17}N_2O_5Br$: M, 420.0320.

Conversion of 13 into 14. To a stirred solution of **13** (68 mg, 0.16 mmol) in DMF (3 ml) was added NaH (20 mg, 0.9 mmol). After stirring at room temperature for 20 min, methyl chloroformate (0.1 ml) was added. The mixture was stirred at room temperature for 2 h, and then poured into

aqueous NH_4Cl. The solution was worked up in the usual way to give **14** (50 mg, 65%): mp 112—114 °C (MeOH); ^1H NMR δ=2.03—3.33 (4H, m), 2.95 (1H, dd, J=16.5 and 8.1 Hz), 3.59 (1H, d, J=16.5 Hz), 3.64 (3H, s), 3.68 (3H, s), 4.03 (3H, s), 5.47 (1H, d, J=8.1 Hz), 7.38 (C_7-H, d, J=8.1 Hz), 7.44 (C_8-H, dd, J=8.1 and 1.6 Hz), and 8.20 (C_{10}-H, s). Found: m/z 478.0361. Calcd for $C_{20}H_{19}N_2O_7Br$: M, 478.0374.

Preparation of 15. As described above, a solution of **2** (103 mg, 0.30 mmol) in $CHCl_3$ (20 ml) was treated with a solution of NBS (59 mg, 0.33 mmol) in $CHCl_3$ (20 ml) to give **6a** quantitatively. Without crystallization, **6a** was dissolved in AcOH (10 ml) to yield a mixture of **12** and **13**. In the same way as mentioned above, the mixture of **12** and **13** was again treated with NBS (59 mg) and then AcOH (10 ml) to give **15** (95 mg, 63%): mp 232—233 °C (MeOH); ^1H NMR δ=2.18—2.99 (4H, m), 3.05 (1H, dd, J=16.1 and 7.3 Hz), 3.23 (1H, dd, J=16.1 and 0.7 Hz), 3.66 (3H, s), 3.88 (3H, s), 5.49 (1H, dd, J=7.3 and 0.7 Hz), 7.29 (C_{10}-H, s), 7.69 (C_7-H, s), and 8.90 (1H, br s). Found: m/z 497.9439. Calcd for $C_{18}H_{16}N_2O_5Br_2$: M, 497.9426.

Preparation of 16. To a solution of **2** (20 mg) in CH_2Cl_2 (2 ml) was added t-BuOCl (3 drops). The solution was kept at room temperature for 10 min and concentrated under reduced pressure to give **6b** quantitatively: ^{13}C NMR δ=29.5 (t), 33.3 (t), 48.6 (d), 52.6 (q), 53.0 (q), 67.1 (s), 67.5 (s), 122.0 (d), 123.1 (d), 127.7 (d), 130.7 (d), 137.9 (s), 152.8 (s), 168.5 (s), 170.0 (s), 175.2 (s), and 177.8 (s). Without further purification, **6b** was dissolved in AcOH (0.5 ml). The solution was allowed to stand at room temperature for 3 h and concentrated under reduced pressure. The residue was worked up in the usual way to give **16** (20 mg, 95%): mp 267—268 °C (MeOH); ^{13}C NMR δ=23.7 (t), 32.4 (t), 38.7 (t), 52.6 (q), 56.8 (d), 58.9 (s), 78.1 (s), 110.7 (d), 122.7 (d), 123.9 (d), 124.7 (s), 129.7 (d), 141.5 (s), 170.8 (s), 171.5 (s), 177.3 (s), and 179.1 (s). Found: m/z 358.1147. Calcd for $C_{18}H_{18}N_2O_6$: M, 358.1163.

Preparation of 17. To a solution of **2** (162 mg) in EtOH-CH_2Cl_2 (0.5—30 ml) was added t-BuOCl (1 ml). The solution was allowed to stand at room temperature for 2 d and concentrated under reduced pressure to give **17** (142 mg, 70%): mp 266—267 °C (EtOH); ^1H NMR (DMSO-d_6) δ= 1.70—2.95 (6H, m), 3.72 (6H, s), 4.78 (1H, t, J=8.4 Hz), 6.84 (C_7-H, d, J=1.8 Hz), 7.53 (C_9-H, d, J=1.8 Hz), and 11.38 (1H, br s). Found: m/z 426.0381. Calcd for $C_{18}H_{16}N_2O_6Cl_2$: M, 426.0383.

Preparation of 18. To a solution of **16** (14 mg) in CH_2Cl_2 (5 ml) was added t-BuOCl (2 drops). The solution was allowed to stand at room temperature for 18 h and concentrated under reduced pressure. Crystallization of the residue from EtOH gave **18**, mp >300 °C, (13 mg, 87%): ^1H NMR (DMSO-d_6) δ=1.70—2.90 (6H, m), 3.70 (6H, s), 4.77 (1H, t, J=8.4 Hz), 6.82 (C_7-H, d, J=2.1 Hz), 6.88 (C_{10}-H, d, J=8.4 Hz), 7.32 (C_9-H, dd, J=8.4 and 2.1 Hz), and 10.87 (1H, br s). Anal. ($C_{18}H_{17}N_2O_6Cl$) C, H, N.

Preparation of 17 from 18. To a mixture of **18** (24 mg) and EtOH-CH_2Cl_2 (0.1—10 ml) was added t-BuOCl (0.2 ml). The mixture was stirred at room temperature for 2 d and worked up as described above to give **17** (20 mg, 77%), which was found to be identical with that obtained as above.

References

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6) For the instruments used see Ref. 1.