ONE-STEP CONVERSION OF OXETANE-FUSED TO 1,3-OXAZINE-FUSED STEROIDS

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In a ring-expansion reaction, alkyl and aryl nitriles, in the presence of tetrafluoroboric acid–diethyl ether complex, react with 3-methoxy-16β,17β-dihydro-4′*H*-oxeto[3′,2′:16,17]estra-1,3,5(10)-triene to give 3-methoxy-16β,17β-dihydro-4′*H*-[1,3]-oxazino[5′,6′:16,17]estra-1,3,5(10)-triene derivatives. Under similar conditions 3-methoxy-16α,17α-dihydro-4′*H*-oxeto[3′,2′:16,17]estra-1,3,5(10)-triene undergoes a Wagner–Meerwein rearrangement.
Key words: Steroids; Ring expansions; Ritter reaction; Oxetanes; Dihydrooxazines.

Epoxides and their substituted derivatives can be converted into vicinal acylamino hydroxy compounds with acid nitriles in the presence of acids under the conditions of the Ritter reaction[1–3]. This reaction results in the formation of vicinal diaxial *trans*-acylamino hydroxy compounds in the case of epoxycholestane. Such stereospecific ring cleavage[4–7] of steroid epoxides condensed to the A or B ring has been realized in acetonitrile employing $HClO_4$. The analogous conversion of epimeric 5,6-epoxysteroids in acetonitrile or benzonitrile in the presence of BF_3–diethyl etherate yields similar products[8–10]. While the stereospecific reactions of epoxides condensed to the six-membered rings in the steroid skeleton result in the corresponding *trans*-acylamino hydroxy steroids in satisfactory yields, the ring cleavage of epoxides condensed to the five-membered ring D is accompanied by several side reactions. It was observed recently that the ring cleavage reaction of the 16β,17β-epoxide effected with various acid nitriles resulted in the formation of the corresponding α-acylamino-β-hydroxy compounds in satisfactory yields. However, the 16α,17α-epoxide, the both 14,15- epoxides and the 15β,16β-epoxide undergo a rearrangement during the ring cleavage under the ex-

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perimental conditions of the Ritter reaction, and the formation of the acylamino group does not take place[11,12].

Recently we extended the ring cleavage reaction of steroid epoxides to the oxetane condensed to the ring D of androstane skeleton. This method provided possibility for the preparation of α-acylamino-γ-hydroxy steroids. 3β-Acetoxy-16β,17β-dihydro-4′*H*-oxeto[3′,2′:16,17]androst-5-ene was reacted with aliphatic and aromatic nitriles in the presence of equivalent amounts of HBF_4–diethyl etherate. Unexpectedly, a 1,3-oxazine fused to the steroid skeleton was obtained instead of α-acylamino-γ-hydroxy steroids[13]. Our investigation has two aimes. We wished to establish the validity of the observation of ring expansion with aromatic nitriles substituted with different electron-withdrawing substituents and we wanted to prepare different heterocycles salts condensed to estrane skeleton, potencially biologically active compounds.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured in chloroform (*c* 1.0) on a Polamat A polarimeter at 23 °C and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a Bruker AM 400 instrument. Chemical shifts are reported in ppm (δ-scale), coupling constants (*J*) are given in Hz. For determination of the multiplicities, the J-MOD pulse sequence was used. Electron impact mass spectra (70 eV) were obtained on a Varian MAT 311A spectrometer. All solvents were distilled prior to use. The reactions were monitored by TLC (Merck Silica gel 60 F_{254}). Products were isolated by flash chromatography (Merck Kieselgel 60, 40–63 μm).

General Procedure for Preparation of Compounds **4a**–**4h**

To a solution of compound **1** (ref.[14]; 0.895 g, 3 mmol) in CH_2Cl_2 (5 ml), a nitrile (5 g) was added. The solution was cooled to 0 °C and HBF_4–diethyl ether complex (0.5 ml, 3 mmol) was added dropwise under stirring. The reaction mixture was allowed to stand at room temperature for 6 h and then anhydrous diethyl ether (100 ml) was added. The crystalline substance separated from the reaction mixture on standing for 24 h was filtered off and recrystallized from a CH_2Cl_2–diethyl ether mixture.

*3-Methoxy-2′-methyl-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4a**): yield 1.20 g (93%), m.p. 227–230 °C.

*2′-Cyclohexyl-3-methoxy-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4b**): yield 1.35 g (90%), m.p. 170–172 °C.

*3-Methoxy-2′-phenyl-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4c**): yield 1.40 g (96%), m.p. 202–205 °C.

*3-Methoxy-2′-(4-methylphenyl)-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4d**): yield 1.45 g (95%), m.p. 210–213 °C.

*3-Methoxy-2′-(4-methoxyphenyl)-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4e**): yield 1.12 g (71%), m.p. 216–218 °C.

*2′-(4-Bromophenyl)-3-methoxy-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4f**): yield 832 mg (48%), m.p. 195–197 °C.

*2′-(4-Chlorophenyl)-3-methoxy-16*β,*17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4g**): yield 725 mg (46%), m.p. 199–202 °C.

*3-Methoxy-2′-(4-nitrophenyl)-16*β,*17*β-*dihydro-4′H-[1,3]-oxazino[5′,6′:16,17]estra-1,3,5(10)-triene fluoroborate* (**4h**): yields 368 mg (22%), m.p. 210–214 °C.

General Procedure for Preparation of Compounds **3a**–**3h**

A solution of compound **4** (2 mmol) in CH_2Cl_2 (10 ml) was layered over with a saturated aqueous solution of $NaHCO_3$ and left to stand at room temperature for 2 h. The organic phase was then separated, washed with water, dried and evaporated to dryness. The residue was recrystallized from acetone.

*3-Methoxy-2′-methyl-16*β,*17*β-*dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3a**): yield 652 mg (96%), m.p. 197–199 °C, $[\alpha]_D$ +124. ^{1}H NMR spectrum ($CDCl_3$): 0.77 s, 3 H (3 × H-18); 1.97 s, 3 H (N=C–CH_3); 2.78–2.86 m, 3 H (2 × H-6 and H_{ax}-16a); 3.63 m, 1 H (H_{eq}-16a); 3.77 s, 3 H (OCH_3); 3.89 d, 1 H *J* = 9.8 (H-17); 6.62 d, 1 H, *J* = 2.5 (H-4); 6.72 dd, 1 H, *J* = 8.6, *J′* = 2.5 (H-2); 7.20 d, 1 H, *J* = 8.6 (H-1). ^{13}C NMR spectrum ($CDCl_3$): 13.2 (C-18), 21.8 (N=C–**C**H_3), 26.2, 27.5, 29.7, 30.1, 31.2, 37.5, 38.2, 44.1, 44.3 (C-13), 47.8, 48.5 (C-16a), 55.2 (OCH_3), 84.6 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.3 (C-10), 137.8 (C-5), 157.5 (C-3), 159.1 (C=N). Mass spectrum, *m/z* (%): 340 (24), 339 (M^+, 100) 268 (7), 227 (9), 186 (15), 173 (18), 160 (12), 147 (14). For $C_{22}H_{29}NO_2$ (339.5) calculated: 77.84% C, 8.61% H, 4.13% N; found: 77.95% C, 8.58% H, 4.30% N.

*2′-Cyclohexyl-3-methoxy-16*β,*17*β-*dihydro-4′H-[1,3]oxazino[5′6′:16,17]estra-1,3,5(10)-triene* (**3b**): yield 795 mg (97%), m.p. 154–155.5 °C, $[\alpha]_D$ +99. ^{1}H NMR spectrum ($CDCl_3$): 0.76 s, 3 H (3 × H-18); 2.82 dd, 1 H, *J* = 14.8, *J′* = 10.8 (H_{ax}-16a); 2.86 m, 2 H (2 × H-6), 3.66 dd, 1 H, *J* = 14.8, *J′* = 7.6 (H_{eq}-16a); 3.77 s, 3 H (OCH_3); 3.84 d, 1 H, *J* = 9.8 (H-17); 6.63 d, 1 H, *J* = 2.4 (H-4); 6.72 dd, 1 H, *J* = 8.6, *J′* = 2.4 (H-2); 7.21 d, 1 H, *J* = 8.6 (H-1). ^{13}C NMR spectrum ($CDCl_3$): 13.1 (C-18), 25.9, 26.0, 26.1, 26.2, 27.5, 29.8, 30.0, 30.1, 30.5, 31.3, 37.6, 38.2, 44.0, 44.1, 44.4 (C-13), 47.9, 48.5 (C-16a), 55.2 (OCH_3), 84.5 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3), 164.9 (C=N). Mass spectrum, *m/z* (%): 407 (M^+, 100), 352 (62), 281 (37), 173 (30), 147 (18). For $C_{27}H_{37}NO_2$ (407.6) calculated: 79.56% C, 9.15% H, 3.44% N; found: 79.45% C, 9.23% H, 3.5% N.

*3-Methoxy-2′-phenyl-16*β,*17*β-*dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3c**): yield 762 mg (94%), m.p. 178–179 °C, $[\alpha]_D$ +57. ^{1}H NMR spectrum ($CDCl_3$): 0.86 s, 3 H (3 × H-18); 2.87 m, 2 H (2 × H-6); 3.06 dd, 1 H, *J* = 14.7, *J′* = 10.8 (H_{ax}-16a); 3.78 s, 3 H (OCH_3); 3.91 dd, 1 H, *J* = 14.7, *J′* = 7.4 (H_{eq}-16a); 4.10 d, 1 H, *J* = 9.8 (H-17); 6.64 d, 1 H, *J* = 2.3 (H-4); 6.73 dd, 1 H, *J* = 8.6, *J′* = 2.3 (H-2); 7.23 d, 1 H, *J* = 8.6 (H-1); 7.40 m, 3 H (H-3′, H-4′ and H-5′); 7.97 d, 2 H, *J* = 8.0 (H-2′- and H-6′). ^{13}C NMR spectrum ($CDCl_3$): 13.4 (C-18), 26.2, 27.5, 29.7, 31.0, 31.7, 37.7, 38.1, 44.0, 44.6 (C-13), 48.0, 48.9 (C-16a), 55.2 (OCH_3), 85.4 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 127.1 (2 C) and 128.0 (2 C) (C-2′, C-6′ and C-3′, C-5′), 130.4 (C-4′), 132.3 (C-10), 134.0 (C-1′), 137.8 (C-5), 157.5 (C-3), 157.7 (C=N). Mass spectrum, *m/z* (%): 401 (M^+, 100), 268 (11), 173 (9), 105 (8). For $C_{27}H_{31}NO_2$ (401.6) calculated: 80.76% C, 7.78% H, 3.49% N; found: 80.68% C, 7.85% H, 3.55% N.

*3-Methoxy-2′-(4-methylphenyl)-16*β,*17*β-*dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3d**): yield 820 mg (98%), m.p. 182–185 °C, $[\alpha]_D$ +56. ^{1}H NMR spectrum ($CDCl_3$): 0.85 s, 3 H (3 × H-18); 2.37 s, 3 H (4′-CH_3); 2.87 m, 2 H (2 × H-6); 3.06 dd, 1 H, *J* = 14.6, *J′* = 10.8 (H_{ax}-16a); 3.78 s, 3 H (OCH_3); 3.88 dd, 1 H, *J* = 14.6, *J′* = 7.4 (H_{eq}-16a); 4.08 d, 1 H, *J* = 9.9 (H-17); 6.64 d, 1 H, *J* = 2.2 (H-4); 6.72 dd, 1 H, J = 8.6, *J′* = 2.2 (H-2); 7.18 d, 2 H, *J* = 8.0 (H-3′ and H-5′); 7.22 d, 1 H, *J* = 8.6 (H-1); 7.85 d, 2 H, *J* = 8.0 (H-2′ and H-6′). ^{13}C NMR spectrum ($CDCl_3$): 13.4 (C-18), 21.4 (4′-CH_3), 26.3, 27.5, 29.7, 31.0, 31.8, 37.7, 38.1, 44.0, 44.6 (C-13), 48.1, 48.9 (C-16a), 55.2 (OCH_3), 85.3 (C-17), 111.6 (C-2), 113.8 (C-4), 126.3 (C-1), 127.0 (2 C) and 128.8 (2 C) (C-2′, C-6′ and C-3′, C-5′), 131.3 (C-1′), 132.4 (C-10), 137.8 (C-5), 140.5 (C-4′), 157.5 (C-3), 157.9 (C=N). Mass spec-

trum, *m/z* (%): 415 (M^+, 100), 268 (22), 173 (16), 119 (23). For $C_{28}H_{33}NO_2$ (415.6) calculated: 80.93% C, 8.00% H, 3.37% N; found: 80.98% C, 7.92% H, 3.50% N.

*3-Methoxy-2′-(4-methoxyphenyl)-16*β*,17*β*-dihydro-4′H-[1,3]-oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3e**): yield 814 mg (94%), m.p. 199–202 °C, $[\alpha]_D$ +47. ^{1}H NMR spectrum ($CDCl_3$): 0.85 s, 3 H (3 × H-18); 2.86 m, 2 H (2 × H-6); 3.03 dd, 1 H, *J* = 14.5, *J′* = 10.9 (H_{ax}-16a); 3.77 s, 3 H (3-OCH_3); 3.83 s, 3 H (4′-OCH_3); 3.86 dd, 1 H, *J* = 14.5, *J′* = 7.1 (H_{eq}-16a); 4.07 d, 1 H, *J* = 9.9 (H-17); 6.63 d, 1 H, *J* = 2.4 (H-4); 6.72 dd, 1 H, *J* = 8.6, *J′* = 2.4 (H-2); 6.88 d, 2 H, *J* = 8.7 (H-3′ and H-5′); 7.21 d, 1 H, *J* = 8.6 (H-1); 7.91 d, 2 H, *J* = 8.7 (H-2′ and H-6′). ^{13}C NMR spectrum ($CDCl_3$): 13.4 (C-18), 26.2, 27.6, 29.8, 31.0, 32.0, 37.7, 38.1, 44.0, 44.6 (C-13), 48.1, 48.8 (C-16a), 55.2 and 55.3 (3-OCH_3 and 4′-OCH_3), 85.3 (C-17), 111.5 (C-2), 113.2 (2 C, C-3′ and C-5′), 113.8 (C-4), 126.3 (C-1), 126.6, 128.7 (2 C, C-2′ and C-6′), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3), 157.7 (C=N), 161.4 (C-4′). Mass spectrum, *m/z* (%): 431 (M^+, 100), 280 (12), 268 (23), 147 (14), 135 (38). For $C_{28}H_{33}NO_3$ (431.6) calculated: 77.93% C, 7.71% H, 3.25% N; found: 77.88% C, 7.50% H, 3.22% N.

*2′-(4-Bromophenyl)-3-methoxy-16*β*,17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3f**): yield 930 mg (96%), m.p. 179–182 °C, $[\alpha]_D$ +38. ^{1}H NMR spectrum ($CDCl_3$): 0.84 s, 3 H (3 × H-18); 2.86 m, 2 H (2 × H-6)′ 3.03 dd, 1 H, *J* = 14.8, *J′* = 10.7 (H_{ax}-16a); 3.78 s, 3 H (OCH_3), 3.89 dd, 1 H, *J* = 14.8, *J′* = 7.5 (H_{eq}-16a); 4.09 d, 1 H, *J* = 9.8 (H-17); 6.64 d, 1H, *J* = 2.5 (H-4); 6.72 dd, 1 H, *J* = 8.6, *J′* = 2.5 (H-2); 7.22 d, 1 H, *J* = 8.6 (H-1); 7.51 d, 2 H, *J* = 8.6 (H-3′ and H-5′); 7.83 d, 2 H, *J* = 8.6 (H-2′ and H-6′). ^{13}C NMR spectrum ($CDCl_3$): 13.4 (C-18), 26.2, 27.5, 29.7, 31.1, 31.4, 37.7, 38.1, 44.0, 44.6 (C-13), 48.0, 48.9 (C-16a), 55.2 (OCH_3), 85.5 (C-17), 111.6 (C-2), 113.8 (C-4), 124.9 (C-4′), 126.3 (C-1), 128.7 (2 C) and 131.2 (2 C) (C-2′, C-6′ and C-3′, C-5′), 132.3 (C-10), 133.0 (C-1′), 137.7 (C-5), 156.8 (C=N), 157.5 (C-3). Mass spectrum, *m/z* (%): 481 (100) and 479 (98): M^+, 268 (17), 173 (16), 147 (15). For $C_{27}H_{30}BrNO_2$ (480.5) calculated: 67.50% C, 6.29% H, 2.92% N; found: 67.42% C, 6.37% H, 3.02% N.

*2′-(4-Chlorophenyl)-3-methoxy-16*β*,17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3g**): yield 857 mg (98%), m.p. 179–180 °C, $[\alpha]_D$ +41. ^{1}H NMR spectrum ($CDCl_3$): 0.84 s, 3 H (3 × H-18); 2.87 m, 2 H (2 × H-6); 3.04 dd, 1 H, *J* = 14.8, *J′* = 10.8 (H_{ax}-16a); 3.78 s, 3 H (OCH_3); 3.90 dd, 1 H, *J* = 14.8, *J′* = 7.5 (H_{eq}-16a); 4.09 d, 1 H, *J* = 9.9 (H-17); 6.64 d, 1 H, *J* = 2.6 (H-4); 6.72 dd, 1 H, *J* = 8.5, *J′* = 2.6 (H-2); 7.21 d, 1 H, *J* = 8.5 (H-1); 7.34 d, 2 H, *J* = 8.5 (H-3′ and H-5′); 7.90 d, 2 H, *J* = 8.5 (H-2′ and H-6′). ^{13}C NMR spectrum ($CDCl_3$): 13.4 (C-18), 26.2, 27.6, 29.8, 31.1, 31.5, 37.7, 38.1, 44.1, 44.6 (C-13), 48.0, 48.9 (C-16a), 55.2 (OCH_3), 85.5 (C-17), 111.6 (C-2), 113.8 (C-4), 126.3 (C-1), 128.3 (2 C) and 128.5 (2 C) (2′,3′,5′- and 6′-C), 132.3 (C-10), 132.5 (C-1′), 136.5 (C-4′), 137.8 (C-5), 156.7 (C=N), 157.5 (C-3). Mass spectrum, *m/z* (%): 437 (35) and 435 (100): M^+, 268 (10), 208 (11), 173 (14), 160 (10), 147 (11), 139 (15). For $C_{27}H_{30}ClNO_2$ (436.0) calculated: 74.38% C, 6.94% H, 3.21% N; found: 74.45% C, 6.85% H, 3.35% N.

*3-Methoxy-2′-(4-nitrophenyl)-16*β*,17*β*-dihydro-4′H-[1,3]oxazino[5′,6′:16,17]estra-1,3,5(10)-triene* (**3h**): yield 860 mg (96%), m.p. 199-202 °C, $[\alpha]_D$ +32. ^{1}H NMR spectrum ($CDCl_3$): 0.85 s, 3 H (3 × H-18); 2.88 m, 2 H (2 × H-6); 3.09 dd, 1 H, *J* = 15.3, *J′* = 10.5 (H_{ax}-16a); 3.78 s, 3 H (OCH_3); 3.97 dd, 1 H, *J* = 15.3, *J′* = 7.6 (H_{eq}-16a); 4.15 d, 1 H, *J* = 9.8 (H-17); 6.64 d, 1 H, *J* = 2.4 (H-4); 6.72 dd, 1 H, *J* = 8.6, *J′* = 2.4 (H-2); 7.22 d, 1 H, *J* = 8.6 (H-1); 8.11 d, 2 H, *J* = 8.8 and 8.23 d, 2 H, *J* = 8.8 (H-2′, H-6′ and H-3′, H-5′). ^{13}C NMR spectrum ($CDCl_3$): 13.4 (C-18), 26.2, 27.5, 29.7, 31.0, 31.2, 37.6, 38.1, 44.0, 44.6 (C-13), 48.0, 49.2 (C-16a), 55.2 (OCH_3), 85.7 (C-17), 111.6 (C-2), 113.8 (C-4), 123.2 (2 C, C-3′ and C-5′), 126.3 (C-1), 128.0 (2 C, C-2′ and C-6′), 132.1 (C-10), 137.7 (C-5), 139.8 (C-1′), 149.0 (C-4′), 155.5 (C=N), 157.5 (C-3). Mass spectrum, *m/z* (%): 447 (28), 446 (M^+, 100), 173 (14), 171 (17), 117 (14), 106 (14), 91 (14), 41 (15). For $C_{27}H_{30}N_2O_4$ (446.6) calculated: 72.62% C, 6.77% H, 6.27% N; found: 72.75% C, 6.86% H, 6.40% N.

16β-Aminomethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**5a**)

Compound **7b** (0.680 g, 2 mmol) was dissolved in ethanol (50 ml) and hydrazine hydrate (2.5 ml, 50 mmol) and Raney-Ni catalyst (20 mg) were added. The reaction mixture was allowed to stand at room temperature for 4 h and then the catalyst was filtered off. The reaction mixture was diluted with water, the crystalline precipitate was filtered off, washed with water until neutral and dried. The product **5a** (0.560 g, 88%) was crystallized from ethanol, m.p. 240–245 °C (dec.). For $C_{20}H_{29}NO_2$ (315.5) calculated: 76.15% C, 9.27% H, 4.44% N; found: 75.98% C, 9.36% H, 4.80% N.

16β-Acetaminomethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**6a**)

a) To a solution of compound **6b** (0.800 g, 2 mmol) in methanol (20 ml), CH_3ONa (0.110 g, 2 mmol) was added and the reaction mixture was refluxed for 1 h. It was then diluted with water, the crystalline precipitate **6a** (0.680 g, 95%) was filtered off and crystallized from a methanol–water mixture, m.p. 235–238 °C, $[\alpha]_D$ +53. ^{1}H NMR spectrum ($CDCl_3$): 0.80 s, 3 H (3 × H-18); 1.97 s, 3 H (CH_3COO); 2.85 m, 2 H (2 × H-6); 3.23 m and 3.57 m, 2 × 1 H (2 × H-16a); 3.77 s, 3 H (OCH_3); 3.86 d, 1 H, J = 9.8 (H-17); 6.26 br s, 1 H (NH); 6.63 d, 1 H, J = 2.3 (H-4); 6.72 dd, 1 H, J = 8.5, J' = 2.3 (H-2); 7.19 d, 1 H, J = 8.5 (H-1). ^{13}C NMR spectrum ($CDCl_3$): 12.2 (C-18), 23.5 (**C**H_3COO), 26.2, 27.4, 29.7 (2 C), 37.5, 38.1, 40.7, 41.0 (C-16a), 43.8, 44.3 (C-13), 48.8, 55.2 (OCH_3), 82.3 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.4 (C-10), 137.9 (C-5), 157.5 (C-3), 169.8 (CH_3**C**OO). For $C_{22}H_{31}NO_3$ (357.5) calculated: 73.92% C, 8.74% H, 3.92% N; found: 73.80% C, 8.83% H, 4.02% N.

b) Compound **4a** (0.214 g, 0.5 mmol) was dissolved in methanol (25 ml) and refluxed with $NaHCO_3$ (0.110 g, 2 mmol) for 1 h. The reaction mixture was diluted with water, saturated with $(NH_4)_2SO_4$, the crystalline precipitate **6a** (0.150 g, 86%) was filtered off and crystallized form a methanol–water mixture.

c) Compound **5b** (0.223 g, 0.5 mmol) was dissolved in dioxane (25 ml) and refluxed with $NaHCO_3$ (0.110 g, 2 mmol) for 1 h. The reaction was diluted with water, saturated with $(NH_4)_2SO_4$, the precipitate **6a** (0.160 g, 89%) was filtered off and crystallized from a methanol–water mixture.

16β-Acetaminomethyl-3-methoxyestra-1,3,5(10)-trien-17β-yl Acetate (**6b**)

Compound **5a** (0.631 g, 2 mmol) was allowed to stand in a mixture of acetic anhydride (3 ml) and pyridine (3 ml) overnight. The reaction mixture was then diluted with water, the crystalline precipitate was filtered off and recrystallized from methanol. Yield 790 mg (98%), m.p. 225–227 °C, $[\alpha]_D$ +59. ^{1}H NMR spectrum ($CDCl_3$): 0.86 s, 3 H (3 × H-18); 1.97 s, 3 H (CH_3CON); 2.10 s, 3 H (CH_3COO); 2.84 m, 2 H (2 × H-6); 3.29 m, 2 H (2 × H-16a); 3.76 s, 3 H (OCH_3); 4.82 d, 1 H, J = 9.8 (H-17); 5.69 br s, 1 H (NH); 6.62 d, 1 H, J = 2.3 (H-4); 6.69 dd, 1 H, J = 8.6, J' = 2.3 (H-2); 7.17 d, 1 H, J = 8.6 (H-1). ^{13}C NMR spectrum ($CDCl_3$): 13.0 (C-18), 20.9 (**C**H_3COO), 23.2 (**C**H_3CON), 26.0, 27.3, 29.6, 30.2, 37.4, 37.8, 38.6, 41.1 (C-16a), 43.6, 43.7 (C-13), 48.6, 55.0 (OCH_3), 82.3 (C-17), 111.4 (C-2), 113.6 (C-4), 126.1 (C-1), 132.1 (C-10), 137.6 (C-5), 157.4 (C-3), 169.8 (CH_3**C**ON), 171.1 (CH_3**C**OO). For $C_{24}H_{33}NO_4$ (399.5) calculated: 72.15% C, 8.33% H, 3.51% N; found: 72.31% C, 8.42% H, 3.45% N.

16β-Azidomethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**7b**)

To a solution **7a** (ref.[15]; 1.20 g, 2 mmol) in dimethylformamide (20 ml), NaN_3 (1.3 g, 20 mmol) was added and the reaction mixture was kept on a water bath at 100 °C for 2 h. It was then diluted with water, the crystalline precipitate was filtered aff and recrystallized from an acetone–water mixture. Yield 610 mg (89%), m.p. 134–136 °C (ref.[16] gives 134–135 °C), $[\alpha]_D$ +80. ^{1}H NMR spectrum

($CDCl_3$): 0.80 s, 3 H (3 × H-18); 2.85 m, 2 H (2 × H-6); 3.31 m and 3.59 m, 2 × 1 H (2 × H-16a); 3.77 s, 3 H (OCH_3); 3.86 dd, 1 H, J = 9.8, J' = 3.8 (H-17); 6.63 d, 1 H, J = 2.5 (H-4); 6.71 dd, 1 H, J = 8.6, J' = 2.5 (H-2); 7.19 d, 1 H, J = 8.6 (1-H). ^{13}C NMR spectrum ($CDCl_3$): 12.2 (C-18), 26.3, 27.5, 29.7, 30.3, 37.6, 38.1, 40.1, 43.9, 44.2 (C-13), 48.8, 53.3 (C-16a), 55.2 (OCH_3), 81.4 (C-17), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.4 (C-10), 137.8 (C-5), 157.5 (C-3). For $C_{20}H_{27}N_3O_2$ (341.5) calculated: 70.35% C, 7.97% H, 12.31% N; found: 70.41% C, 7.93% H, 12.24% N.

16β-Aminomethyl-3-methoxyestra-1,3,5(10)-trien-17β-yl Acetate Tetrafluoroborate (**5b**)

a) To a solution of compound **4a** (0.427 g, 1 mmol) in dioxane (15 ml), several drops of water were added and the solution was allowed to stand for 24 h. The reaction mixture was diluted with water, the precipitate **5b** (0.430 g, 96%) was filtered off and recrystallized from a CH_2Cl_2–diethyl ether mixture, m.p. 208–212 °C, $[\alpha]_D$ +38 (*c* 1.0 methanol). For $C_{22}H_{31}NO_3 \cdot HBF_4$ (445.3) calculated: 59.34% C, 7.02% H, 3.15% N; found: 59.45% C, 7.16% H, 3.38% N.

b) To a solution of compound **6a** (0.180 g, 0.5 mmol) in dioxane (15 ml), $HBF_4 \cdot Et_2O$ (0.3 ml, 2 mmol) was added to it and the solution was kept at 45 °C for 6 h. After cooling, diethyl ether (50 ml) was added to it and the fine precipitate **5b** (0.165 g, 72%) was filtered off.

16α-Hydroxymethyl-3-methoxy-17β-methyl-18-norestra-1,3,5(10),13-tetraene (**10**)

Compound **9** (ref.[14]; 0.300 g, 1 mmol) was converted with acetonitrile (3 g) into the title compound under the conditions given in procedure for preparation of compound **4**. The reaction mixture was diluted with water, saturated with $(NH_4)_2SO_4$, the crystalline precipitate **10** (0.260 g, 86%) was filtered off and crystallized from an acetone–water mixture, m.p. 119–120 °C (ref.[17] gives 118–120 °C), $[\alpha]_D$ +44.

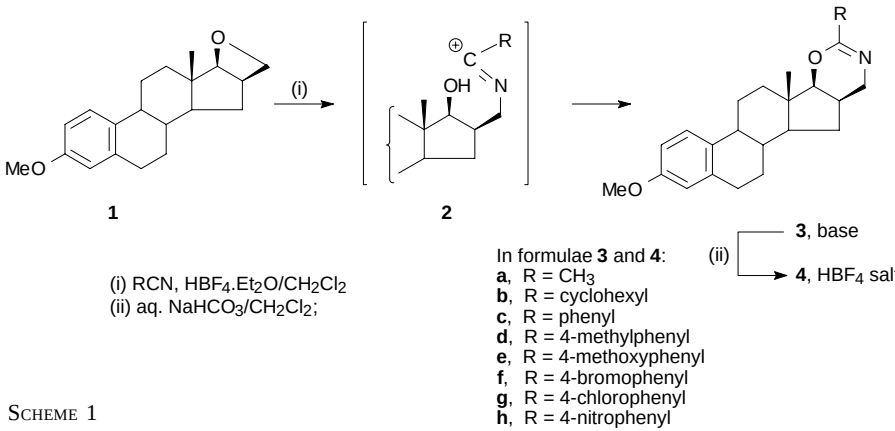
RESULTS AND DISCUSSION

We have previously reported[14] the preparation of the two isomeric epoxides **1** and **9**. In the present paper compound **1** was reacted with aliphatic and aromatic nitriles in the presence of equivalent amounts of HBF_4–diethyl etherate and the corresponding fluoroborate of 1,3-oxazine-fused steroid was obtained.

Employing thus the appropriate nitriles, the compounds **4a**–**4h** were prepared (Scheme 1). The corresponding bases (**3a**–**3h**) can be liberated from the salts with an aqueous solution of $NaHCO_3$. The stability of the bases is different. Compound **4a** transforms readily into the corresponding 16β-acetaminomethyl-3-methoxyestra-1,3,5(10)-triene-17β-ol (**6a**) by the action of the $NaHCO_3$ solution. A analogous compounds **4b**–**4h**, in turn, proved to be stable in the presence of alkali alcoholates. The unstable nature of **4a** is surprising, since substituted dihydrooxazine rings fused to ring A of steroids are usually more stable[7]. In the presence of 1 M CH_3ONa the dihydrooxazine ring of cyclohexyl, and aryl substituted analogues **4b**–**4h** remained unchanged at room temperature.

The structure of dihydrooxazine-fused steroids and their conversion products were established by spectroscopic methods. The H-17 doublet in the ^{1}H NMR spectrum of type **3** shows no significant change as compared to the 17-hydroxy compounds **5**–**7**; it

appears between 3.8 and 3.9 ppm (R = alkyl), and at about 4.10 ppm (R = aryl), respectively. In the 17-acetoxy derivatives this signal is at about 4.8 ppm. The chemically non-equivalent methylene protons in the hetero ring give double doublets in the ranges 2.7–3.1 and 3.6–4.0 ppm, and the coupling constants deduced for geminal, diaxial and axial–equatorial coupling will be 14–15.3, 10.5–10.9 and 7.1–7.7 Hz, respectively.

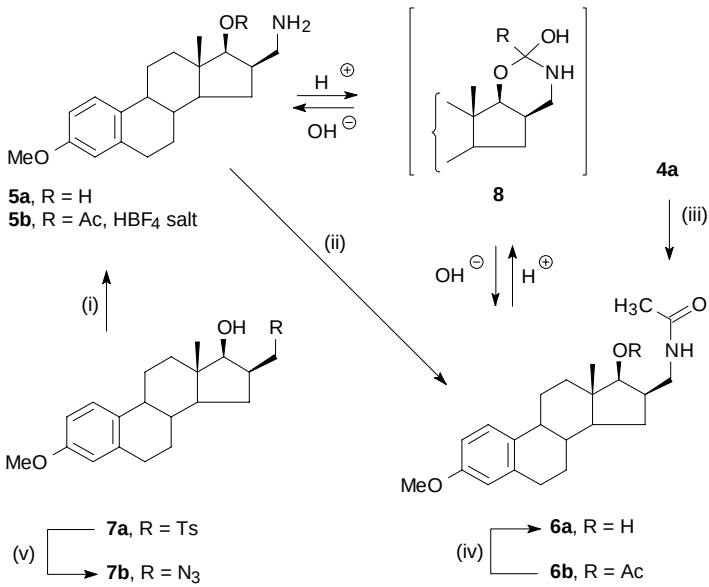


SCHEME 1

Of the ^{13}C NMR data, the downfield signal of the sp^2 carbon atom in the hetero ring should be mentioned confirming structures of type **3**. It appears at about 157–158 ppm for compounds **3c**, **3d**, **3f**–**3h** and is sensitive to substituent R: in the spectra of **3a**, **3b** and **3e**, it is dowhfield shifted to 159.1, 164.9 and 161.4 ppm, respectively; thus, electron-donating substitution in the hetero cycle decreases the shielding. The shift of the heterocyclic methylene carbon deviates characteristically (≈49 ppm) from that in open-chain derivatives **6b** (41.1 ppm) and **7b** (53.3 ppm), thus confirming the heterocyclic structure. In addition to the NMR and MS spectroscopic methods, an X-ray analysis was performed[18] for **3b**. The tetrafluoroborate of **4a** decomposed in aqueous dioxane at room temperature and 16β-aminomethyl-3-methoxyestra-1,3,5(10)-triene-17β-yl acetate tetrafluoroborate (**5b**) was formed. The dioxane solution of **5b** with $NaHCO_3$ transformed into **6a**. The conversion, in accordance with the N→O acyl migration reaction of 1,3-aminoalcohols, is reversible[19], and, in the presence of fluoroboric acid, it yields **5b** again, presumably *via* the intermediate **8**. Thus, compound **3** obtained in the ring-expansion reaction of the steroid oxetane can be regarded as an intermediate in the N→O acyl migration reaction of 1,3-aminoalcohols stabilized under kinetic control. Compound **5a** was prepared by the conversion of tosylate (**7a**) having a configuration confirmed earlier[17] into **7b** with NaN_3 and subsequent reduction with hydrazine hydrate in the presence of Raney-Ni (Scheme 2).

The ring-expansion reaction of non-fused oxiranes and oxetanes under the condition of the Ritter reaction, yielding the corresponding 4,5-dihydrooxazoles and dihydro-1,3-

oxazines, is well known[20–22]. The stereochemical conditions, however, are not known for ring expansion of oxiranes fused to the steroid skeleton to 4,5-dihydrooxazoles. Conversion of steroid oxiranes into dihydro-1,3-oxazines *via* a secondary reaction with free hydroxy groups in the molecule has already been observed in the case of 3β-hydroxy-4,5-epoxycholestan epimers[7]. During the conversion of 9β,11β-epoxypregn-4-ene-16α,17α,21-triol, the 5α,9α-dihydroxyoxazine ring is formed, owing to the presence of the 4,5-double bond[23].



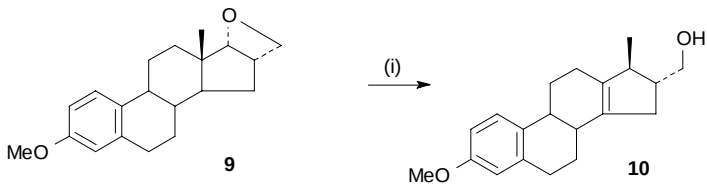
(i) $N_2H_4.H_2O$, Ra-Ni/EtOH; (ii) MeONa/MeOH, reflux; (iii) $NaHCO_3$/MeOH, reflux; (iv) $NaHCO_3$/dioxane, reflux; (v) NaN_3/DMF, 100 °C

SCHEME 2

In acid medium compound **1** transforms into oxonium ion which the substitution of the nucleophilic nitrile can take place at both the 16-methylene and the 17-carbon atom. The attack at C-16 is favoured sterically, and the carbo cation forms a dihydro-1,3-oxazine ring fused to the steroid skeleton in an intramolecular reaction with the 17-hydroxy group. The nucleophilic attack at C-17 would involve inversion, and stabilization of the carbocation formed would yield the 16β-hydroxymethyl-17α-acylamino steroid. Its cyclization would lead to the sterically unfavoured *trans*-fused dihydrooxazine. The 16β,17β-oxetane ring can easily be attacked in a nucleophilic reaction. It is, therefore, justified that in the Ritter reaction the nitrogen function is attached to the primary

carbon atom, in contrast to the general observation assuming the attack at the carbon atom of higher order[1].

However, the Ritter reaction of the epimeric compound **9** leads to the cleavage of the oxetane ring followed by stabilization of the carbocation developing by a Wagner–Meerwein rearrangement. Under such conditions, the attack by the nitrile function does not occur, and 16α-hydroxymethyl-3-methoxy-17β-methyl-18-norestra-1,3,5(10),16-tetraene (**10**) is formed (Scheme 3).



SCHEME 3

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