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Short communicaiton

SHORT COMMUNICATION

An improved approach to B-norsteroids: An one-pot preparation of 3β-acetoxy-5-oxo-5,6-seco-cholestan-6-oic and 3β-acetoxy-5,17-dioxo-5,6-seco-androstan-6-oic acids

LJUBOMIR S. STEVOVIĆ,[a] VLADIMIR D. PAVLOVIĆ,[a,b] SAŠA B. MARTINOVIĆ,[b] MILAN M. DABOVIĆ,[b] and IVAN O. JURANIĆ[a,b]

[a]*Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, YU-11000 Belgrade and* [b]*Center for Chemistry, Institute of Chemistry, Technology and Metallurgy, Njegoševa 12, YU-11000 Belgrade, Yugoslavia*

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A simple one-pot procedure for the synthesis of the 5,6-seco-steroidal acids **9a,b** in described in this paper. It consists of the epoxidation of the Δ^5-steroids, *i.e.*, cholesteryl acetate (**8a**) and 17-oxo-aandrost-5-en-3β-yl acetate (**8b**) with peracetic acid (generated *in situ* by the H_2WO_4/H_2O_2 system), followed by the CrO_3/H_2SO_4 oxidation of the thus formed epoxides. The 5,6-seco-steroidal acids **9a,b** (obtained in about 90% and 77% yield, respectively) are transformed to the corresponding B-norsteroids by the known method (Beayer-Villiger oxidation and subsequent thermolysis of the respective β-lactones).

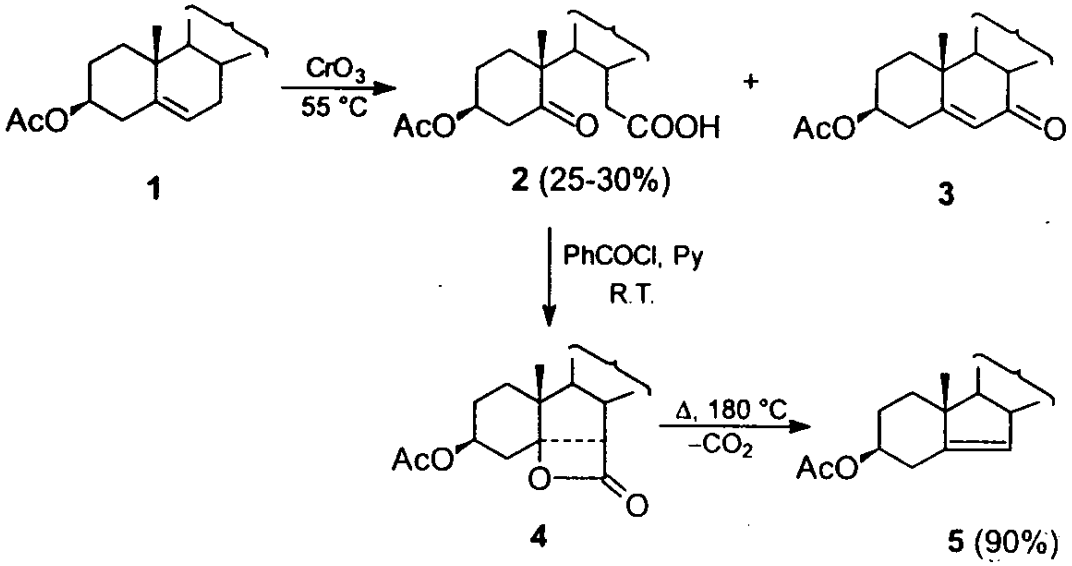
Key words: Δ^5-steroids, oxidation, 3β-acetoxy-5-oxo-5,6-secocholestan-6-oic acid, 3β-acetoxy-5,17-dioxo-5,6-secoandrostan-6-oic acid, B-norsteroids.

In the search for steroid hormone analogs with improved biological properties, many modifications of the natural steroid sceleton have been attempted, including the contraction and expansion of the steroid rings.[1,2] Of these reactions the contraction of the ring B has attracted much attention, since some of the B-norsteroid derivatives have shown themselves to be useful substrates for the synthesis of 5-azasteroids.[3]

The most important routes to B-norsteroids involve the fission of the 5,6-double bonds to keto acids or keto aldehydes wich are then closed to the five-membered ring derivatives by condensation reactions. Two of the best synthetic methods known, proceeding *via* keto acids, are: (i) the chromium trioxide oxidation of the Δ^5-steroids; and (ii) the Baeyer-Villiger oxidation of the 5-hydroxy-6-oxo-steroids.

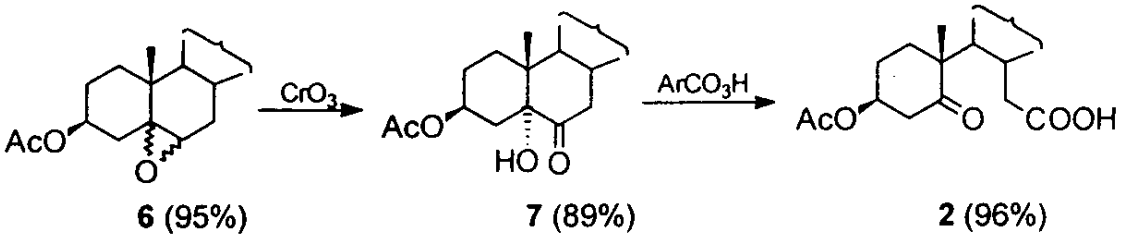
(i) Šorm found[4] that when cholesteryl acetate (**1**) is oxidized by chromic acid in acetic acid–water solution at 55 °C two products are obtained: the crystalline seco-oxoacid **2** (in 25–30% yield) and 7-oxocholesteryl acetate (**3**) (in 33% yield) (Scheme 1). The seco-oxoacid **2** reacts with benzoyl chloride in pyridine to give the

β-lactone **4** which, upon pyrolysis at 180 °C, is transformed to B-norcholesteryl acetate (**5**) (in 90% yield) (Scheme 1). Similar experiments were also performed in the pregnane and androsterone series.[5]



Scheme 1.

(ii) Knof prepared B-norsteroids[6-8] by a multistep process (Scheme 2). Δ^5-Androstane or pregnane derivatives were epoxidized with perbenzoic or *m*-chloroperbenzoic acid to a mixture of the corresponding 5α,6α- and 5β,6β-epoxides **6** (in 95% yield). The mixture was then oxidized with aqueous chromium trioxide in methyl ethyl ketone to the 5α-hydroxy-6-ketone **7** (in 89% yield). Baeyer-Villiger oxidation of the hydroxy ketone **7** gave an oxoacid of the type **2** (in 96% yield) as a complex with benzoic or chlorobenzoic acid. This complex was transformed to the corresponding Δ^5-B-norsteroid as shown in Scheme 1.

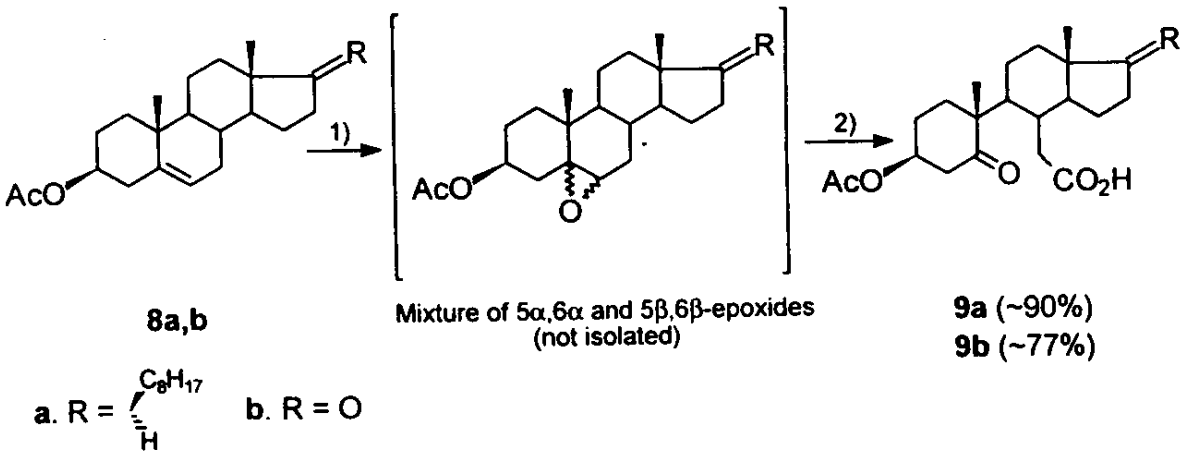


Scheme 2.

Therefore, the Šorm method gives seco-oxoacids in low yields, while the yields using the Knof procedure, although high, refer to the raw products.

In this paper we described a simple one-pot procedure[9] for the synthesis of the 5,6-seco-oxoacids **9a,b** (Scheme 3), *i.e.*, the key intermediates to B-norsteroids. It was found that when cholesteryl acetate (**8a**) or 17-oxoandrost-5-en-3β-yl acetate (**8b**) are epoxidized with peracetic acid, generated *in situ* by the H_2WO_4/H_2O_2 system, in AcOH-benzene solution at 55 °C, followed by CrO_3/H_2SO_4 oxidation,

performed at the same temperature, the 5,6-seco-acids **9a,b** are obtained in a pure state in ≈ 90 and ≈77% yields, respectively (Scheme 3). Further transformations of these acids to the corresponding B-norsteroids (in the cholestene and 17-oxoandrostene series) are carried out in the usual way.



Reaction conditions: 1) H_2O_2/H_2WO_4/AcOH/benzene, 55 °C, 1.5 h
2) $CrO_3/H_2SO_4/H_2O$, 55 °C, 1 h

Scheme 3.

It can be assumed the first step in this procedure involves epoxidation of the Δ^5-double bond with peracetic acid,* generated in the reaction between tungstic acid and hydrogen peroxide in several steps as follows:

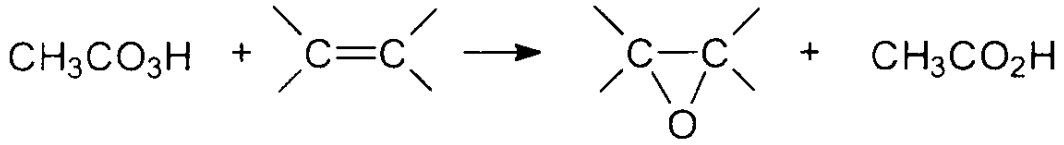
(1) oxidation of tungstic acid to pertungstic acid (H_2WO_5)[10]

$$H_2O_2 + H_2WO_4 \rightarrow H_2WO_5 + H_2O$$

(2) formation of peracetic acid

$$H_2WO_5 + CH_3CO_2H \rightarrow CH_3CO_3H + H_2WO_4$$

(3) epoxidation of the olefinic double bond by peracetic acid



The oxidative decompositon of the epoxides to the corresponding 5,6-seco-acids **9a** and **9b** is achieved by the CrO_3/H_2SO_4 reagent added to the reaction mixture.

EXPERIMENTAL

General

Removal of solvents was carried out under reduced pressure. Dry-flash chromatography (DFC): silica gel, 12-26 ICN Biomedicals. TLC: control of the reaciton and the separation of products on silica gel G (Stahl) with benzene/AcOEt (90:10 or 70:30), detection with 50% aq. H_2SO_4 soln. M. ps:

* This procedure is also efficient for preparation of epoxides,[9] since the epoxide ring is stable under the experimental conditions used for its formation.

uncorrected. IR spectra: Perkin-Elmer 457 grating spectrophotometer, ν in cm $^{-1}$. NMR-spectra: Varian Gemini 200 (^{1}H at 200 MHz, ^{13}C at 50 MHz), $CDCl_3$ soln. at r.t., TMS as internal standard, δ in ppm, *J* in Hz.

*3β-Acetoxy-5-oxo-5,6-secocholestan-6-oic acid (***9a***)*

A mixture of cholesteryl acetate (2.14 g), tungstic acid (0.125 g), glacial acetic acid (2.5 ml), hydrogen peroxide (30%, 2.5 ml) and benzene (7.5 ml) was stirred in a round bottom flask placed in a water-bath at 55 °C. The reaciton was monitored by TLC (benzene: EtOAc =9:1). When the starting material had been completely transformed to a mixture of the corresponding epoxides, a solution of CrO_3 (1.5 g), conc. H_2SO_4 (1.5 ml) and dest. H_2O (5 ml) was gradually added. The reaction mixture was stirred at 55 °C for 2.5 h. After addition of MeOH (1–3 ml), the mixture was extracted with benzene. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to dryness. The resulting mixture was separated by dry-flash column chromatography. Elution with benzene:EtOAc (90:10; 80:20; 70:30) afforded a complex mixture of undefined products (0.190 g); further elution with benzene:EtOAc (60:40) gave the pure, oily 5,6-secoacid **9a** (2.15 g: 90.38%), which was crystallized from methanol to afford 3β-acetoxy-5-oxo-5,6-secocholestan-6-oic acid (1.84 g, 77.14%). M.p. 125–127 °C. $[\alpha]_D^{25}$ = + 77.2 (*c* = 1, $CHCl_3$), (lit.[4,11] m.p. 130 °C, $[\alpha]_D$ + 77.9). IR (KBr): 3453, ≈ 3300-2500, 1737, 1714, 1251. ^{1}H-NMR: 0.69 (3H, *s*, Me-18), 0.86 (6H, 2*d*, *J*=6.4 Hz, Me-26, Me-27), 0.91 (3H, *d*, Me-21, *J*=6.4 Hz), 1.05 (3H, *s*, Me-19), 2.01 (3H, *s*, AcO), 3.19 (1H, *dd*, *J* = 4.6, 14.2 Hz, Hβ-C(4)), 5.39 (1H, *s*, H-C(3)). ^{13}C-NMR: 216.4 (*s*, C(5)), 178.9 (*s*, C(6)), 170.3 (*s*, MeCO)), 73.4 (*d*, C(3)), 55.8 (*d*, C(17)), 54.4 (*d*, C(14)), 52.3 (*s*, C(13)), 43.0 (*t*, C(4)), 42.5 (*d*, C(8)), 41.5 (*s*, C(10)), 39.7 (*t*, C(7)), 39.3 (*t*, C(24)), 35.9 (*t*, C(22)), 35.6 (*d*, C(9)), 35.5 (*d*, C(20)), 34.3 (*t*, C(12)), 34.1 (*t*, C(1)), 27.9 (*d*, C(25)), *t*, C(16)), 25.1 (*t*, C(11)), 24.3 (*t*, C(15)), 23.7 (*t*, C(2)), 22.9 (*t*, C(23)), 22.7 (*q*, C(26)), 22.4 (*q*, C(27)), 21.1 (*q*, *Me*CO)), 18.5 (*q*, C(21)), 17.6 (*q*, C(19)), 11.6 (*q*, C(18)). Anal. calc. for: $C_{29}H_{48}O_5$ (476.69): C 73.07, H 10.15; found C 73.20, H 10.08.

*3β-Acetoxy-5,17-dioxo-5,6-secoandrostan-6-oic acid (***9b***)*

The same reaction procedure was performed in the androstane serie using 3β-acetoxyandrost-5-en-17-one (1.65 g), tungstic acid (0.125 g), glacial acetic acid (2.5 ml), hydrogen peroxide (30%, 2.5 ml) and benzene (7.5 ml). The reaction was monitored by TLC (benzene:EtOAc = 7:3). After complete consumption of the substrate, a mixture of 1.5 g CrO_3, 1.5 ml conc. H_2SO_4 and 5 ml H_2O was gradually added and the reaction continued for an additional 3 h. The reaction mixture obtained, after work-up as above, was separated by dry-flash column chromatography. Elution with benzene: EtOAc (95:5; 90:10; 85:15; 80:20) afforded a complex mixture of undefined products (0.109 g); further elution with benzene:EtOAc (75:25) gave the oily 3β-acetoxy-5,17-dikoxo-5,6-secoandrostan-6-oic acid **9b** (1.45 g; 76.61%). IR (film): 3446, ≈3300–2500, 1733, ≈1710, 1245, 756. ^{1}H-NMR: 0.90 (3H, *s*, Me-18), 1.08 (3H, *s*, Me-19), 2.03 (3H, *s*, AcO), 3.15 (1H, *dd*, *J* = 4.4, 14.4 Hz, Hβ-C(4)), 5.38 (1H, *s*, H-C(3)). ^{13}C-NMR: 220.4 (*s*, C(5)), 215.9 (*s*, C(17)), 177.0 (*s*, C(6)), 170.3 (*s*, MeCO), 73.2 (*d*, C(3)), 52.2 (*s*, C(13)), 49.3 (*d*, C(14)), 47.6 (*s*, C(10)), 42.9 (*t*, C(4)), 41.7 (*d*, C(8)), 35.6 (*t*, C(15)), 34.9 (*d*, C(9)), 34.3 (*t*, C(7)), 32.9 (*t*, C(12)), 31.2 (*t*, C(16)), 24.9 (*t*, C(11)), 22.1 (*t*, C(1)), 21.9 (*t*, C(2)), 21.0 (*q*, *Me*CO), 17.4 (*q*, C(19)), 13.2 (*q*, C(18)). Anal. calc. for: $C_{21}H_{30}O_6$ (378.47): C 66.64, H 7.99; found: C 66.56, H 8.24.

И З В О Д

ПОБОЉШАНИ ПОСТУПАК ЗА СИНТЕЗУ B-НОРСТЕРОИДА: ДОБИВАЊЕ 3β-АЦЕТОКСИ-5-ОКСО-5,6-СЕКО-6-ХОЛЕСТАНСКЕ И 3β-АЦЕТОКСИ-5,17-ДИОКСО-5,6-СЕКО-6-АНДРОСТАНСКЕ КИСЕЛИНЕ

ЉУБОМИР С. СТЕВОВИЋ,[а] ВЛАДИМИР Д. ПАВЛОВИЋ,[а,б] САША Б. МАРТИНОВИЋ,[б] МИЛАН М. ДАБОВИЋ[б] и ИВАН О. ЈУРАНИЋ[а,б]

[а]*Хемијски факултет, Универзитет у Београду, Студентски трг 12-16, 11000 Београд* и [б]*Центар за хемију, Институт за хемију, технологију и металургију, Његошева 12, 11000 Београд*

У овом раду је описан једноставан поступак за синтезу 5,6-секо-стероидних киселина **9a,b**. Он се састоји од епоксидације Δ^5-стероида, то јест, холестерил ацетата (**8a**) и 17-оксо-андрост-5-ен-3β-ил ацетата (**8b**) персирћетном киселином (која се ствара *in situ* помоћу H_2WO_4/H_2O_2 система), после чега следи оксидација овако добивених епоксида помоћу CrO_3/H_2SO_4 реагенса. 5,6-Секо-стероидне киселине **9a,b** (које су добивене у приносу од око 90%, односно 77%), трансформисане су у одговарајуће B-норстероиде познатом методом (Baeyer-Villiger-овом оксидацијом кето секо-киселина и термолизом тако добивених β-лактона).

(Примљено 10. августа 1998)

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