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First Synthesis of Steroidal 1,2,4-Trioxolanes

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Abstract—Griesbaum ozonolysis of mixtures of methyl 3-(methoxyimino)-5β-cholan-24-oate with ketones (cyclohexanone, methyl trifluoromethyl ketone, and phenyl trifluoromethyl ketone) afforded for the first time steroidal 1,2,4-trioxolanes which were isolated as mixtures of stereoisomers.

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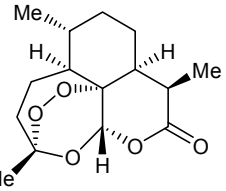
Interest in the chemistry and pharmacological properties of natural metabolites possessing a peroxide fragment [1–3] has increased considerably when unique antimalarial activity of artemisinin has been disclosed [4]. Since that time studies related to the design of antimalarial drugs on the basis of peroxide compounds develop along three main lines: (1) synthetic transformations of artemisinin [5, 6], (2) elaboration of new methods [7] and synthesis of various peroxy compounds [8–10], and (3) study of physicochemical properties and mechanism of antimalarial action of 1,2,4-trioxolanes and 1,2,4,5-tetraoxanes [11–17]. Important advances have been achieved in all these directions. It should be especially emphasized that some 1,2,4-trioxolane and 1,2,4,5-tetraoxane derivatives turned out to be superior to artemisinin in antimalarial activity [18]. One of these, second generation ozonide OZ439, is now successfully passing the final step of clinical trials [12, 19].

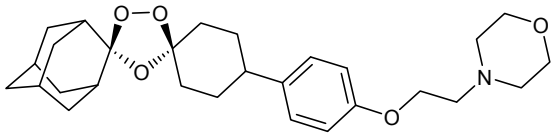
Compounds with a 1,2,4-trioxolane fragment are commonly synthesized by ozonolysis of unsaturated compounds [9, 10, 20], as well as by ozonolysis of *O*-methyl ketone oximes in the presence of carbonyl compounds, which was proposed by Griesbaum [21]. Following the latter approach, several hundred adamantan-2-one-based 1,2,4-trioxolanes have been prepared [22, 23], including OZ277 and OZ439 proposed for clinical trials. No examples of synthesis of steroidal 1,2,4-trioxolanes according to Griesbaum have been reported, though 1,2,4,5-tetraoxanes derived from bile acids are known to exhibit high antimalarial and antitumor activity [24, 25]. Therefore, synthesis of 1,2,4-trioxolanes based on steroids seems to be topical.

As starting compound we used methyl 3-oxo-5β-cholan-24-oate (**II**) which was prepared from commercially available lithocholic acid (**I**) according to standard procedures. The reaction of **II** with a slight excess of *O*-methylhydroxylamine hydrochloride in boiling methanol–pyridine (1 : 1) gave 93% of *O*-methyl ketone oxime **III** which was isolated as a mixture of two isomers at a ratio of 1 : 1 (according to the NMR data; Scheme 1).

Methyl 3-(methoxyimino)-5β-cholan-24-oate (**III**) was subjected to ozonolysis in the presence of 2 equiv of ketones (cyclohexanone, methyl trifluoromethyl ketone, phenyl trifluoromethyl ketone) at 0°C in a mixture of methylene chloride with cyclohexane (TLC monitoring). Compounds **IV**–**VI** were isolated by column chromatography in 53–82% yield. According



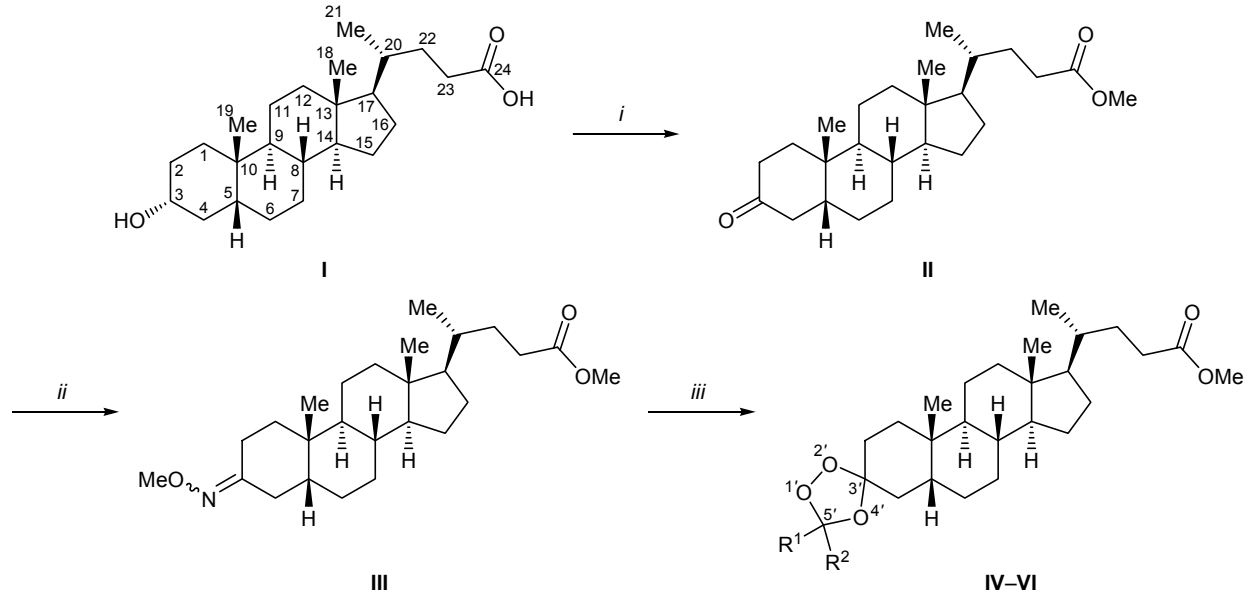
Artemisinin



OZ439

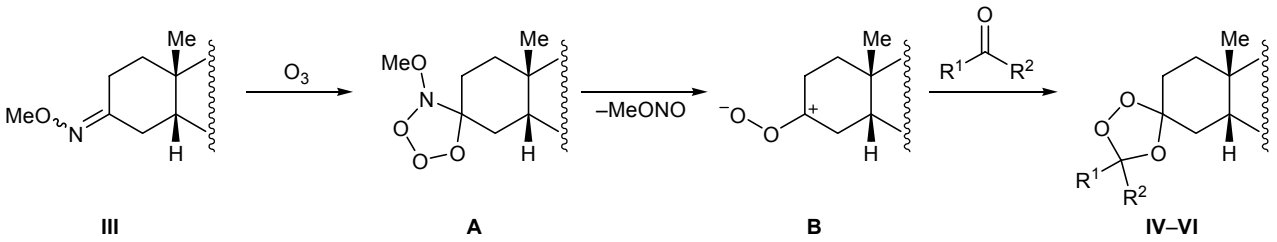
[†] Deceased.

Scheme 1.



IV, $R^1R^2 = (CH_2)_5$; **V**; $R^1 = CF_3$, $R^2 = Me$; **VI**, $R^1 = CF_3$, $R^2 = Ph$; Reagents and conditions: *i*: (1) H_2SO_4–MeOH, 64°C, 3 h; (2) Jones reagent, acetone, 0°C, 1 h; *ii*: $MeONH_2 \cdot HCl$, MeOH–C_5H_5N, 115°C, 4 h; *iii*: $R^1R^2C{=}O$, O_3, 0°C, CH_2Cl_2–*cyclo*-C_6H_{12}.

Scheme 2.



to the NMR data, peroxide **IV** was a pure compound while peroxides **V** and **VI** were mixtures of four possible stereoisomers at ratios of 0.3 : 0.2 : 0.3 : 0.2 (**V**) and 0.1 : 0.2 : 0.4 : 0.3 (**VI**). It was difficult to isolate pure diastereoisomers of **V** and **VI** because of their similar chromatographic mobilities. Peroxides **IV**–**VI** remained unchanged during the isolation and purification procedures, in contrast to trioxolanes derived from 29-norlupan-20-one *O*-methyloxime, which were converted into methyl diacetoxy-29,30-bisnorlupan-20-oate [26].

In keeping with the mechanism proposed by Griesbaum [21], the formation of steroidal 1,2,4-trioxolanes includes oxidation of the $C^3{=}NOCH_3$ double bond in **III** with ozone to unstable five-membered molozonide **A** which decomposes to give carbonyl oxide **B** and cyclization (intramolecular [3+2]-cycloaddition of intermediate carbonyl oxide to the carbonyl group of ketone) to form five-membered 1,2,4-trioxolane ring (Scheme 2).

Thus, by joint ozonolysis of methyl 3-(methoxyimino)-5β-cholan-24-oate with ketones we have synthesized for the first time steroidal 1,2,4-trioxolanes which attract interest as potential antimalarial and antitumor agents.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75.5 MHz, respectively, using tetramethylsilane as internal reference. The melting points were determined on a Boetius micro hot stage. The optical rotations were measured on a Perkin Elmer 241 MC polarimeter using a 10-cm tube. Thin-layer chromatography was performed on Sorbfil plates (*Sorbpolimer* closed corporation, Russia) using chloroform–ethyl acetate (40 : 1) as eluent; spots were detected by treatment with 10% sulfuric acid, followed by heating to 100–120°C for 2–3 min. Ozone was generated with the aid of an Ozon-4K ozonizer. Lithocholic acid (**I**), *O*-methylhydroxylamine hydro-

chloride, cyclohexanone, methyl trifluoromethyl ketone, and phenyl trifluoromethyl ketone were commercial products (from Aldrich). Neutral alumina (*Reakhim*) was used for column chromatography.

Methyl 3-oxo-5β-cholan-24-oate (II). A solution of 0.76 g (2 mmol) of lithocholic acid (**I**) in 60 mL of anhydrous methanol containing 0.3 mL of 98% H_2SO_4 was heated for 3 h under reflux. The mixture was poured into 300 mL of cold water, and the precipitate was filtered off, washed with water, and dried. Yield of lithocholic acid methyl ester 0.74 g (95%). The resulting ester, 0.39 g (1 mmol), was dispersed in 50 mL of acetone, the suspension was cooled to 0°C, and 2.6 mL of freshly prepared Jones reagent was added. The mixture was stirred for 1 h and poured into 150 mL of cold water, and the precipitate was filtered off, washed with water, and dried. Yield 0.36 g (93%), mp 185–187°C, $[\alpha]_D^{20}$ = +38° (*c* = 0.10, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.65 s (3H, $C^{19}H_3$), 0.93 d (3H, $C^{18}H_3$, *J* = 6.0 Hz), 1.15 s (3H, $C^{21}H_3$), 1.17–2.40 m (28H, CH_2, CH), 3.65 s (3H, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.1 (C^{19}), 18.3 (C^{18}), 21.2 (C^{21}), 22.6 (C^{11}), 24.2 (C^2), 25.8 (C^{15}), 26.6 (C^{16}), 28.1 (C^6), 30.9 (C^{10}), 31.1 (C^{23}), 34.9 (C^{22}), 35.3 (C^7), 35.5 (C^4), 37.0 (C^{20}), 37.2 (C^8), 40.0 (C^1), 40.7 (C^{12}), 42.4 (C^{13}), 42.8 (C^5), 44.3 (C^9), 51.5 (C^{17}), 55.9 (C^{14}), 56.4 (OCH_3), 174.7 (C^{24}), 213.3 (C^3). Found, %: C 77.26; H 10.35. $C_{25}H_{40}O_3$. Calculated, %: C 77.27; H 10.38.

Methyl 3-(methoxyimino)-5β-cholan-24-oate (III). *O*-Methylhydroxylamine hydrochloride, 0.1 g (2 mmol), was added to a solution of 0.38 g (1 mmol) of compound **II** in 30 mL of a 1:1 mixture of anhydrous methanol and pyridine, and the mixture was heated for 4 h under reflux. The mixture was poured into 150 mL of 5% aqueous HCl, and the precipitate was filtered off, washed with water, and dried. Yield 0.39 g (93%), amorphous substance, $[\alpha]_D^{20}$ = +14° (*c* = 0.10, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.70 s (3H, $C^{19}H_3$), 0.80 s (3H, $C^{18}H_3$), 0.90 d (3H, $C^{21}H_3$, *J* = 19.5 Hz), 1.00–2.40 m (28H, CH_2, CH), 3.65 s (3H, OCH_3), 3.80 s and 3.81 s (1.5H each, $=NOCH_3$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.2 and 11.3 (0.5C each, C^{19}), 18.2 (C^{18}), 20.4 and 20.5 (0.5C each, C^{21}), 21.0 and 21.1 (0.5C each, C^{11}), 21.5 and 21.6 (0.5C each, C^2), 23.0 and 23.1 (0.5C each, C^{15}), 24.1 and 24.12 (0.5C each, C^{16}), 25.6 and 25.7 (0.5C each, C^6), 26.3 and 26.4 (0.5C each, C^{10}), 26.5 and 26.6 (0.5C each, C^{23}), 26.7 and 26.8 (0.5C each, C^{22}), 28.6 and 28.7 (0.5C each, C^7), 30.9 and 31.00 (0.5C each, C^4), 32.2 and 32.3 (0.5C each, C^{20}), 35.2 and 35.3 (0.5C each, C^8), 36.1 and 36.2 (0.5C each, C^1), 40.0 and 40.1 (0.5C each, C^{12}), 42.4 and 42.5 (0.5C each, C^{13}), 42.7 and 42.8 (0.5C each, C^5), 45.6 and 45.7 (0.5C each, C^{14}), 47.8 and 47.9 (0.5C each, C^9), 51.0 and 51.1 (0.5C each, C^{17}), 56.4 and 56.5 (0.5C each, OCH_3), 60.8 and 60.9 (0.5C each, $=NOCH_3$), 161.0 and 161.2 (0.5C each, C^3), 174.7 (C^{24}). Found, %: C 74.76; H 10.39; N 3.36. $C_{26}H_{43}NO_3$. Calculated, %: C 74.78; H 10.38; N 3.35.

Methyl 5β-dispiro[cholane-3,3′-[1,2,4]trioxolane-5′,1″-cyclohexan]-24-oate (IV). A solution of 0.42 g (1 mmol) of compound **III** and 0.2 mL (2 mmol) of cyclohexanone in 30 mL of methylene chloride–cyclohexane (1:1) was cooled to 0°C, and ozone was passed through the solution until the initial compound disappeared (TLC). The mixture was evaporated under reduced pressure, and the residue was subjected to column chromatography on alumina using hexane as eluent. Yield 0.27 g (53%), amorphous substance, $[\alpha]_D^{20}$ = +18° (*c* = 0.10, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.73 s (3H, $C^{19}H_3$), 0.83 s (3H, $C^{18}H_3$), 0.95 d (3H, $C^{21}H_3$, *J* = 7.8 Hz), 1.05–2.45 m (38H, CH_2, CH), 3.66 s (3H, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.0 (C^{19}), 18.2 (C^{18}), 21.1 (CH_2), 22.6 (CH_2), 22.9 (CH_2), 23.8 (C^{21}), 24.1 (C^{11}), 24.9 (C^2), 25.9 (C^{15}), 26.5 (C^{16}), 28.1 (C^6), 29.5 (C^{10}), 29.6 (C^{23}), 30.0 (C^{22}), 31.0 (C^7), 34.3 (C^4), 34.5 (C^{20}), 34.7 (CH_2), 34.9 (C^8), 35.4 (C^1), 35.5 (CH_2), 39.7 (C^{12}), 40.2 (C^{13}), 40.8 (C^5), 42.7 (C^{14}), 51.4 (C^9), 56.0 (C^{17}), 56.5 (OCH_3), 108.5 (C^3), 109.9 ($C^{5'}$), 174.7 (C^{24}). Found, %: C 74.07; H 10.04. $C_{31}H_{50}O_5$. Calculated, %: C 74.06; H 10.02.

Methyl 5′-methyl-5′-trifluoromethyl-5β-spiro-[cholane-3,3′-[1,2,4]trioxolan]-24-oate (V) was synthesized in a similar way from 0.42 g (1 mmol) of compound **III** and 0.20 mL (2 mmol) of methyl trifluoromethyl ketone. Yield 0.42 g (82%), $[\alpha]_D^{20}$ = +18° (*c* = 0.30, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.60 s (3H, $C^{19}H_3$), 0.90 d (3H, $C^{18}H_3$, *J* = 6.0 Hz), 0.98 s (3H, $C^{21}H_3$), 1.00–2.35 m (31H, CH_2, CH), 3.63 s (3H, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.9 (C^{19}), 17.0 (CH_3), 18.0 (C^{18}), 28.1 (0.3C, C^{21}), 28.2 (0.2C, C^{21}), 28.3 (0.3C, C^{21}), 28.4 (0.2C, C^{21}), 30.7 (0.3C, C^{11}), 30.8 (0.2C, C^{11}), 30.9 (0.3C, C^{11}), 31.0 (0.2C, C^{11}), 32.0 (C^2), 33.1 (C^{15}), 33.7 (C^{16}), 34.1 (C^6), 34.6 (C^{10}), 35.3 (C^{23}), 35.4 (0.3C, C^{22}), 35.5 (0.2C, C^{22}), 35.5 (0.3C, C^{22}), 35.6 (0.2C, C^{22}), 35.7 (C^7), 36.8 (C^4), 37.7 (C^{20}), 37.8 (0.3C, C^8), 39.9 (0.3C, C^8), 39.9 (0.3C, C^8), 40.0 (0.3C, C^8), 40.5 (C^1), 40.6 (C^{12}), 40.7 (C^{13}), 40.8 (0.3C, C^5), 40.9 (0.2C, C^5), 41.1 (0.3C, C^5), 41.2 (0.2C, C^5), 42.6 (C^9), 43.6 (C^{17}), 51.4 (C^{14}), 56.4 (OCH_3), 102.4 (0.3C, C^3), 102.6 (0.2C, C^3),

102.7 (0.3C, C^3), 102.8 (0.2C, C^3), 109.8 (0.3C, $C^{5'}$), 109.9 (0.2C, $C^{5'}$), 110.6 (0.3C, $C^{5'}$), 110.9 (0.2C, $C^{5'}$), 113.1 (0.3C, CF_3), 113.2 (0.2C, CF_3), 120.6 (0.3C, CF_3), 122.8 (0.2C, CF_3), 174.7 (C^{24}). Found, %: C 65.12; H 8.37; F 11.07. $C_{28}H_{43}F_3O_5$. Calculated, %: C 65.10; H 8.39; F 11.05.

Methyl 5′-phenyl-5′-trifluoromethyl-5β-spiro-[cholane-3,3′-[1,2,4]trioxolan]-24-oate (VI) was synthesized in a similar way from 0.42 g (1 mmol) of compound **III** and 0.29 mL (2 mmol) of phenyl trifluoromethyl ketone. Yield 0.44 g (76%), $[\alpha]_D^{20} = +15°$ (c = 0.10, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.65 s (3H, $C^{19}H_3$), 0.73 s (3H, $C^{18}H_3$), 0.98 d (3H, $C^{21}H_3$, J = 6.8 Hz), 1.00–2.50 m (28H, CH_2, CH), 3.58 s (3H, OCH_3), 7.20 s (1H, Ph), 7.41–7.50 m (2H, Ph), 7.63–7.70 m (2H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.0 (C^{19}), 21.0 (C^{18}), 22.8 (C^{21}), 22.9 (C^{11}), 24.1 (C^2), 25.7 (C^{15}), 26.3 (0.1C, C^{16}), 26.4 (0.2C, C^{16}), 26.5 (0.4C, C^{16}), 26.6 (0.3C, C^{16}), 27.3 (C^6), 28.1 (C^{10}), 28.6 (0.1C, C^{23}), 28.7 (0.2C, C^{23}), 28.8 (0.4C, C^{23}), 28.9 (0.3C, C^{23}), 30.9 (C^{22}), 32.2 (C^7), 33.4 (C^4), 34.0 (0.1C, C^{20}), 34.1 (0.2C, C^{20}), 34.2 (0.4C, C^{20}), 34.3 (0.3C, C^{20}), 34.5 (C^8), 35.3 (C^1), 39.8 (C^{12}), 40.0 (C^{13}), 40.1 (C^5), 41.0 (C^9), 42.7 (OCH_3), 51.3 (C^{17}), 55.6 (0.1C, C^{14}), 55.7 (0.2C, C^{14}), 55.8 (0.4C, C^{14}), 55.9 (0.3C, C^{14}), 103.5 (0.1C, C^3), 104.0 (0.2C, C^3), 104.2 (0.4C, C^3), 104.5 (0.3C, C^3), 107.6 (0.1C, $C^{5'}$), 108.3 (0.2C, $C^{5'}$), 109.4 (0.4C, $C^{5'}$), 109.5 (0.3C, $C^{5'}$), 119.76 and 123.6 (CF_3), 126.5 (C_{arom}), 126.6 (C_{arom}), 128.2 (C_{arom}), 130.2 (C_{arom}), 132.1 (C_{arom}), 132.2 (C_{arom}), 174.6 (C^{24}). Found, %: C 68.51; H 7.80; F 9.83. $C_{33}H_{45}F_3O_5$. Calculated, %: C 68.49; H 7.84; F 9.85.

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