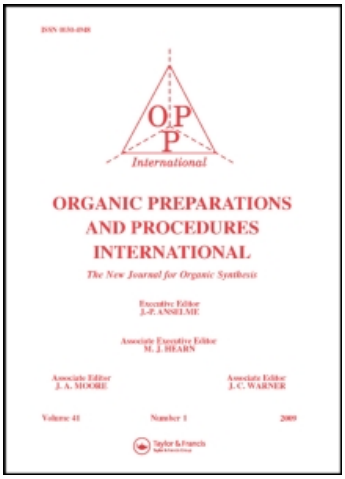

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STUDIES DIRECTED TOWARD SYNTHESIS OF QUASSINOIDS - IV. D-RING CLEAVAGE OF CHOLIC ACID DERIVATIVES - 2

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STUDIES DIRECTED TOWARD SYNTHESIS OF QUASSINOIDS - IV.[1] D-RING CLEAVAGE OF CHOLIC ACID DERIVATIVES - 2.

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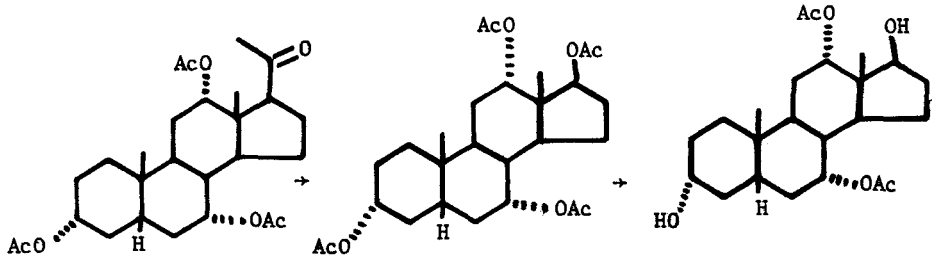
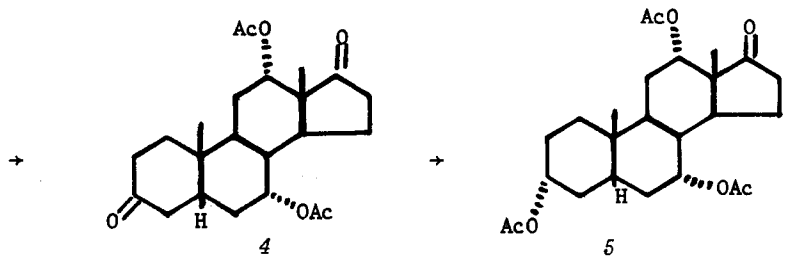
We investigated three routes for converting 20-ketone *1* to 17-ketone *5*. Direct oxidation with O_2 of the enolate anion of *1* generated by potassium t-butoxide[2] gave after acetylation, minor amounts of 3α,7α,12α,17α-tetracetoxy-20-oxo-5β-pregnane along with isomerization of the 17-configuration to give 3α,7α,12α-triacetoxy-20-oxo-5β,17α-pregnane. Using greater than ten-fold excess of potassium butoxide in t-butanol and HMPA[3] or lithium N-isopropycyclohexylamide in THF and HMPA to generate the enolate anion led to no appreciable improvement; application of UV[4] irradiation or converting *1* to tris(tetrahydropyranyl) ether was also without effect.

Baeyer-Villiger oxidation of *1* with trifluoroperacetic acid yielded *2* which was selectively hydrolyzed with methanolic HCl to give *3*. Jones

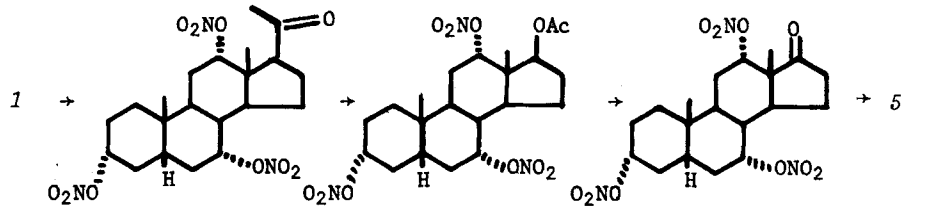


1 *2* *3*



4 5

oxidation of diol *3* produced diketone *4*. Selective reduction of *4* with sodium borohydride in pyridine-methanol[5] followed by acetylation yielded *5*. Alternatively, *1* is first converted to *6* by saponification with 5%



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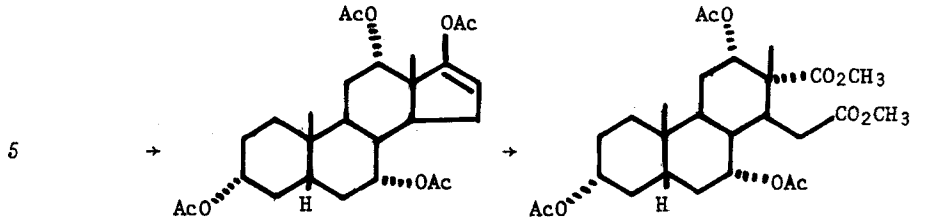
methanolic KOH followed by treatment with fuming nitric acid in acetic anhydride.[6] Baeyer-Villiger oxidation of *6* to *7* proceeded smoothly. Saponification and subsequent Jones oxidation of *7* yielded *8* which was converted to *5* by reduction with Zn dust in glacial acetic acid followed by acetylation in pyridine-acetic anhydride.

Ketone *5* was transformed to enol acetate *9* with isopropenyl acetate.[7] Ozone oxidation yielded an acid mixture which upon treatment with diazomethane yielded diester *10* previously obtained by another route.[1]



9 10

EXPERIMENTAL

All melting points were determined with a Fisher-Johns apparatus and are corrected. Infrared data, reported in cm^{-1}, were obtained in $CHCl_3$; pmr data, reported in ppm (δ) from internal TMS were determined in $CDCl_3$ on a Varian A-60 or T-60 pmr spectrometer; mass spectra were obtained at an ionization voltage of 70 eV with a Nuclide 12-90-G single focusing instrument having a resolution capability of 10,000.

Column chromatography was performed using silica gel (MCB Grade 62) and thin-layer chromatography (TLC) was performed on silica gel HF_{254} (E. Merck). Hexane + ethyl acetate (4:1 or 1:1) was generally used as a solvent phase for TLC and visualization was effected by spraying with 2% ceric sulfate in *2N* sulfuric acid followed by brief heating; all compounds discussed below exhibited one TLC spot. Microanalysis was performed by Galbraith Laboratories, Knoxville, TN.

Reaction of *1* with t-BuOK and O_2. A mixture of potassium t-butoxide prepared from 1.0 g of potassium and 10 ml of t-butanol, and 1.0 g of *1* in 5 ml of THF was vigorously stirred under an oxygen atmosphere for 8 hr (approx. 60 ml was absorbed). After being heated at reflux for 30 min, the mixture was poured into 200 g of ice containing 10 ml of concentrated HCl which was subsequently extracted with ether. The ether phase was washed with H_2O and evaporated, and the residue was reacetylated with acetic anhydride in pyridine. Chromatography yielded starting ketone *1* (0.2 g) from fraction #1. Fraction #2 (0.4 g) was adduced to be the 17α-isomer of ketone *1* from the following spectral data: $\bar{\nu}_{max}$ 1730 & 1250 (ester) and 1720 (ketone) K; pmr ($CDCl_3$) 4.95 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 4.47 (peak, 1H, 12β-H), 2.57 (t, 1H, 17β-H), 2.03 (s, 12H, OAc's +C-21), 1.00 (s, 3H, C-19), and 0.97 (s, 3H, C-18) δ; pmr (C_6F_6) 4.9 (peak, 1H, 7β-H), 4.5 (hump, 1H, 3β-H), 4.4 (peak, 1H, 12β-H), 2.05 & 1.93 (s, 6H ea, OAc's + C-21), and 1.17 (s, 6H, C-18 & C-19) δ; *m/e* 433 (M-43). The compound obtained from fraction #3 (0.15 g) was assigned as 3α,7α,12α,17α-tetraacetoxy-5β-pregnan-20-one: $\bar{\nu}_{max}$ 1760 (ketone) and 1730 & 1250 (ester); pmr ($CDCl_3$) 5.28 (peak, 1H, 12β-H), 4.98 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 2.20 (s, 3H, C-21), 2.12 (s, 3H, OAc), 2.07 (s, 6H, OAc's), 2.03 (s, 3H, OAc), 0.94 (s, 3H, C-19), and 0.67 (s, 3H, C-18) δ; pmr (C_6F_6) 5.27 (peak, 1H, 12β-H), 5.06 (peak, 1H, 7β-H), 4.5 (hump, 1H, 3β-H), 2.27 (s, 3H, C-21), 2.15 (s, 3H, OAc), 2.13 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.93 (s, 3H, OAc), 1.24 (s, 3H, C-19), and 0.81 (s, 3H, C-18) δ; *m/e* 491 (M-43).

3α,7α,12α,17α-Tetracetoxy-5β-androstane (*2*). A mixture of ketone *1* (0.8 g), trifluoroperacetic acid [0.67 ml $(CF_3CO)_2O$, 0.11 ml 90% H_2O_2, 1 ml

CH_2Cl_2],[8] K_2HPO_4 (1.75 g), and CH_2Cl_2 (2 ml) was heated at reflux for 1 hr. The reaction mixture was poured in 100 g of ice, the precipitate filtered, and the collected solid was chromatographed through 25 g of silica gel. Gradient elution with hexane-EtOAc yielded 0.53 g of *2*, mp 160-162° (needles from hexane-EtOAc); ν_{max} 1730 and 1250 (ester) K; pmr 4.90 (m, 3H, 7β,12β,17α-H's), 4.65 (hump, 1H, 3β-H), 2.13 (s, 3H, 12α-OAc), 2.07 (s, 3H, 7α-OAc), 2.03 (s, 3H, 3α-OAc), 2.00 (s, 3H, 17α-OAc), 0.93 (s, 3H, C-19), 0.87 (s, 3H, C-18)δ; *m/e* (%) 450 (100, M-42), 390 (19), 372 (15), 330 (26), 312 (47), 297 (44), 276 (19), 269 (32), 252 (70), 237 (41), 226 (37), 211 (19), 338 (m*), 261.5 (m*), and 203.5 (m*).

Anal. Calcd $C_{27}H_{40}O_8$ (492): C, 65.83; H, 8.18. Found: C, 65.99; H, 7.94.

3,17-Dioxo-7α,12α-diacetoxy-5β-androstane (*4*). Acetate *2* (2.5 g) was dissolved in a minimum quantity of $CHCl_3$ and diluted with CH_3OH (25 ml) containing acetyl chloride (2.5 ml). After standing at room temperature for 8 hrs, this mixture was poured into 100 g of ice, neutralized with $NaHCO_3$, and extracted with ether. The residue obtained upon removal of the ether was column chromatographed through 60 g of silica gel to yield 1.54 g of diol *3*: pmr 4.89 (peak, 2H, 7β,12β-H's), 3.6 (m, 2H, 3β,17α-H's), 3.0 (sharp peak, 2H, exch with D_2O), 2.17 (s, 3H, 12α-OAc), 2.09 (s, 3H, 7α-OAc), 0.94 (s, 3H, C-19), and 0.82 (s, 3H, C-18)δ. If the reaction time was much briefer than 8 hr, then some 7α,12α,17β-triacetoxy-3α-hydroxy-5β-androstane having a higher R_f could be isolated: pmr 4.90 (m, 3H, 7β,12β, 17α-H's), 3.43 (hump, 1H, 3β-H), 2.8 (peak, 1H, exch with D_2O), 2.13 (s, 3H, 12α-OAc), 2.08 (s, 3H, 7α-OAc), 2.01 (s, 3H, 17α-OAc), 0.93 (s, 3H, C-19), and 0.87 (s, 3H, C-18)δ. Diol *3* (1.54 g) was dissolved in acetone (120 ml), chilled on an ice bath and oxidized with Jones' reagent (2 ml). Excess CrO_3 was destroyed with isopropanol. After removal of the solvent, the green residue was treated with benzene which was percolated through silica gel to yield dione *4* (1.20 g): mp 170-172° (granulated crys from EtOAc-hex); $\bar{\nu}_{max}$ 1730 (broad with shoulder) and 1250 (ester) K; 5.21 (peak, 2H, 7β,12β-H's), 2.08 (s, 3H, 12α-OAc), 2.02 (s, 3H, 7α-OAc), 1.07 (s, 3H, C-19), and 0.94 (s, 3H, C-18)δ; *m/e* (%) 404 (5, M^+), 389 (11, M-CH_3), 361 (6, M-CH_3CO), 344 (5, M-HOAc), 329 (20, M-HOAc-CH_3), 284 (35, M-2HOAc), 260 (19, 329-HOAc), and 278 (m*).

Anal. Calcd for $C_{23}H_{32}O_6$ (404): C, 68.29; H, 7.97. Found: C, 67.99; H, 8.03.

3α,7α,12α-Triacetoxy-5β-androstan-17-one (*5*). Dione *4* (0.45 g) was dissolved in pyridine (1 ml) and diluted with CH_3OH (10 ml). To this solution was added $NaBH_4$ solution (4 ml) made from combining 0.22 g $NaBH_4$, 25 ml CH_3OH and 5 ml H_2O. After a total of 15 minutes this reaction mixture was poured into salt H_2O which was subsequently extracted with ether. The ether was removed and the dried residue was acetylated with Ac_2O (1 ml) and pyridine (2 ml). TLC with EtOAc-hexane (1:1) yielded 0.44 g of the desired product (*5*): mp 168-169° (granulated crystals from CH_3OH); $\bar{\nu}_{max}$ 1730 and 1250 (ester) K; 5.10 (peak, 2H, 7β,12β-H's), 4.46 (hump, 1H, 3β-H), 2.09 (s, 3H, 12α-OAc), 2.02 (s, 6H, 3 ,7α-OAc's), 0.95 (s, 3H, C-19), and 0.89 (s, 3H, C-18) δ; *m/e* (%) 448 (4, M^+), 433 (10, M-CH_3), 388 (10, M-HOAc), 373 (18, M-CH_3-HOAc), 328 (18, M-2HOAc), 313 (10, 328-CH_3), 286 (10), 268 (50, M-3HOAc), 253 (22, 268-CH_3), 240 (19), 225 (14), and 321.5 (m*); $[\theta]_{295}$ = + 10,100.

Anal. Calcd for $C_{25}H_{36}O_7$ (448): C, 66.94; H, 8.09. Found: C, 67.14; H, 8.16.

3α,7α,12α-Trinitroxy-5β-pregnan-20-one (*6*). Ketone *1* (6.0 g) was heated at reflux in 5% KOH-CH_3OH (200 ml) for 3 hrs. The cooled solution was neutralized with *3N* HCl and most of the CH_3OH was removed *in vacuo*. The aqueous residue was extracted with EtOAc which was separated and evaporated to dryness to yield a residue that was recrystallized from benzene-hexane to afford crystalline 3α,7α,12α-trihydroxy-5β-pregnan-20-one (3.5 g), mp 162-163° (lit[9] mp 120-127°); $\bar{\nu}_{max}$ 3500 (OH stretch) & 1720 (C=O stretch); pmr 3.93 (peak, 1H, 12β-H), 3.87 (peak, 1H, 7β-H), 3.22 (hump, 1H, 3β-H), 2.15 (s, 3H, C-21), 0.90 (s, 3H, C-19), and 0.65 (s, 3H, C-18); *m/e* (%) 350 (3, M^+), 332 (28, M-H_2O), 314 (10, M-2H_2O), 299 (9, M-2H O-CH_3), 296 (5, M-3H_2O), 281 (12, M-3H_2O-CH_3), 265 (28, M-C_5H_9O), 253 (16, M-3H_2O-CH_3CO), 247 (25, 265-H_2O), 229 (100, 265-2H_2O), 211 (13, 265-3H_2O), 315 (m*), 297 (m*), 148 (m*), and 167 (m*).

A mixture of fuming HNO_3 (4.5 ml) and conc HNO_3 (4.5 ml) was added dropwise to Ac_2O (30 ml) at -5° followed by addition of the above triol (3.0 g) in $CHCl_3$ (15 ml). The salt-ice bath was removed and the mixture stirred for 1 hr before being poured into ice. After the ice melted, the aqueous mixture was extracted with $CHCl_3$ which was washed with H_2O and then satd $NaHCO_3$ solution. The $CHCl_3$ was evaporated and the residue was column chromatographed to yield trinitrate ketone *6* (2.8 g); mp 181.5-3.0° (crys from benzene-Et_2O); $\bar{\nu}_{max}$ 1715 (C=O stretch) and 1625, 1280 &

860 ($-NO_3$) K; pmr 5.40 (peak, 1H, 12β-H), 5.07 (peak, 1H, 7β-H), 4.77 (hump, 1H, 3β-H), 3.00 (t, 1H, 17β-H), 2.07 (s, 3H, C-21), 1.01 (s, 3H, C-19), and 0.86 (s, 3H, C-18) δ; *m/e* 422 ($M-CH_3CO$).

3α,7α,12α-Trinitroxy-17β-acetoxy-5β-androstane (*7*). To *6* (2.4 g) in $CHCl_3$ (100 ml) containing K_2HPO_4 (2 g) was added trifluoroperacetic acid (prepared from 3 ml trifluoroacetic anhydride, 2.5 ml CH_2Cl_2 and 0.4 ml 90% H_2O_2). After heating at reflux for 12 hrs, the cooled reaction mixture was filtered and the filtrate was washed with H_2O; the filter cake was dissolved in H_2O and was washed with $CHCl_3$. The combined $CHCl_3$ layers were evaporated to yield acetate *7* (2.2 g): mp 142-144° (from CH_3OH) δ; $\bar{\nu}_{max}$ 1740 (C=O stretch) and 1635, 1280, & 870 (NO_3) K; pmr 5.10 (peak, 2H, 12β-H & 17α-H), 4.92 (peak, 1H, 7β-H), 4.75 (hump, 1H, 3β-H), 2.01 (s, 3H, 17α-OAc), 1.00 (s, 3H, C-19), and 0.91 (s, 3H, C-18) δ.

3α,7α,12α-Trinitroxy-5β-androstan-17-one (*8*). A 5% KOH-CH_3OH solution (100 ml) containing acetate *7* (2.0 g) was heated at reflux for 1 hr, cooled, neutralized with dil HCl, and concentrated. The remaining aqueous suspension was extracted with EtOAc which was subsequently washed with H_2O and concentrated. The residue thus obtained was crystallized from $CHCl_2$-Et_3O to yield 3α,7α,12α-trinitroxy-5β-androstan-17-ol (1.6 g): mp 196-197°; $\bar{\nu}_{max}$ (nujol) 3600 & 3300 (OH stretch) and 1625, 1280 & 860 (NO_3) K; pmr 5.17 (peak, 1H, 12β-H), 5.07 (peak, 1H, 7β-H), 4.75 (hump, 1H, 3β-H), 4.03 (crude t, J=8Hz, 1H, 17β-H), 0.97 (s, 3H, C-19), and 0.88 (s, 3H, C-18) . The above alcohol (1.5 g) was dissolved in acetone (100 ml) and cooled to 10°. A slight excess of Jones reagent was added followed by addition of isopropanol. The acetone was removed on a rotary evaporator and the green residue extracted with EtOAc which was washed with H_2O and concentrated to afford colorless crystals of *8* (1.2 g): mp 228-230° (dec); $\bar{\nu}_{max}$ (nujol) 1750 (C=O stretch) and 1620, 1280 & 860 (NO_3) K; *m/e* 457 (M^+).

3α,7α,12α-Triacetoxy-5β-androstan-17-one (*5*). A solution of ketone *8* (0.30 g) in acetic acid (200 ml) was concentrated by distillation (60 ml). To this cooled (50°) solution, Zn dust (1.5 g) was added in portions. After stirring for 1 hr, the zinc salt was filtered and the acetic acid solution was concentrated *in vacuo* and the residue was acetylated with Ac_2O-py to afford ketone *5* (0.35 g) of mp 167-169° (from Et-OAc-hexane) and having spectra identical to the product synthesized *via* the other route.

Oxidation of 3α,7α,12α-triacetoxy-5β-androstan-17-one (*5*) to methyl 3α, 7α,12α-triacetoxy-16,17-seco-5β-androstane-16,17-dioate (*10*). Ketone *5* (100 mg) was converted to enol acetate *9* with isopropenyl acetate: pmr 5.46 (peak, 1H, C-16), 5.10 (peak, 1H, 12β-H), 5.0 (peak, 1H, 7β-H), 4.56 (hump, 1H, 3β-H), 2.09, 2.07, 2.05, 2.03 (s, 3H ea, OAc's), and 0.98 (s, 6H, C-18 & C-19) δ. Ozone was passed through an EtOAc solution of enol acetate *9* (90 mg) cooled by a dry ice-acetone bath until a deep blue solution was obtained. After the solvent was removed, the residue was dissolved in glacial HOAc (10 ml) and 30% H_2O (3 ml) was added. The mixture was stirred for 12 hrs, the solvent removed on a rotating evaporator, and the residue was dissolved in ether. The ether layer was extracted with 5% NaOH solution which was acidified with conc HCl and extracted with EtOAc. The residue remaining after EtOAc was evaporated and esterified with diazomethane followed by treatment with Ac_2O and pyridine. TLC yielded diester *10* (20 mg) as a non-crystalline solid and having R_f and spectra identical to material previously obtained by another synthetic route.[1]

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