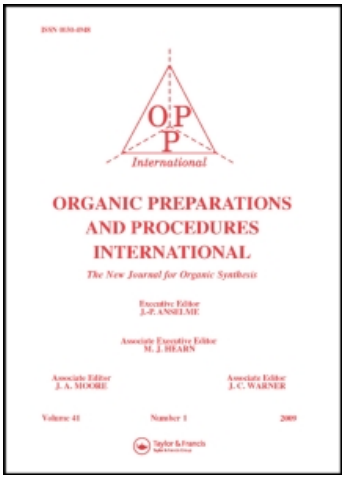

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SYNTHESIS OF A 3α,12β-DIMETHOXY-11-KETO DERIVATIVE OF CHOLIC ACID

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SYNTHESIS OF A 3α,12β-DIMETHOXY-11-KETO DERIVATIVE OF CHOLIC ACID

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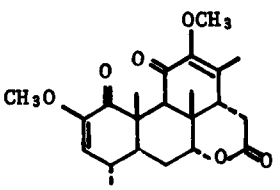
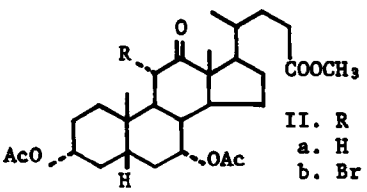
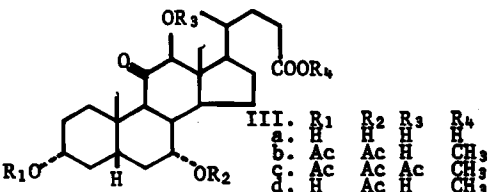
This paper describes the synthesis of a cholic acid analog (IIIf) containing the requisites for construction of the C-ring of quassin (I).[1] Methyl 3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (IIa) was brominated at the 11-position by treatment with a stoichiometric amount of bromine at 55° in 90% yield in 2 hrs. Conversion of this bromoketone (IIb) to the



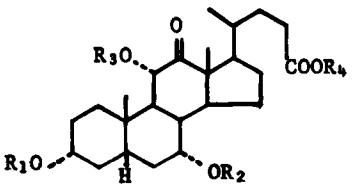
I



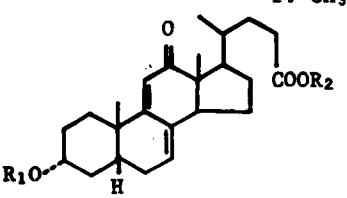
II. R
a. H
b. Br



III. R1 R2 R3 R4
a. H H H H
b. Ac Ac H CH3
c. Ac Ac Ac CH3
d. H Ac H CH3
e. CH3 Ac CH3 CH3
f. CH3 H CH3 CH3



IV. R1 R2 R3 R4
a. H H H H
b. Ac Ac Ac CH3



V. R1 R2
a. H H
b. Ac Ac

tautomerized ketol IIIa[2] was optimized by using 5% potassium hydroxide in 80% aqueous ethanol. Minor by-products accompanying the desired product

were the untautomerized ketol IVa and elimination by-product Va, stronger base (20%) treatment in methanol[2b] resulted in a complex mixture which after esterification and chromatography gave product Vb as the major component. Separation of the products from the 5% base treatment was accomplished by first methylation of the acid side chain, either with diazomethane in ether or by acetyl chloride and methanol, followed by acetylation of the mixture with acetic anhydride in pyridine and chromatography. Identification of the compounds was achieved on basis of PMR data (see Experimental). Since the initial ketol IVa is a thermodynamically less stable compound than its tautomer IIIa,[2c] the crude product from hydrolysis was refluxed in benzene to give more complete conversion to the tautomer IIIa. Selective acetylation of the products in the crude mixture was performed by the same method used for cholic acid,[3] but the reaction was less selective. Column chromatography of the product mixture afforded a moderate yield of methyl 3α,7α-diacetoxy-11-keto-12β-hydroxy-5β-cholan-24-oate (IIIb)(41% from the bromo analog). This was accompanied by triacetylated compound IIIc (18%) and the elimination product dienone Vb (11%). In addition some monoacetoxy and other diacetoxy compounds having close R_f values were observed but not completely purified.

The derivative IIIb was selectively deblocked at the 3-position with acetyl chloride in methanol[4] to give IIId in quantitative yield. Treatment of IIId with diazomethane in methylene chloride catalyzed by fluoboric acid,[5] in small scales up to 300 mg, furnished the 3α,12β-dimethoxy-7α-acetoxy steroid IIIe in yields better than 90%. However this reaction using larger amounts (gram quantities) of the diol was less efficient because of polymethylene formation which retards and soon completely stops the methylation of the alcohol groups. Upon hydrolysis followed by esterification of the side chain, IIIe was converted to the final product IIIf,

which has a sterically inert keto group at the 11-position,[2d] and can be converted to the δ-lactone analog of quassin.[6]

EXPERIMENTAL

All melting points were determined with a Fisher-Johns apparatus and are corrected. IR data reported in inverse centimeters (cm^{-1}) were obtained as a solid film on a salt plate; PMR data, reported in ppm (δ) from Me_4Si, were obtained in $CDCl_3$ on a Varian A-60 or T-60 or a Hitachi Perkin-Elmer model R-241 instrument; and mass spectra were obtained at an ionization voltage of 70eV 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 TLC was performed on silica gel HF_{254} (E. Merck), the latter were usually developed with 1:1, 2:1 or 4:1 hexane-ethyl acetate. Visualization of the TLC was effected by spraying with 2% ceric sulfate in *2N* sulfuric acid followed by brief heating. All reactions were monitored by TLC.

Methyl 3α,7α,12β-Triacetoxy-11-oxo-5β-cholan-24-oate (IIIc), *Methyl 3α,7α,11α-Triacetoxy-12-oxo-5β-cholan-24-oate* (IVb) and *Methyl 3α-Acetoxy-7,9(11)-dien-12-oxo-5β-cholan-24-oate* (Vb).- To a refluxing solution of the bromo compound IIb (5g) in 95% EtOH (160 mL), a solution of KOH (10g) in H_2O (40 mL) was slowly added. The solution was stirred for 1.5 hrs while maintaining the temp between 45-50°. The reaction flask was then placed on an ice bath and a 10% solution of HCl was added to the mixture until it was acidic. The resulting solution was diluted with ice water and extracted with ethyl acetate which was passed through a layer of Na_2SO_4 and evaporated to dryness. The crude product obtained was dissolved in EtOH (60 mL), cooled in an ice bath, and treated with an ethereal solution of diazomethane with stirring. The excess diazomethane was destroyed with 5 drops of HOAc and the solution was evaporated to dryness under vacuum. This product was treated with Ac_2O (10 mL) in pyridine (30 mL) at 50°C for 12 hrs, poured into ice water (300 mL) containing concd HCl (10 mL) which was extracted with EtOAc. The ethyl acetate layer was percolated through anhyd Na_2SO_4 and evaporated to afford crude product (4.4g) showing 3 major spots on TLC, two of which had very close R_f values. The mixture was column chromatographed through silica gel eluting with hexane-ethyl acetate

(gradient) to give Vb (0.33g, 9% from IIb) as the first fraction, mp. 153-155° (ether) (lit[3] 152-153°).

ν_{max}1720 (OAc & $COOCH_3$), 1245 (OAc & $COOCH_3$), 1660 (C=C-C=O), 1570 and 1620 (C=C); PMR δ 5.80 (s, 1p, 11-H), 5.73 (peak, 1p, 7-H), 4.72 (hump, 1p, 3β-H), 3.70 (s, 3p, $COOCH_3$), 1.99 (s, 3p, OAc), 1.16 (s, 3p, C-19), 0.87 (s, 3p, C-18); *m/e* (%) 442 (10, $[M]^+$), 382 (30, $[M-HOAc]^+$), 185 (100).

The other two components were eluted as a mixture which was deposited on 0.75 mm thick silica gel coated TLC plates and developed twice in 2:1 hexane-ethyl acetate to afford the tautomerized product IIIc (2.86g, 59% from IIb) as the less polar fraction mp. 159-161° (ethyl acetate-hexane).

ν_{max}1740 (multiplet C=O, OAc and $COOCH_3$), 1250 (OAc & $COOCH_3$); PMR δ 5.02 (peak, 1p, 7β-H), 4.98 (s, 1p, 12α-H), 4.59 (hump, 1p, 3β-H), 3.7 (s, 3p, $COOCH_3$), 2.19, 2.12 and 2.01 (s, 3p ea, 12-OAc, 7-OAc and 3-OAc), 1.17 (s, 3p, C-19), 0.70 (s, 3p, C-18); *m/e* (%) 562 (10, $[M]^+$), 502 (15, $[M-HOAc]^+$), 442 (75, $[M-2HOAc]^+$), 382 (100, $[M-3HOAc]^+$).

Anal. Calcd for $C_{31}H_{46}O_9$: C, 66.17; H, 8.24. Found: C, 66.48; H, 8.40.

The more polar component was IVb (1.04g, 21%) mp. 175-177° (ethyl acetate-hexane).

ν_{max}1740 (multiplet C=O, OAc & $COOCH_3$) 1255 (OAc & $COOCH_3$); PMR δ 5.52 (d, 1p, 11β-H), 5.01 (peak, 1p, 7β-H), 4.60 (hump, 1p, 3β-H), 3.68 (s, 3p, $COOCH_3$), 2.14 and 2.06 (s, 3p and 6p, respectively, 11-OAc, 7-OAc and 3-OAc), 1.20 (s, 3p, C-19), 1.13 (s, 3p, C-18); *m/e* (%) 562 (4, $[M]^+$), 502 (72, $[M-HOAc]^+$), 442 (51, $[M-2HOAc]^+$), 382 (93, $[M-3HOAc]^+$), 267 (100).

Anal. Calcd for $C_{31}H_{46}O_9$: C, 66.17; H, 8.24. Found: C, 66.32, H, 8.45.

Methyl 3α,7α-Diacetoxy-12β-hydroxy-11-oxo-5β-cholan-24-oate (IIIb).— The 11-bromo ester II (12g) was treated with KOH and then diazomethane as described in previous experiment. The crude ester product was refluxed for 3 hrs in benzene (65 mL) using a Dean-Stark trap (15 mL). The dried solution was diluted with pyridine (13 mL) and treated with Ac_2O (13 mL) and stirred at rt for 18 hrs. The product was poured into ice water (250 mL) containing concd HCl (6 mL) and extracted with $CHCl_3$ to give a crude product (11.8g) showing 1 major spot and several minor spots on TLC with close R_f values. Column chromatography through silica gel eluting with hexane-ethyl acetate (gradient) gave the desired product IIIb (4.4g) mp.

155-157° (ethyl acetate-hexane).

ν_{max}3460 (OH str), 1740 (C=O), 1730 (multiplet OAc & $COOCH_3$), 1245 (OAc & $COOCH_3$); PMR δ 4.98 (peak, 1p, 7β-H), 4.52 (hump, 1p, 3β-H), 3.90 (s, 1p, 12α-H), 3.68 (s, 3p, $COOCH_3$), 2.13 and 2.02 (s, 3p ea, 7-OAc and 3-OAc), 1.17 (s, 3p, C-19), 0.54 (s, 3p, C-18); *m/e* (%) 520 (3,$[M]^+$), 502 (1, $[M-H_2O]^+$), 460 (8,$[M-HOAc]^+$), 442 (6,$[M-HOAc-H_2O]^+$), 400 (11,$[M-2HOAc]^+$), 382 (10,$[M-2HOAc-H_2O]^+$), 43 (100).

Anal. Calcd for $C_{29}H_{44}O_8$: C, 66.90; H, 8.52. Found: C, 66.40; H, 8.62.

In addition to the above product a less polar fraction being the elimination product Vb (1g, 11%) and a more polar fraction which proved to be the triacetate analog IIIc (2.08g, 18%) were isolated in pure form. Other components were not identified but seemed to be other acetate analogs. Combination of these fractions added to the triacetoxy product were hydrolized and recycled to afford more of the desired product.

Methyl 3α,12β-Dihydroxy-7α-acetoxy-11-oxo-5β-cholan-24-oate (IIId).- A solution of the diacetoxy ester IIIb (3.72g) in anhyd MeOH (37 mL) was treated with acetyl chloride (2 mL). After stirring this solution for 1 hr at rt, TLC showed complete conversion of the starting material to the more polar dihydroxy product IIId. The solution was treated with pyridine (2 mL) to destroy the excess AcCl and then evaporated to an oily residue. This residue was diluted with EtOAc and washed with H_2O. The solution was dried by $MgSO_4$ and the solvent was removed by a rotary evaporator and the residue vacuum dried to give a chromatographically pure product(3.4g,100%).

ν_{max}3460 (OH str), 1730 (multiplet C=O, OAc & $COOCH_3$), 1250 (OAc & $COOCH_3$); PMR δ 4.92 (peak, 1p, 7β-H), 3.86 (s, 1p, 12α-H), 3.55 (hump, 1p, 3β-H), 3.63 (s, 3p, $COOCH_3$), 2.1 (s, 3p, OAc), 1.16 (s, 3p, C-19), 0.51 (s, 3p, C-18); *m/e* (%) 478 (5,$[M]^+$), 460 (3,$[M-H_2O]^+$), 4.8 (8,$[M-HOAc]^+$), 442 (2, $[M-2H_2O]^+$), 382 (8,$[M-HOAc-2H_2O]^+$) 41 (100).

Methyl 3α,12β-Dimethoxy-7α-acetoxy-11-oxo-5β-cholan-24-oate (IIIe).- To a solution of IIId (0.3g) in methylene chloride (15 mL), catalyzed by HBF_4 stock solution (0.1 mL), a methylene chloride solution of diazomethane was added until the reaction was completed (by TLC). Then the solution was treated with a small amount of powder $NaHCO_3$ (0.05g) to neutralize the

catalyst and subsequently filtered and evaporated to a small volume (2 mL). Preparative TLC gave IIIe (0.285g, 90%).

ν_{max}1735 (multiplet C=O, OAc, $COOCH_3$), 1250 (multiplet $COCH_3$, OAc, $COOCH_3$); PMR δ 4.92 (peak, 1p, 7β-H), 3.64 (s, 3p, $COOCH_3$), 3.44 (s, 3p, 12α-H), 3.33 (s, 6p, 3α-OCH_3 and 12β-OCH_3), 3.30 (hump, 1p, 3β-H), 2.08 (s, 3p, OAc), 1.17 (s, 3p, C-19), 0.60 (s, 3p, C-18); *m/e* (%) 506 (7,$[M]^+$), 474 (2,$[M-CH_3OH]^+$), 446 (3,$[M-HOAc]^+$), 414 (8,$[M-HOAc-CH_3OH]^+$), 382 (8,$[M-HOAc-2CH_3OH]^+$), 55 (100).

Methyl 3α,12β-Dimethoxy-7α-hydroxy-11-oxo-5β-cholan-24-oate (IIIf).– A solution of IIIe (1.80g), KOH (10g) in MeOH (200 mL) was refluxed for 14 hrs. The solvent was evaporated to a small volume (30 mL) by rotary evaporation, then the solution was neutralized by dropwise addition of a 10% HCl (65 mL) while stirring and chilling on an ice bath. The resulting mixture was extracted with EtOAc and evaporated to dryness. This product was subsequently dissolved in MeOH (16.5 mL) to which acetyl chloride (0.8 mL) was added. Esterification of the side chain acid was completed after 3 hrs (by TLC) at which time the solution was quenched by pyridine (0.8 mL). MeOH was evaporated and the residue was diluted with H_2O (20 mL) and extracted with EtOAc. Evaporation of the solvent followed by preparative TLC gave IIIf (1.590g, 92%), mp. 133-135° (ethyl acetate-hexane).

ν_{max}3475 (OH str), 1740 (C=O), 1720 ($COOCH_3$), 1250 ($COCH_3$ and $COOCH_3$); PMR δ 3.94 (peak, 1p, 7β-H), 3.66 (s, 3p, $COOCH_3$), 3.45 (s, 1p, 12α-H), 3.33 (s, 6p, 3α-OCH_3 and 12β-OCH_3), 3.30 (hump, 1p, 3β-H), 1.14 (s, 3p, C-19), 0.60 (s, 3p, C-18); *m/e* (%) 464 (6,$[M]^+$), 446 (2,$[M-H_2O]^+$), 432 (4,$[M-CH_3OH]^+$), 414 (3,$[M-CH_3OH-H_2O]^+$), 382 (4,$[M-2CH_3OH-H_2O]^+$), 117 (100).

Anal. Calcd for $C_{27}H_{44}O_6$: C, 69.79; H, 9.55. Found: C, 69.69; H, 9.67.

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