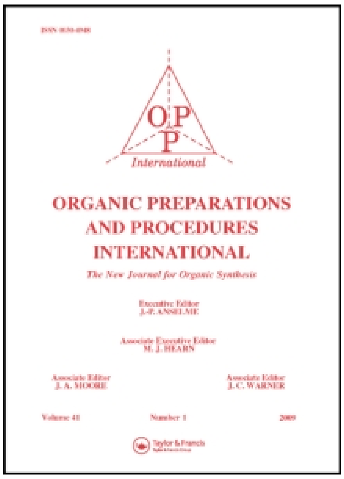

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SYNTHESIS OF C-24 THIAZOLIDINONE AND OXAZOLIDINONE DERIVATIVES OF BILE ACIDS

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solvent was removed under reduced pressure to yield 0.71 g (64%) of **4** (bp. 160-162°/0.5 torr., lit.[5] bp 140°/0.15 torr.[5]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.9 (t, 3H), 1.25- 1.35 (m, 18H), 1.55 (q, 2H), 2.05 (m, 4H), 3.65 (t, *J* = 6.64 Hz, 3H, CH_2O, OH), 5.35 (t, *J* = 4.89, 2H).

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SYNTHESIS OF C-24 THIAZOLIDINONE AND OXAZOLIDINONE DERIVATIVES OF BILE ACIDS

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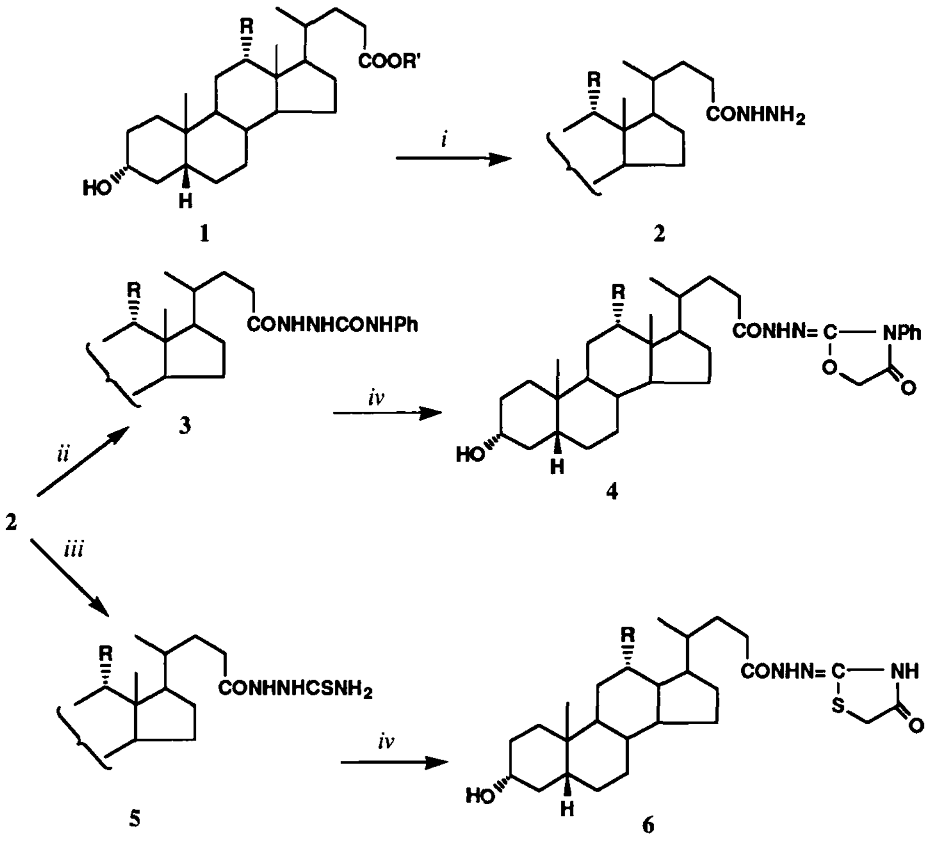
The chemistry[1] and wide spectrum of pharmacolgical activities of thiazolidinone[2] and oxazolidinone[3] derivatives have been cited in the literature. This paper describes the synthesis of C-24 thiazolidinone and oxazolidinone derivatives of bile acids, lithocholic acid (**1a**) and deoxycholic acid (**1b**). The present work was stimulated by reports that C-24 derivatives of bile acids possess useful biological activities.[4]

The methyl ester of bile acids, methyl-3α-hydroxy-5β-cholan-24-oate (**1c**) and methyl-3α,12α-dihydroxy-5β-cholan-24-oate (**1d**) on reaction with hydrazine afforded acid hydrazides **2a** and **2b**. The ^{1}H NMR spectra of **2a** and of **2b** exhibited broad singlets at δ 5.9 and δ 8.1, exchangeable with deuterium for NH_2 and CO$\underline{NH}$ protons , and IR spectra showed absorptions at 3250, 3100 (NH_2, NH) and 1660 cm^{-1} (CONH). Reaction of **2a** and **2b** with phenyl isocyanate[5] afforded 24-N-phenylsemicarbazide derivatives **3a** and **3b** whose ^{1}H NMR spectra showed broad exchangeable singlet at δ 6.45 for NHPh proton and signals for aromatic protons at δ 7.3-7.7. The IR spectra of **3a** and **3b** displayed absorptions at 3250 (NH) and 1610 cm^{-1} (C=C). Similarly, reaction of **2a** and **2b** with ammonium thiocyanate[6] gave respectively 24-thiosemicarbazide derivatives **5a** and **5b** whose IR spectra exhibited absorptions at 3250, 3080 (NH_2, NH) and 1190 cm^{-1} (C=S). The ^{1}H NMR spectra of **5a** and **5b** showed broad exchangeable singlets at δ 6.95 and δ 7.5 for NH_2 and NHCS protons. Compounds **5a** and **5b** were also prepared by the reaction of **2a** and **2b** with potassium thiocyanate[7] in the presence of HCl.

Cyclization of **3a** and **3b** with monochloroacetic acid afforded oxazolidinone derivatives **4a** and **4b** whose IR exhibited absorptions at 1715 (oxazolidinone C=O), 1600 (C=C) and 1470 cm^{-1} (C=N) and ^{1}H NMR showed a singlet for oxazolidinone ring protons at δ 4.5. Similarly, cyclization of **5a** and **5b** with monochloroacetic acid[8] gave thiazolidinone derivatives **6a** and **6b**. The structure of **6a** and **6b** is supported by ^{1}H NMR downfield signal for NH proton at δ 8.3, exchangeable with



a) R = H, R' = H **b)** R = OH, R' = H **c)** R = H, R' = Me **d)** R = OH, R' = Me

i) NH_2NH_2 *ii)* PhNCO *iii)* NH_4SCN or KSCN *iv)* $ClCH_2COOH$

deuterium and a singlet at δ 3.8 for thiazolidinone ring protons. IR spectrum showed absorptions at 3200 (NH), 1720 (thiazolidinone C=O) and 1450 cm^{-1} (C=N).

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were obtained as KBr pellets on a Perkin-Elmer 283B spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$-CD_3OD 4:1 (v/v) on a JEOL FX-90 Q FT instrument with TMS as internal standard. The petroleum ether refers to fraction of bp. 60-80°. Chemical shifts are given in ppm (δ). Lithocholic acid (1a) and deoxycholic acid (**1b**) were purchased from Sigma Chemical Company (St. Louis, MO, USA). Methyl esters of bile acids (**1c, 1d**) were prepared by treatment of **1a** and **1b** with diazomethane.

3α-Hydroxy-5β-cholan-24-hydrazide (2a).- A mixture of methyl-3α-hydroxy-5β-cholan-24-oate (1c) (4 g, 10.24 mmol), methanol (100 mL), hydrazine monohydrochloride (0.35g, 10.24 mmol) and 98% hydrazine hydrate (1.03g, 20.48 mmol) was refluxed for 4 hrs. The mixture was concentrated under reduced pressure and then poured onto ice. The precipitate was collected and recrystallized from ethanol to give 3.40 g (85%) of **2a** as a colorless solid, mp. 210-211°. IR: 3450 (OH), 3250, 3080 (NH_2, NH), 1660 (CONH) cm^{-1}; ^{1}H NMR: δ 8.10 (br s, 1H, CONH exchangeable), 5.9 (br s, 1H, NH_2 exchangeable), 3.52 (m, 1H, C_3-βH), 0.95 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.68 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{24}H_{42}N_2O_2$: C, 73.74; H, 10.76; N, 7.17. Found: C, 73.72; H, 10.68; N, 7.13

3α,12α-Dihydroxy-5β-cholan-24-hydrazide (2b).- A mixture of methyl-3α,12α-dihydroxy-5β-cholan-24-oate (**1d**) (3 g, 7.37 mmol), methanol (75 mL), hydrazine monohydrochloride (0.25g, 7.37mmol) and 98% hydrazine hydrate (0.737g, 14.75 mmol) was refluxed for 5 hours. The mixture was concentrated under reduced pressure and then poured onto ice. The precipitate was collected and recrystallized from ethanol to give 2.43 g (81%) of **2b** as colorless solid, mp. 262-64°. IR: 3470 (OH), 3260, 3070 (NH_2 NH), 1655 (CONH) cm^{-1}; ^{1}H NMR: δ 8.15 (br s, 1H, CONH exchangeable), 5.94 (br s, 1H, NH_2 exchangeable), 4.02 (m, 1H, C_{12}-βH), 3.58 (m, 1H, C_3-βH), 1.05 (d, 3H, J=6.5 Hz, C_{21}-H_3), 0.94 (s, 3H, C_{19}-H_3), 0.72 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{24}H_{42}N_2O_3$: C, 70.93; H, 10.34; N, 6.89. Found: C, 70.87; H, 10.32 N, 6.85

3α-Hydroxy-5β-cholan-24-N-phenylsemicarbazide (3a).- A mixture of **2a** (1.5 g, 3.84 mmol), benzene (50 mL) and phenyl isocyanate (0.91g, 7.68 mmol) was refluxed on a water bath for 3 hrs. The mixture was concentrated under reduced pressure and the residue was poured onto ice-water and extracted with ether (3x75 mL). The combined extracts were washed with water and dried over Na_2SO_4. After the evaporation of ether, the residue was chromatographed on silica gel (45 g; 70-230 mesh). The product was eluted with petroleum ether-ether (3:1) to give 1.52 g (78%) of **3a** as a colorless solid, mp. 234-236°. IR: 3450 (OH), 3250 (NH), 1650 (CONH), 1600 (C=C) cm^{-1}; ^{1}H NMR: δ 8.26 (s, 2H, 2xCONH exchangeable), 6.42 (s, 1H, NHPh exchangeable), 3.54 (m, 1H, C_3-βH), 0.94 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.65 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{47}N_3O_3$: C, 73.04; H, 9.25; N, 8.25. Found: C, 73.12; H, 9.34; N, 8.22

3α,12α-Dihydroxy-5β-cholan-24-N-phenylsemicarbazide (3b).- A mixture of **2b** (1.5 g, 3.69 mmol), benzene (50 mL) and phenyl isocyanate (0.88g, 7.38 mmol) was refluxed on a water bath for 3 hrs. The mixture was concentrated under reduced pressure and the residue was poured onto ice-water and extracted with ether (3x75 mL). The combined extracts were washed with water and dried over Na_2SO_4. After the removal of solvent the crude product was chromatographed on silica gel (45 g; 70-230 mesh). The product was eluted with petroleum ether-ether (6:4) to give 1.43 g (74%) of **3b** as colorless solid, mp. 238-240°. IR: 3460 (OH), 3250 (NH), 1655 (CONH), 1610 (C=C) cm^{-1}; ^1H NMR: δ 8.22 (s, 2H, 2xCO<u>NH</u> exchangeable), 6.46 (s, 1H, <u>NH</u>Ph exchangeable), 4.0 (m, 1H, C_{12}-βH), 3.57 (m, 1H, C_3-βH), 1.04 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.95 (s, 3H, C_{19}-H_3), 0.72 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{31}H_{47}N_3O_4$: C, 70.85; H, 8.95; N, 8.00. Found: C, 70.92; H, 8.90; N, 8.05

3α-Hydroxy-5β-cholan-24-[4'-oxo-3'-phenyl-1',3'-oxazolidin-2'-ylidene]hydrazide (4a).- A mixture of **3a** (1.5 g, 2.94 mmol), chloroacetic acid (0.556 g, 5.88 mmol), anhydrous sodium acetate (0.221 g, 2.94 mmol) and acetic acid (50 mL) was refluxed for 6 hrs. The excess of acetic acid was removed *in vacuo*, the residue poured into dilute $NaHCO_3$ and extracted with ether (3x75 mL). The combined extracts were washed with water and dried over Na_2SO_4. After the removal of ether, the residue was chromatographed on silica gel (40 g; 70-230 mesh). Elution with petroleum ether-ether (7:3) gave the product which was recrystallized from methanol to give 1.10 g (68%) of **4a** as a colorless solid, mp. 114-115°. IR: 3455 (OH), 1715 (oxazolidinone C=O), 1655 (CONH), 1610 (C=C), 1490 (C=N) cm^{-1}; ^1H NMR: δ 8.14 (br s, 1H, CO<u>NH</u> exchangeable), 7.3-7.7 (m, 5H, aromatic), 4.55 (s, 2H, oxazolidinone CH_2), 3.55 (m, 1H, C_3-βH), 0.96 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.92 (s, 3H, C_{19}-H_3), 0.68 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{33}H_{47}N_3O_4$: C, 72.13; H, 8.56; N, 7.65. Found: C, 72.10; H, 8.50; N, 7.58

3α,12α-Dihydroxy-5β-cholan-24-[4'-oxo-3'-phenyl-1',3'-oxazolidin-2'-ylidene]hydrazide (4b).- A mixture of **3b** (1 g, 1.90 mmol), chloroacetic acid (0.36 g, 3.8 mmol), anhydrous sodium acetate (0.156 g, 1.90 mmol) and acetic acid (30 mL) was refluxed for 6 hrs. The excess of acetic acid was removed *in vacuo*, the residue poured into dilute $NaHCO_3$ and extracted with ether (3x50 mL). The combined extracts were washed with water and dried over Na_2SO_4. After the removal of solvent the crude product was chromatographed on silica gel (30 g; 70-230 mesh). Elution with petroleum ether-ether (1:1) gave 1.05 g (62%) of **4b** as a colorless solid, mp.118-120°. IR: 3460 (OH), 1710 (oxazolidinone C=O), 1650 (CONH), 1600 (C=C), 1480 (C=N) cm^{-1}; ^1H NMR: δ 8.18 (br s, 1H, CO<u>NH</u> exchangeable), 7.3-7.7 (m, 5H, aromatic), 4.52 (s, 2H, oxazolidinone CH_2), 4.0 (m, 1H, C_{12}-βH), 3.52 (m, 1H, C_3-βH), 1.06 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.93 (s, 3H, C_{19}-H_3), 0.72 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{33}H_{47}N_3O_5$: C, 70.08; H, 8.31; N, 7.43. Found: C, 70.00; H, 8.35; N, 7.40

3α-Hydroxy-5β-cholan-24-thiosemicarbazide (5a).- A mixture of **2a** (1.5 g, 3.84 mmol), benzene (50 mL) and ammonium thiocyanate (0.585g, 7.68 mmol) was refluxed on a water bath for 3 hrs. The excess of benzene was removed under reduced pressure. After cooling to 5°C, the precipitated solid was collected, washed with cold water and recrystallized from methanol to give 1.31 g (76%) of **5a** as a colorless solid, mp. 101-102°. IR: 3450 (OH), 3250, 3080 (NH_2, NH), 1660 (CONH), 1190 cm^{-1} (C=S); ^1H NMR: δ 8.12 (br s, 1H, CO<u>NH</u> exchangeable), 7.46 (br s, 1H, <u>NH</u>CS exchangeable), 6.95 (br s, 1H, NH_2 exchangeable), 3.50 (m, 1H, C_3-βH), 0.96 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.91 (s, 3H, C_{19}-H_3), 0.68 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{25}H_{43}N_3O_2S$: C, 66.81; H, 9.58; N, 9.35. Found: C, 66.78; H, 9.54; N, 9.32

b) A mixture of **2a** (1 g, 2.56 mmol), ethanol (30 mL), potassium thiocyanate (0.5g, 5.12 mmol) and HCl (1 mL; 6N) was refluxed for 4 hrs. The hot mixture was filtered, concentrated *in vacuo* and then poured onto ice. The precipitate was collected, washed with cold water and recrystallized from methanol to give 0.86 g (75%) of **5a** as a colorless solid, mp. 100-102°.

3α,12α-Dihydroxy-5β-cholan-24-thiosemicarbazide (5b).- A mixture of **2b** (1 g, 2.45 mmol), benzene (30 mL) and ammonium thiocyanate (0.375g, 4.90 mmol) was refluxed on a water bath for 4 hrs. The excess of benzene was removed under reduced pressure. After cooling to 5°C, the precipitated solid was collected, washed with cold water and recrystallized from ethyl acetate-methanol to give 0.855 g (75%) of **5b** as colorless solid, mp. 122-124°. IR: 3470 (OH), 3260, 3070 (NH_2, NH), 1655 (CONH), 1180 cm^{-1} (C=S); ^1H NMR: δ 8.18 (br s, 1H, CO<u>NH</u> exchangeable), 7.5 (br s, 1H, <u>NH</u>CS exchangeable), 6.92 (br s, 1H, NH_2 exchangeable), 4.02 (m, 1H, C_{12}-βH), 3.58 (m, 1H, C_3-βH), 1.05 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.95 (s, 3H, C_{19}-H_3), 0.73 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{25}H_{43}N_3O_3S$: C, 64.51; H, 9.24; N, 9.03. Found: C, 64.43; H, 9.18; N, 9.00

b) A mixture of **2b** (1 g, 2.45 mmol), ethanol (30 mL), potassium thiocyanate (0.48g, 4.9 mmol) and HCl (1 mL; 6N) was refluxed for 4 hrs. The hot mixture was filtered, concentrated *in vacuo* and then poured onto ice. The resulting precipitate was collected, washed with cold water and recrystallized from ethyl acetate-methanol to give 0.83 g (73%) of **5b** as a colorless solid, mp. 122-124°.

3α-Hydroxy-5β-cholan-24-[4'-oxo-1',3'-thiazolidin-2'-ylidene]-hydrazide (6a).- A mixture of **5a** (1.5 g, 3.34 mmol), chloroacetic acid (0.631 g, 6.68 mmol), anhydrous sodium acetate (0.27 g, 3.34 mmol) and acetic acid (50 mL) was refluxed for 6 hrs. The excess of acetic acid was removed under reduced pressure, the residue poured onto ice. The precipitate was collected, washed with 5% $NaHCO_3$ (100 mL), water and recrystallized from ethanol to give 0.79 g (61%) of **6a** as a colorless solid, mp. 94-96°. IR: 3450 (OH), 3210 (NH), 1720 (thiazolidinone C=O), 1660 (CONH), 1470 (C=N) cm^{-1}; ^1H NMR: δ 8.32 (br s, 2H, NH and CO<u>NH</u> exchangeable), 3.82 (s, 2H, thiazolidinone CH_2), 3.35 (m, 1H, C_3-βH), 0.96 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.92 (s, 3H, C_{19}-H_3), 0.65 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{27}H_{43}N_3O_3S$: C, 66.25; H, 8.79; N, 8.58. Found: C, 66.29; H, 8.80; N, 8.52

3α,12α-Dihydroxy-5β-cholan-24-[4'-oxo-1',3'-thiazolidin-2'-ylidene]-hydrazide (6b).- A mixture of **5b** (1 g, 2.22 mmol), chloroacetic acid (0.42 g, 4.44 mmol), anhydrous sodium acetate (0.185 g, 2.22 mmol) and acetic acid (30 mL) was refluxed for 8hrs. The excess of acetic acid was removed *in vacuo*, the residue poured onto ice. The precipitate was collected, washed with 5% $NaHCO_3$ (75 mL), water and recrystallized from ethanol to give 0.67 g (60%) of **6b** as a colorless solid, mp. 112-113°.

IR: 3460 (OH), 3220 (NH), 1720 (thiazolidinone C=O), 1665 (CONH), 1480 (C=N) cm^{-1}; ^{1}H NMR: δ 8.28 (br s, 2H, NH and CONH exchangeable), 3.98 (m, 1H, C_{12}-βH), 3.85 (s, 2H, thiazolidinone CH_2), 3.55 (m, 1H, C_3-βH), 1.05 (d, 3H, J=6.3 Hz, C_{21}-H_3), 0.94 (s, 3H, C_{19}-H_3), 0.74 ppm (s, 3H, C_{18}-H_3).

Anal. Calcd. for $C_{27}H_{43}N_3O_4S$: C, 64.15; H, 8.51; N, 8.31. Found: C, 64.10; H, 8.48; N, 8.36

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