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UTILIZATION OF COMMON NATURAL PRODUCTS AS SYNTHONS: PREPARATION OF PROGESTERONE FROM LITHOCHOLIC ACID

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ABSTRACT.—Progesterone [**2**] was prepared from lithocholic acid [**1**] in eight steps with an overall yield of 32%. The transformation of the bile acids side chain into the C-21 progesterone series was performed with an overall yield of 66%, the highest thus far reported from any laboratory.

The bile acids are attractive starting materials, particularly for those hormones of the pregnane series, which include progesterone and cortisone. The major challenge in this transformation is the modification of the side chain. Many methods of degradation of the side chain of bile acids and related compounds have been described (1–6) since the classical work of Weiland.

We report our efforts to improve the conversion of lithocholic acid [**1**] to progesterone [**2**] by a short sequence utilizing simple and inexpensive reagents.

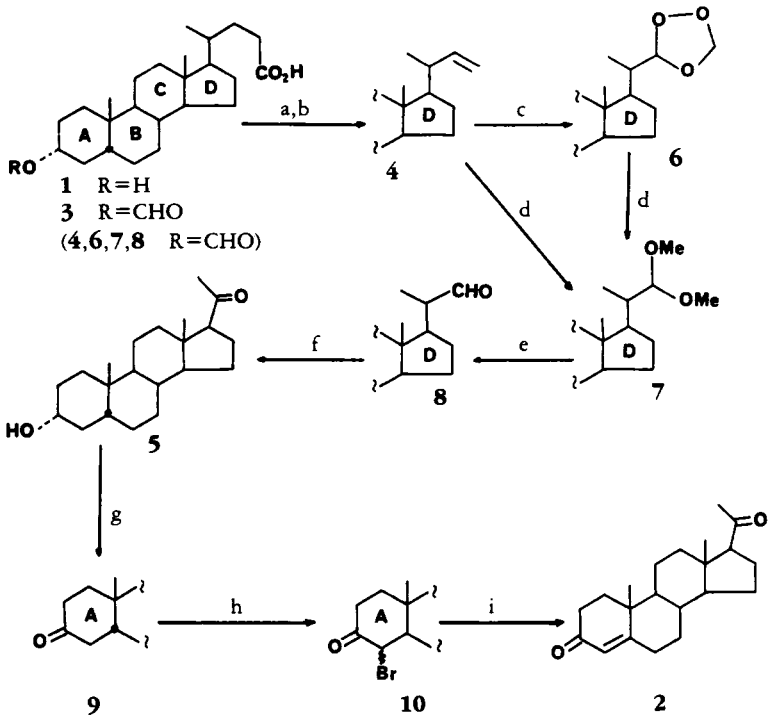
Comparative study of structures of progesterone [**2**] and lithocholic acid [**1**] reveals that we must make transformations in two different parts of the molecule: the side chain and the A ring.

We elected to modify the side chain to that of the progesterone series first and then to transform the A ring. The first problem in this sequence was to find a good protecting group for the hydroxyl at C-3 of lithocholic acid. Attempts to make the acetate and carbonate of **1** failed to provide the esters in satisfactory yields. Formylation (7,8) gave **3** in high yield. The presence of a formyl group is easily visualized in ^{1}H nmr by the presence of a singlet around δ 8.0–8.3; in lithocholic acid formate [**3**] a one-proton singlet at δ 8.10 is assigned to the formyl proton.

With the C-3 alcohol successfully protected, we then turned to the modification of the side chain. Photochemical decarboxylation using t-butyl hypoiodite (9) to produce the alkyl iodide was unsuccessful. Lead tetraacetate has been reported to afford decarboxylation of acids to the corresponding olefins (10,11), the highest yield reported for bile acids being 65% (12). Careful evaluation and modification of reaction conditions allowed us to improve the reaction so that the overall yield was raised to 81%. The conditions applied to improve the yield of the oxidative decarboxylation were: (a) pyridine was used as a co-solvent instead of a catalytic amount as previously reported (10–12), (b) anhydrous reagents and dry solvents were used, and (c) lead tetraacetate was added in portions over 5 h, instead of all at once as previously reported (10–12).

Olefin **4** proved unreactive to photochemical oxygenation. Ozonolysis of olefin **4** followed by photo-oxidative transformation of the resultant aldehyde to the methylketone was expected to provide the progesterone side chain (13) (Scheme 1).

The ozonolysis reaction was first attempted in CH_2Cl_2 (14). The product, obtained in 98% yield, after Me_2S workup (14), was identified as the ozonide **6**. Redissolution of the ozonide in CH_2Cl_2 and Me_2S and reflux of the mixture for 2 h gave back the same ozonide unchanged. A mixture of



a, HCO_2H/Ac_2O; b, $Pb(OAc)_4/Cu(OAc)_2$/pyridine/C_6H_6; c, $O_3/CH_2Cl_2/Me_2S$; d, O_3/CH_2Cl_2/MeOH/Me_2S; e, 0.1 N HCl; f, O_2/MeOH/10% KOH/hν; g, Jones reagent; h, $C_6H_5N^+ HBr_3$/HOAc; i, LiCl/$LiCO_3$/DMF.

SCHEME 1

MeOH and CH_2Cl_2 was then used as solvent for the ozonolysis (15,16). Ozone was passed into the solution at −70° for 5 min; Me_2S was added and the mixture refluxed. The product obtained in high yields (95%) was characterized as the acetal **7**. Acetal **7** was hydrolyzed to form the expected aldehyde, **8**, in 99% yield. In the hydrolysis process a very small amount of aldehyde with the free alcohol at C-3 was occasionally detected. The aldehyde was transformed by photooxidation in MeOH/KOH with sensitization to the expected methyl ketone (pregnanolone), **5**, in 87% yield (13). The acetal **7** and the aldehyde **8** are unstable and undergo decomposition after a few hours, so the processes of ozonolysis, hydrolysis, and photooxidation were carried out on the same day. Treatment of ketone **9** with pyridinium bromide perbromide according to the literature (17) furnished the expected brominated product **10** in 98% yield. Dehydrobromination of **10** with LiCl in DMF (18) provided the expected progesterone in only 48% yield along with a rearranged product, in 24% yield, and other unidentified compounds. Co-chromatography of the crude reaction mixture with commercial progesterone allowed the identification of the principal product as progesterone. The overall yield obtained from the conversion of lithocholic acid to progesterone was 32%. The transformation of the bile acid side chain into the C-21 progesterone series was performed with an overall yield of 66%, the highest yield reported by any laboratory to date (19).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Thomas-Hoover Uni-Melt and digital Mettler, model PF-5, and are uncorrected. Optical rotations were taken on a Perkin-Elmer Model 141 automatic

polarimeter using $CHCl_3$ solutions. Ir spectra were measured in KBr pellets, $CHCl_3$ solutions, or neat films on a Perkin-Elmer 281B spectrophotometer. Mass spectral data were obtained on a Finnigan 3200 spectrometer with INCOS data system. Continuous wave ^{1}H-nmr spectra were recorded on a Varian EM-390 nmr spectrometer using $CDCl_3$. Fourier transform ^{1}H- and ^{13}C-nmr spectra were obtained on a JEOL JNM-FX60 Fourier transform nmr spectrometer.

All starting materials were purchased from Aldrich Chemical Company. Si gel, neutral alumina, and Florisil were used for chromatography. Tlc was performed on Si gel G plates. The developed plates were visualized with 10% H_2SO_4 in HOAc, and then the plates were heated in an oven until the spots developed the maximum intensity of color.

LITHOCHOLIC ACID FORMATE [3].—A stirred solution of lithocholic acid [1] (10 g) in 40 ml of 89.9% HCO_2H containing 6 drops of 70% perchloric acid was heated in an H_2O bath at 55° for 2 h. The solution was removed from the bath and allowed to cool to about 40°. Ac_2O was then added dropwise while the temperature was maintained between 55 and 60° until a large quantity of bubbles appeared (35 ml of Ac_2O was required). The solution was then cooled to room temperature and poured into 300 ml of H_2O, with stirring. The precipitate was filtered under vacuum, washed with H_2O, and dried to yield 10.3 g (96%) of formyl lithocholic acid [3]. Recrystallization from EtOH/H_2O gave white needles: mp 135–137° [lit. (11) 139–141°]; $[\alpha]^{23}$D +38.5 (c = 10, $CHCl_3$); ir (KBr) ν max 3420, 2920, 1730, 1700, 1190, 1170 cm^{-1}; ms *m/z* (rel. int.) $[M]^+$ 404 (0.87), $[M-H_2O]^+$ 386 (0.2), $[M-HCO_2H]^+$ 358 (35.4), $[M-HCO_2H-Me]^+$ 343 (8.0), 215 (100.0), 149 (62.2), 107 (88.7); ^{1}H nmr ($CDCl_3$) δ 0.75 (s, 3H), 0.90 (s, 6H), 4.9 (m, 1H), 8.1 (s, 1H); ^{13}C nmr ($CDCl_3$) δ 180.3 (s), 160.7 (d), 74.3 (d), 56.4 (d), 42.6 (s), 41.9 (t), 40.4 (t), 40.1, 35.8 (d), 35.2 (d), 34.9, 34.5 (s), 32.2 (d), 30.9 (t), 30.7, 28.1 (t), 26.9, 26.5, 26.3, 24.1 (t), 23.2 (q), 20.8 (t), 18.2 (q), 12.0 (q).

3α-FORMYL-24-NOR-5β-CHOL-22-ENE [4].—Lithocholic acid formate [3] (5 g), was dissolved in 70 ml of dried C_6H_6 and 40 ml of freshly distilled pyridine, and 900 mg of anhydrous cupric acetate was added. The solution was poured into a 0.5-liter 3-necked round bottom flask equipped with a reflux condenser and an overhead mechanical stirrer. This mixture was kept under N_2 atmosphere and refluxed with stirring. Lead tetraacetate (15 g) was added every hour for 5 h in 3-g portions, and the reaction mixture was refluxed for an additional 12 h. At this point the reaction mixture was cooled, and 3 ml of ethylene glycol was added to destroy the excess oxidant. Addition of 50 ml of H_2O and extraction with C_6H_6 yielded an organic layer that was further stirred with 1 N HCl (100 ml) for 30 min. The C_6H_6 layer was separated and washed with H_2O followed by 10% $NaHCO_3$ solution and H_2O, dried over anhydrous Na_2CO_3, and evaporated at reduced pressure. The crude product was chromatographed over neutral alumina. Elution with hexane-C_6H_6 (1:1) and C_6H_6 gave 3.60 g (81%) of a white solid, 3α-formyl-24-nor-5β-chol-22-ene [4]. The hexane/C_6H_6 fraction was recrystallized from hexane to give 4 as white needles: mp 85.5–87°; $[\alpha]^{23}$D +41.2 (c = 0.4, $CHCl_3$); ir (KBr) ν max 2910, 1710, 1625, 1160 cm^{-1}; ms *m/z* (rel. int.), $[M]^+$ 358 (0.6); ^{1}H nmr ($CDCl_3$) δ 0.70 (s, 3H), 0.98 (s, 3H), 1.07 (d, J = 6 Hz, 3H), 4.94 (m, 2H), 5.73 (m, 3H, 2H at C-23 and 1H at C-3), 8.15 (s, 1H); ^{13}C nmr ($CDCl_3$) δ 160.5 (d), 145.0 (d), 111.6 (t), 74.2 (d), 56.5 (d), 55.6 (d), 42.6 (s), 41.9 (d), 41.0, 40.5, 40.0 (t), 35.8, 35.0, 34.5 (s), 32.2 (t), 28.3, 26.9, 26.6, 26.3, 24.1, 23.3 (q), 20.8 (t), 20.0 (q), 12.2 (q). Recrystallization of the C_6H_6 fraction from C_6H_6 gave 3α-hydroxy-24-nor-5β-chol-22-ene (300 mg, white needles): mp 156–157° [lit. (20) 125–126 from Me_2CO]; $[\alpha]^{23}$D +5.75 (c = 0.4, $CHCl_3$); ir (KBr) ν max 3280, 2920, 1630 cm^{-1}; ms *m/z* (rel. int.) $[M]^+$ 330 (1.3), $[M-H_2O]^+$ 312 (3.6), $[M-H_2O-C_4H_7]^+$ 257 (85.0), 95 (100.0); ^{1}H nmr ($CDCl_3$) δ 0.72 (s, 3H), 0.98 (s, 3H), 1.05 (d, J = 6 Hz, 3H), 3.70 (m, 1H), 4.94 (m, 2H), 5.75 (m, 1H). Calcd for $C_{23}H_{38}O$, C 83.57, H 11.59, found C 83.18, H 12.00.

OZONOLYSIS OF 3α-FORMYL-24-NOR-5β-CHOL-22-ENE [4].—The alkene 4 (2.0 g) was dissolved in 15 ml of CH_2Cl_2 and 15 ml of MeOH. The solution was cooled in a dry ice-Me_2CO bath and treated with ozone until a blue color persisted in the solvent. To the mixture 1.5 ml of Me_2S was added, and the mixture was refluxed for 1 h with stirring. The solvent was evaporated under vacuum, and the residue was filtered over a small column filled with silica to yield 2.15 g (95%) of a colorless oil as the only product. This oil was identified as acetal 7: ir (neat) ν max 2920, 1715, 1190, 1175, 1070 cm^{-1}; ms *m/z* (rel. int.) $[M-2OMe]^+$ 344 (0.1), 93 (100.0); ^{1}H nmr ($CDCl_3$), δ 0.64 (s, 3H), 0.90 (s, 6H), 3.38 (s, OMe), 3.45 (s, OMe), 4.15 (d, J = 3 Hz, 1H), 4.90 (m, 1H), 8.05 (s, 1H); ^{13}C nmr ($CDCl_3$) δ 160 (d), 109.1 (d), 74.3 (d), 56.8 (d), 56.0 (q), 55.6 (q), 52.1 (d), 42.8 (s), 41.9 (d), 40.5 (t), 40.0, 39.6, 35.8 (d), 35.0 (t), 34.5 (s), 32.2 (t), 27.7 (t), 27.0, 26.6 (t), 26.3, 24.3, 23.3 (q), 20.8 (t), 11.9 (q), 11.7 (q).

3α-FORMYL-23,24-NOR-5β-CHOLAN-22-AL [8] AND 3α-HYDROXYL-23,24-NOR-5β-CHOLAN-22-AL.—The acetal 7 (500 mg) was dissolved in

10 ml of THF followed by addition of 15 ml of 0.5 N of HCl. The mixture was stirred at room temperature for 1 h. The mixture was extracted with $CHCl_3$, dried over Na_2SO_4, and evaporated under vacuum. The residue was chromatographed over a small column of Si gel G to give 398 mg of the aldehyde formate **8** and 20 mg of its aldehyde alcohol, which was directly photooxygenated to pregnanolone [**5**]. The aldehyde-formate **8** was characterized as an oil $[\alpha]^{23}D$ +15.0 (c = 0.3, $CHCl_3$); ir (neat) ν max 2680, 1710, 1190, 1170 cm^{-1}; ms *m/z* (rel. int.) $[M]^+$ 360 (0.5), $[M-HCO_2H]^+$ 314 (7.8), $[M-HCO_2H-Me]^+$ 299 (5.5), 215 (95.0), 93 (100.0); ^1H nmr ($CDCl_3$) δ 0.68 (s, 3H), 1.00 (s, 3H), 1.12 (d, J = 6 Hz, 3H), 4.90 (m, 1H), 8.15 (s, 1H), 9.72 (d, J = 3 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 202.9 (d), 160.0 (d), 73.8 (d), 55.4 (d), 51.3 (d), 49.4, 43.2 (s), 41.9, 40.6, 39.8, 35.8, 35.1, 34.5 (s), 32.5 (t), 27.1, 26.9, 26.4, 24.6, 23.2 (q), 20.9 (t), 13.4 (q), 12.3 (q). The hydroxy aldehyde was recrystallized from hexane to give white needles: mp 137–139° [lit. (21) 145]; $[\alpha]^{23}D$ +14.0 (c = 0.2, $CHCl_3$), ir (KBr) ν max 3270, 2680, 1715 cm^{-1}; ms *m/z* (rel. int.) $[M]^+$ 332 (9.3), 93 (100.0).

PREGNANOLONE [**5**].—The aldehyde **8** (260 mg) was dissolved in 5 ml of 10% methanolic KOH solution, and the solution was cooled to 0°. After the addition of 4 mg of rose bengal sensitizer, O_2 was bubbled through the solution for 30 min with continuous irradiation from a Sylvania DWY 650 W quartz-halogen lamp. The reaction mixture was poured into H_2O, extracted with Et_2O, and washed successively with dilute HCl, saturated $NaHCO_3$ solution, and H_2O. Evaporation of the dried Et_2O extract gave a white solid residue (235 mg). Analysis by gc-ms of the residue indicated the major product as the ketone **5** in 87% yield. Crystallization of the material from hexane gave 210 mg of white needles: mp 131—132° [lit. (22) 149.5]; $[\alpha]^{23}D$ +59.6 (c = 0.3, $CHCl_3$); ms *m/z* (rel. int.) $[M]^+$ 318 (2.8). Calcd for $C_{21}H_{34}O_2$, C 79.19, H 10.76; found C 78.80, H 11.00.

PREGNA-3,20-DIONE [**9**].—Pregnanolone [**5**] (500 mg) was oxidized with Jones reagent (5.0 ml) followed by the usual workup. The product, 486 mg, was recrystallized from Me_2CO to give 455 mg (93%) of **9** as white needles: mp 121–122° [lit. (23) 123]; $[\alpha]^{23}D$ +99.6 (c = 0.6, $CHCl_3$); ir (KBr) ν max 2930, 1705 cm^{-1}; ms *m/z* (rel. int.) $[M]^+$ 316 (20.4).

4-BROMOPREGNA-3,20-DIONE [**10**].—Pregna-3,20-dione (140 mg) was dissolved in 5 ml of HOAc followed by addition of 124 mg of pyridinium bromide perbromide. The reaction mixture was placed in an H_2O bath at 50° for 5 min. H_2O (10 ml) and $CHCl_3$ (10 ml) were added, the H_2O phase was separated and extracted with $CHCl_3$ (3×), and the combined $CHCl_3$ extracts were evaporated under vacuum. Crystallization of the crude material from Me_2CO yielded 140 mg of 4-bromopregna-3,20-dione [**10**]: mp 172.5–173.6° [lit. (24) 185]; $[\alpha]^{23}D$ +67.1 (c = 0.28 $CHCl_3$); ir (KBr) ν max 2920, 1720, 1700, 840 cm^{-1}; ms *m/z* (rel. int.) 396, $[M]^+$ 394 (0.6), $[M-Br]^+$ 315 (7.4); ^1H nmr ($CDCl_3$) δ 0.60 (s, 3H), 1.10 (s, 3H), 2.13 (s, 3H), 4.90 (d, J = 11 Hz, 1H).

PROGESTERONE [**2**].—The bromoketone **10** (25 mg) was dissolved in 12 ml of dried DMF under an N_2 atmosphere. To this solution LiCl (25 mg) and $LiCO_3$ (25 mg) were added, and the mixture was heated under reflux in an atmosphere of N_2 for 10 h. The reaction mixture was cooled, poured into ice, and extracted 4× with Et_2O. The combined Et_2O extract was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated under vacuum. The residue was chromatographed over a small column of silica (10 g) and eluted with hexane-$CHCl_3$ (1:3) to yield 17 mg of a white solid. Gc-ms of the sample showed the presence of progesterone [**2**] (79%, 67% conversion). Co-chromatography of the mixture with commercial progesterone verified the major component to be progesterone. Crystallization of the sample from EtOH gave a white solid, mp 127.5–129°; mixture melting point with authentic progesterone gave no depression; $[\alpha]^{23}D$ +170.6 (c = 1.0, dioxane); ms *m/z* (rel. int.) $[M]^+$ 314 (12.1).

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