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CHOLIC ACID - AN ATTRACTIVE SOURCE FOR THE PREPARATION OF 5β-PREGNANE-3,20-DIONE, 3α-HYDROXY-5β-PREGNAN-20-ONE AND PROGESTERONE

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Abstract: An efficient synthesis of 5β-pregnane-3,20-dione (5), progesterone and 3α-hydroxy-5β-pregnan-20-one (11) from cholic acid (1) is presented.

5β-Pregnane-3,20-dione (5) as well as 3α-hydroxy-5β-pregnan-20-one (11) has been reported to be of pharmaceutical value as hypnotic-anaesthetic agent[1,2]. Additionally both products reveal high anticonvulsive activity[3] and counteract androgen-induced defeminization[2]. Preparation and indication of the female sex hormone progesterone are well known either.

Older processes[4-6] for preparing 5 and 11 on the basis of bile acids are relatively complicated and uneconomical. It is known that 5β-pregnane-3,20-dione (5) as well as 3α-hydroxy-5β-pregnan-20-one (11) can be obtained from progesterone by selective hydrogenation[7]. But especially yields for 11 (from progesterone via 5) are not satisfying. Additionally in 1980 D. Onken[8] reported on a shortage of diosgenin, the most essential source for the technical preparation of progesterone[9].

Now we herein describe a new method for preparing 5β-pregnane-3,20-dione (5) and 3α-hydroxy-5β-pregnan-20-one (11) from cholic acid (1), an attractive starting material because of its easy supply from cow bile. The key step of our synthesis is the photochemical side chain degradation of suitable bile acid derivatives (3 → 4; 7 → 9; 8 → 10).

5β-Pregnane-3,20-dione (5) was prepared as follows. For isolation of cholic acid (1) from cow bile we choosed the method of Koppe and Becker[10]. Modificaton of this procedure yielded 60 g 1 from two litres of cow bile (the purity of the isolated cholic acid (1) was identical with an authentic sample[11]). Treatment of 1 with MeOH/AcOCl (catalytical amount) (25 h, 55 °C) gave the methylester 2 (94 %), which was transformed to 3[12] in 79 % yield (three steps)[13].

Treatment of 3 with a slight exess of N,N-carbonyldiimidazole in THF (0.18 M concentration of 3, 5 h at 25 °C) led to imidazole 3a[14], which was in situ irradiated in 0.033 M tetrahydrofuran solution with a low pressure mercury lamp (Hanau, TNN 15/32) (Iwasaki method[15]) to give after chromatography on silica gel a 69 % yield of 4[16].

Ozonolysis of 4 in CH_2Cl_2 (15 min at -78 °C) followed by treatment with Zn/HCOOH afforded, after silica chromatography, 73 % of 5β-pregnane-3,20-dione (5), whose

physical constants and spectra were identical with those of an authentic sample[17].

The conversion of 5 (by bromination followed by dehydrobromination) into the very important female sex hormone progesterone is well known[18].

3α-Hydroxy-5β-pregnan-20-one (11) could be obtained from cholic acid (1) in a similar way.

Transformation of 1 into lithocholic acid (7) starts with selective acylation and oxidation to 6 (95 % overall). 7 was obtained from 6 by the modified Wolff-Kishner reduction[19] (91 % yield).

Treatment of 7 with one equivalent of N,N-carbonyldiimidazole in THF (0.15 M concentration of 7, 5 h at 25 °C) and irradiation of the imidazole 7a as described above (see preparation of 4) yielded after silica gel chromatography 40 % 3α-hydroxy--20-methylene-5β-pregnane (9)[20], which was transformed into the desired 3α-hydroxy--5β-pregnan-20-one (11)[21] via ozonolysis (yield 70 %).

Improved yields can be obtained by protection of the 3α-hydroxy-function by the t-butyl--dimethylsilyl group[22]. It is very easy to introduce and nearly quantitatively removable. The stability of the silyl ether during the photochemically side chain degradation is essential.

So, lithocholic acid (7) was treated with TBDMSCl (2.7 equivalent) and diethylamine in CH_2Cl_2 (24 h at 25 °C). Refluxing the raw material with equivalent KOH in ethanol for 1 h gave an 88 % overall yield of 8[23]. The side chain degradation of 8 via 8a yielded 76 % 10[24]. Ozonolysis of 10 in CH_2Cl_2 at -78 °C (the ozonide was decomposed with zinc dust and acetic acid) and treatment with tetrabutylammonium fluoride in THF afforded, after silica gel chromatography, 89 % of 3α-hydroxy-5β-pregnan-20-one (11)[21].

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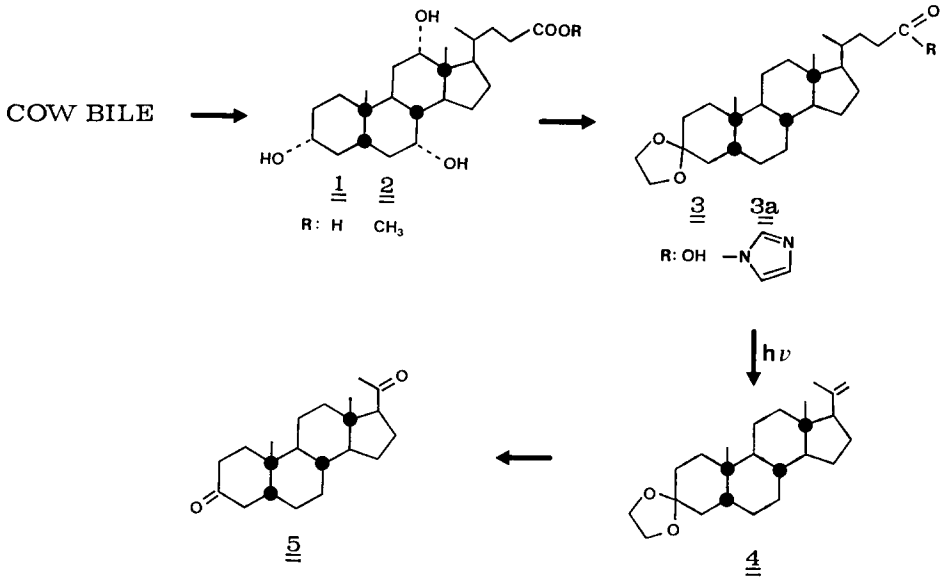
References and notes:

1) a) L.Gyermek; Proc. Soc. Exp. Biol. Med. 125 (1967), 1058
b) L.Gyermek, J.Iriarte, P.Crabbé; J.Med.Chem. 11 (1968), 117
2) G.Gonzalez-Mariscal, A.Fernandez-Guasti, C.Beyer; Neuroendocrinology 34 (1982), 357
3) C.R.Craig, J.R.Deason; Arch.int.Pharmacodyn. 172 (1968), 366
4) a) Can. Pats. 370,634 (Butenandt)
b) U.S. Pats. 2,156,275 (Butenandt)
5) W. Hoehn, H.Mason; J.Am.Chem.Soc. 62 (1940), 569
6) a) B.A.Koechlin, T.E.Kritchevsky, T.F.Gallagher; J.Biol.Chem. 184 (1950), 393
b) M.Fetizon, F.J.Kakis, V.Ignatiadou-Ragoussis; J.Org.Chem. 38 (1973), 4308
7) a) M.G.Combe, H.B.Henbest, W.R.Jackson; J.Chem.Soc.(C) 22 (1967), 2467
b) G.Bach, J.Capitaine, Ch.R.Engel; Can.J.Chem. 46 (1968), 733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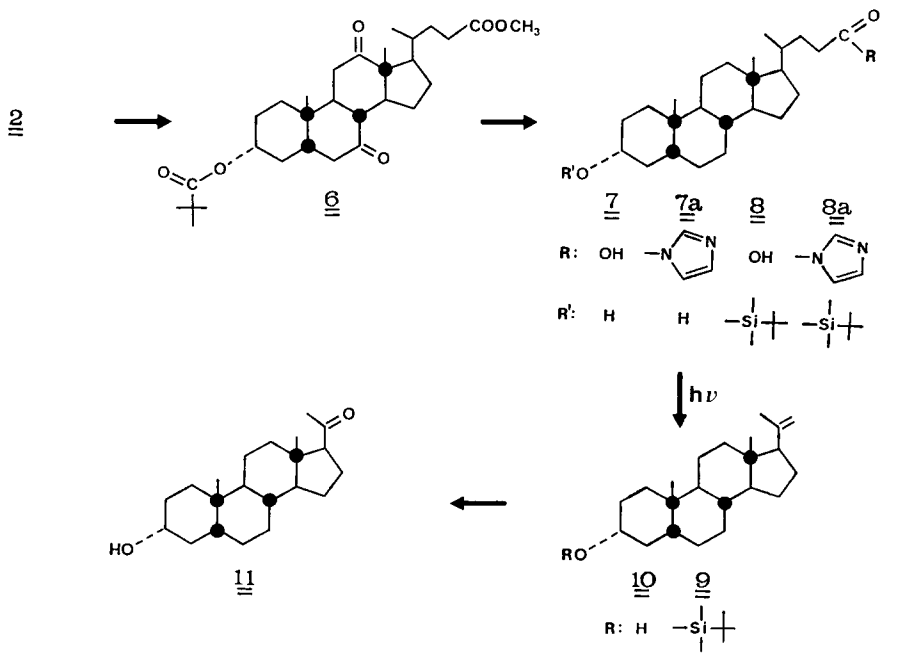
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c) G.Kruger; U.S. 3,647,829 (1972);
d) N.Tsuji, J.Susuki, M.Shiota, I.Takahashi, J.Org.Chem. 45 (1980), 2729
e) E.D'Incan, A.Loupy, A.Restelli, J.Seyden-Penne, P.Viout; Tetrahedron 38 (1982) 1755
8) D.Onken and D.Onken, Die Pharmazie 35 (1980) 193
9) R.E.Marker, R.B.Wagner, P.R.Ushafer, E.L.Wittbecker, D.P.J.Goldsmith, C.H.Ruof; J.Am.Chem.Soc. 69 (1947) 2167
10) L.Koppe, M.Becker; Ger. (East) 79481 (1971)
11) Fluka Feinchemikalien GmbH, Neu-Ulm
12) compound 3, m.p.=181-2°C; α_D^{25}=+26,8°($CHCl_3$,c=0.99); ^{1}H-NMR ($CDCl_3$):δ/ppm=0.61(s,3H, C-18 CH_3);0.87(d,3H,C-21 CH_3);0.91(s,3H,C-19 CH_3);3.91(s,4H,-O-CH_2-CH_2-O); IR (KBr) cm^{-1} 3220(ν_{st},C-OOH);2860(ν_{st},O-CH_2);1725(ν_{st},C=O);1095(ν_{stas},C-O-C);945(ν_{st}, C-OC)
13) H.B.Kagan, J.Jacques;Bull.Soc.Chim.France 1957, 699
14) H.A.Staab, M.Lüking, F.H.Dürr; Chem.Ber. 95 (1962) 1275
15) Shigeo Iwasaki; Helv.Chim.Acta 59 (1976) 2753
16) compound 4, colourless oil; α_D^{25}=+19.0° ($CHCl_3$,c=1.262); ^{1}H-NMR ($CDCl_3$):δ/ppm=0.53(s, 3H,C-18 CH_3);0.93(s,3H,C-19 CH_3);1.72(s,3H,C-21 CH_3);3.92(s,4H,-O-CH_2-CH_2-O-);4.69 and 4.82(2s,2H,C-20 CH_2)
17) Sigma Chemie GmbH, München
18) a) A.Butenandt, J.Schmidt; Chem.Ber. 67 (1934), 1901; b) F.Johnson, G.T.Newbold, F.S.Spring; J.Chem.Soc. 1954, 1302; c) U.Halpern; U.S. 3,475,464 (1969)
19) Huang-Minlon; J.Am.Chem.Soc. 71 (1949), 3301
20) compound 9, m.p.=143-45°C; α_D^{25}=+16.9° ($CHCl_3$,c=1.018) ^{1}H-NMR ($CDCl_3$):δ/ppm=0.53(s, 3H,C-18 CH_3);0.94(s,3H,C-19 CH_3);1.77(s,3H,C-21 CH_3);4.73 and 4.87(2s,2H,C-20 =CH_2); IR (KBr) cm^{-1} 3300(ν_{st},O-H);1030(ν_{st},CH-OH);880(ν_{oop},C=CH_2)
21) phyical constants and spectra were identical with those of an authentic sample (Sigma GmbH, München)
22) E.J.Corey, A.Venkateswarlu; J.Am.Chem.Soc. 94 (1972), 6190
23) compound 8, m.p.=196-98°C; α_D^{25}=+31.4° ($CHCl_3$,c=0.494); ^{1}H-NMR ($CDCl_3$):δ/ppm=0.07 (s,6H,Si-CH_3);0.64(s,3H,C-18 CH_3);0.92(s,15H,C-19 CH_3,C-21 CH_3 and Si-t-butyl);3.50 (br.s,1H,C-3 βH); IR (KBr) cm^{-1} 1700(ν_{st},C=O);1245(δ_{sy},Si-CH_3);830,770(γ,SiCH_3)
24) compound 10, m.p.=83-84°C; α_D^{25}=+22.7° ($CHCl_3$,c=1.008) ^{1}H-NMR ($CDCl_3$):δ/ppm=0.06(s, 6H,Si-CH_3);0.55(s,3H,C-18 CH_3);0.91(s,12H,C-19 CH_3,Si-t-butyl);1.25(s,3H,C-21 CH_3); 3.55(br.s.,1H,C-3 βH);4.71 and 4.84(s,2H,C-20 =CH_2); IR ($CHCl_3$ cm^{-1} 1640(ν_{st},C=C); 1250(ν_{sy},Si-CH_3);835,775(ν,Si-CH_3).

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