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Review

Natural Occurrence and Chemical Synthesis of Bile Alcohols, Higher Bile Acids, and Short Side Chain Bile Acids

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Both bile acids and bile alcohols, a subclass of steroids, are made from cholesterol as its major end metabolites by the liver of vertebrates. Their conjugates are the major constituents of the bile and possess a special function as an aid to intestinal lipid digestion and absorption.

The most common naturally occurring bile acids in mammals, birds, most snakes, and various teleostean fishes, are cholic acid, chenodeoxycholic acid, deoxycholic acid, and lithocholic acid. In addition to these 3α-, 7α-, or 12α-hydroxy derivatives of 5β-cholan-24-oic acid, a number of 5β-cholan-24-oic acids carrying a hydroxyl group at C-1, C-2, C-4, C-6, C-16, C-22, or C-23 position, a β-oriented hydroxyl group, or a keto group have been found in the bile, serum, urine and feces of these vertebrates. 5α-Cholan-24-oic acid derivatives occur as a high proportion of the bile acids in some lizards and in lesser amounts in various vertebrates.

Biles of evolutionarily primitive vertebrates such as some lizards, crocodiles, alligators, turtles, tortoises, all amphibians, certain bony fishes, sharks, and rays contain, in place of the C_{24} bile acid conjugates, other types of bile salts, sulfate esters of bile alcohols and unconjugated or taurine-conjugated bile acids with more than 24 carbon atoms (higher bile acids). Bile alcohols and higher bile acids have the C_{24} bile acid type of nuclear structure and all or part of the cholesterol type side chain in their carbon skeleton. Although the distribution of bile alcohols and higher bile acids in nature was long considered to be confined to the primitive vertebrates, it is now recognized that these compounds are accummulated in patients with inherited diseases related to abnormal cholesterol metabolism. They are present in trace amounts even in healthy humans. Furthermore, a few 4- or 5-cholen-24-oic acid derivatives and a few C_{22} and C_{23} bile acids with the shortened side chain have been found in biological fluids of healthy and diseased humans.

Several excellent reviews about the naturally occurring bile acids and bile alcohols have appeared[61, 74, 75, 101, 105, 183]. It should be mentioned, however, that there is no review covering all the known bile acids and bile alcohols including chemically synthetic derivatives. The present review is a detailed tabulation of bile alcohols, higher bile acids, and short side chain bile acids. Derivatives of 5α- and 5β-cholan-24-oic acids and of 4- and 5-cholen-24-oic acids are not included in this review. Natural occurrence and chemical synthesis of these C_{24} bile acids are the subject of our forthcoming review.

Bile Alcohols

Bile alcohols are here defined as neutral steroidal alcohols biochemically related bile acids.

Tables 1-6 list all the naturally occurring bile alcohols of established structure and most chemically derived C_{27}-C_{22} bile alcohols. Artifacts formed from native bile alcohol sulfates by alkaline hydrolysis, dehydro-derivatives having no hydroxyl group, esterified derivatives, and derivatives containing other elements than oxygen, e.g. nitrogen, sulfur, or halogens, are not included in the tables. Mono- and di-oxygenated cholestane derivatives, e.g. 7α-hydroxycholesterol, are not listed in the tables because they are usually called sterols rather than bile alcohols. Similarly, polyoxygenated steroids found in marine invertebrates and shark-repelling and ichthyotoxic steroids obtained from some fishes are also excluded.

The trivial names of bile alcohols, isolated from the bile of vertebrates other than humans, include as a prefix part of the Latin name of the genus of the animal from which they were first isolated. When both isomers differing in the configuration at C-5 are known, the prefix 5α or 5β is then used with the original name. For bile alcohols with epimeric hydroxyl groups for which there is no accepted trivial name, the prefix "epi" is used preceded by a number and a hyphen, indicating the position at which the epimeric hydroxyl group is present, e.g. 3-epimyxinol. For deoxy derivatives, the prefix "deoxy" will be used, preceded by a number and a hyphen, indicating the place where the hydroxyl group is missing, e.g. 26-deoxy-5β-ranol. Bile alcohols found only in the biological fluids of humans and unnatural bile alcohols have no trivial names; they are usually designated their systematic names.

Table 1. Hexa-oxygenated C_{27} bile alcohols

No.	Systematic name (Trivial name)	Natural source[a]	Synthetic source[b]
0101	5β-Cholestane-2β, 3α, 7α, 12α, 26,27-hexol (Arapaimol-B)	*Arapaima gigas*[78]	—[c]
0102	5β-Cholestane-3α, 7α, 12α, 23, 24, 25-hexol	CTX-U[226]	—
0103	5β-Cholestane-3α, 7α, 12α, 24, 25, 26-hexol	Human-U[82, 83], -S[84]; CTX-U[251]; LD-U[83]	0311[82]; 0312[82]
0104	(24R)-5β-Cholestane-3α, 7α, 12α, 24, 26, 27-hexol (Scymnol)	Sharks and rays[32, 111, 112, 121, 158]	CA[32]
0105	5α-Cholestane-3α, 7α, 12α, 25, 26, 27-hexol (5α-Dermophol)	Amphibians[136]	0325[137]
0106	5β-Cholestane-3α, 7α, 12α, 25, 26, 27-hexol (5β-Dermophol)	Amphibians[136]	0326[136]

a. All natural sources refer to bile, unless otherwise referred to specific source details, which are shown by the following abbreviations:U, urine; S, serum; F, feces; L, liver; AF, amniotic fluid; GC, gastric content; M, meconium; UCB, umbilical cord blood.
Diseases are shown by the following abbreviations:CTX, cerebrotendinous xanthomatosis; HS, hyper-sitosterole mia; HSDD, 3α-hydroxysteroid dehydrogenase deficiency; LD, liver diseases; ZS, Zellweger syndrome; CHO, cholestasis; RF, Refsum disease; COA, coprostanic acidemia; THD, thiolase deficiency; βOD, β-oxidation deficiency; IO, intestinal obstruction; NALD, neonatal adrenoleukodystrophy; IBDA, intrahepatic bile duct anomalies; IMA, intestinal malabsorption; SH, subdural hematoma.

b. Bile acids and bile alcohols having no trivial names are shown as their compound numbers which are given in the first column of each tables.
Abbreviations for bile acids and bile alcohols (systematic name or compound number in parenthese): CA, cholic acid (3α, 7α, 12α-trihydroxy-5β-cholan-24-oic acid); DCA, deoxycholic acid (3α, 12α-dihydroxy-5β-cholan-24-oic acid; CDCA, chenodeoxycholic acid (3α, 7α-dihydroxy-5β-cholan-24-oic acid); UDCA, ursodeoxycholic acid (3α, 7β- dihydroxy-5β-cholan-24-oic acid); HDCA, hyodeoxycholic acid (3α, 6α-dihydroxy-5β-cholan-24-oic acid); LCA, lithocholic acid (3α-hydroxy-5β-cholan-24-oic acid); 22-OH-CDCA, 22R-hydroxychenodeoxycholic acid (formerly haemulcholic acid, (22R)-3α, 7α, 22-trihydroxy-5β-cholan-24-oic acid)[99, 139]; 23-OH-CDCA, 23R-hydroxychenodeoxycholic acid (formerly phocaecholic acid, (23R)-3α, 7α, 23-trihydroxy-5β-cholan-24-oic acid)[208]; 6-OH-7-ODCA, 6α-hydroxy-7-oxodeoxycholic acid (3α, 6α, 12α-trihydroxy-7-oxo-5β-cholan-24-oic acid)[235]; ACA, allocholic acid (3α, 7α, 12α-trihydroxy-5α-cholan-24-oic acid)[185]; 7-EACA, 7-epiallocholic acid (3α, 7β, 12α-trihydroxy-5α-cholan-24-oic acid)[8]; NCA, norcholic acid (1204); NHDCA, norhyodeoxycholic acid (1213); NCDCA, norchenodeoxycholic acid (1214); NUDCA, norursodeoxycholic acid (1215); NDCA, nordeoxycholic acid (1216); NLCA, norlithocholic acid (1218); BNCA, bisnorcholic acid (1303); BNDCA, bisnordeoxychlic acid (1308); HoCA, homocholic acid (1107); HoCDCA, homochenodeoxycholic acid (1114); CAld, cholyl aldehyde (0613); CDCAld, chenodeoxycholyl aldehyde (0620); NCAld, norcholyl aldehyde (0624); BNCAld, bisnorcholyl aldehyde (0640); CY, 5α-cyprinol (0222); DECY, 27-deoxy-5α-cyprinol (0323); ANSC, anhydroscymnol (24, 26-epoxy-5β-cholestane-3α, 7α, 12α, 27-tetrol)[65]; ANCY, anhydro-5α-cyprinol (26, 27-epoxy-5α-cholestane-3α, 7α, 12α-triol)[90]; DNCT, (26, 27-dinor-5α-cholest-24-ene-3α, 7α, 12α-triol)[179]; TADNC, (3α, 7α, 12α-triformoxy-25-acetoxy-26, 27-dinor-5β-cholestan-24-one)[214].

c. not reported.

Table 2. Penta-oxygenated C_{27} bile alcohols

No.	Systematic name (Trivial name)	Natural source	Synthetic source
0201	5β-Cholestane-2β, 3α, 7α, 12α, 26-pentol (Arapaimol-A)	*Arapaima gigas*[78]; Frogs[14]	—
0202	5β-Cholestane-3α, 6α, 7β, 25, 26-pentol (ω-Trichechol)	Manatee[173]	—
0203	5β-Cholestane-3α, 6β, 7α, 25, 26-pentol (α-Trichechol)	Manatee[173]; Rat[86]	1105[256]
0204	5β-Cholestane-3α, 6β, 7β, 25, 26-pentol (β-Trichechol)	Manatee[173]	—
0205	(22R)-5β-Cholestane-3α, 7α, 12α, 22, 25-pentol	CTX[226], -U[226, 251]	BNCAld[135]
0206	(22S)-5β-Cholestane-3α, 7α, 12α, 22, 25-pentol	—	BNCAld[135]
0207	(22R, 25R)-5β-Cholestane-3α, 7α, 12α, 22, 26-pentol	—	0806[247]
0208	(22S, 25R)-5β-Cholestane-3α, 7α, 12α, 22, 26-pentol	—	0806[247]
0209	(23S)-5α-Cholestane-3α, 7α, 12α, 23, 25-pentol	CTX-U[149]	—
0210	(23R)-5β-Cholestane-3α, 7α, 12α, 23, 25-pentol	CTX-U[226]	0306[141]; 1104[103, 146]
0211	(23S)-5β-Cholestane-3α, 7α, 12α, 23, 25-pentol	CTX[104, 225, 226], -U[226, 251], -F[225, 226, 255]	0307[141]; 1104[103, 146]
0212	(23R)-5β-Cholestane-3α, 7α, 12α, 23, 26-pentol	—	0306[247]
0213	(23S)-5β-Cholestane-3α, 7α, 12α, 23, 26-pentol	—	0307[247]
0214	(24R)- and (24S)-5β-Cholestane-3α, 7α, 12α, 24, 25-pentols	Human[172], -S[84], -U[82, 83, 174]; CTX[104, 221, 225, 226], -U[226, 251], -F[221, 225, 226, 255]; HS-F, U[55] LD-U[83]	0405[44, 91]
0215	Cholest-5-ene-3β, 7α, 12α, 24, 25-pentol	HSDD[108]	—
0216	5α-Cholestane-3α, 7α, 12α, 24, 26-pentol (5α-Chimaerol)	White sucker[13]; Fishes[15]; Lungfish[6]	—
0217	5β-Cholestane-3α, 7α, 12α, 24, 26-pentol (5β-Chimaerol)	*Chimaera monstrosa*[33]; Sharks and rays[32, 112, 202]; Rat[86]; Human[172], -S[84], -U[82, 83]; CHO-U[107, 120]; LD-U[83]	ANSC[42]
0218	5α-Cholestane-3α, 7α, 12α, 25, 26-pentol (5α-Bufol)	Coelacanth[6, 142]; Lungfish[6]; Frogs[14, 240]; Newt[98]; Rat[86]	0403[98]
0219	5α-Cholestane-3β, 7α, 12α, 25, 26-pentol	Coelacanth[142]	0404[142]
0220	5β-Cholestane-3α, 7α, 12α, 25, 26-pentol (5β-Bufol)	Toads and frogs[14, 97, 161, 166, 201, 240, 257]; Rat[86]; Human[172], -S[84, 85], -U[82, 83, 174, 177]; CTX-U[226], -F[52]; CHO-U[107, 120]; HS-U, F[55]; LD-U[83, 177]	HoCA[146]; 0406[91]
0221	Cholest-5-ene-3β, 7α, 12α, 25, 26-pentol	HSDD[108]	—
0222	5α-Cholestane-3α, 7α, 12α, 26, 27-pentol (5α-Cyprinol)	Carp and related fishes[9, 15, 93, 94, 216]; White sucker[13]; Coelacanth[6, 142]; Lungfishes[6]; Giant salamander[5]; Frogs[14, 161, 197, 240]	—
0223	5α-Cholestane-3β, 7α, 12α, 26, 27-pentol (Latimerol)	Coelacanth[6, 10, 142]	—
0224	5β-Cholestane-3α, 7α, 12α, 26, 27-pentol (5β-Cyprinol)	Fishes[15, 43, 76, 95]; Toads and frogs[14, 131, 161, 240]; Human[172], -U[174]; CHO-U[106, 107]	CA[76, 92]

For abbreviations, see Table 1.

Table 3. Tetra-oxygenated C_{27} bile alcohols

No.	Systematic name (Trivial name)	Natural source	Synthetic source
0301	5β-Cholestane-3α, 6β, 7α, 26-tetrol	Manatee[173)]	—
0302	(22R)-5β-Cholestane-3α, 7α, 12α, 22-tetrol	—	BNCAld[165)]
0303	(22S)-5β-Cholestane-3α, 7α, 12α, 22-tetrol	—	BNCAld[165)]
0304	(23R)-5β-Cholestane-3α, 7α, 12α, 23-tetrol	CTX[104, 226)], -U[226, 251)], -F[140, 226, 255)]	0307[141)]; 0308[165)]
0305	(23S)-5β-Cholestane-3α, 7α, 12α, 23-tetrol	—	0308[165)]
0306	(23R)-5β-Cholest-25-ene-3α, 7α, 12α, 23-tetrol	—	NCAld[141)]
0307	(23S)-5β-Cholest-25-ene-3α, 7α, 12α, 23-tetrol	—	NCAld[141)]
0308	3α, 7α, 12α-Trihydroxy-5β-cholestan-23-one	—	NCA[165)]
0309	5α-Cholestane-3α, 7α, 12α, 24-tetrol	Fishes[15)]; Lungfish[6)]; Rabbit[193)]; Human[172)]; CTX[226)]	—
0310	(24R)- and (24S)-5β-Cholestane-3α, 7α, 12α, 24-tetrols	Rabbit[193)]; Human[172)]; CTX[104, 226)], -U[226)], -F[226, 255)]; HS-U, F[55)]	0313[180, 227)]; 0809[241)]; 0405[48)]
0311	(24R)-5β-Cholest-25-ene-3α, 7α, 12α, 24-tetrol	—	CAld[82)]
0312	(24S)-5β-Cholest-25-ene-3α, 7α, 12α, 24-tetrol	—	CAld[82)]
0313	3α, 7α, 12α-Trihydroxy-5β-cholestan-24-one	—	CA[227)]
0314	Cholest-5-ene-3β, 7α, 12α, 24-tetrol	HSDD[108)]	—
0315	5α-Cholestane-3α, 7α, 12α, 25-tetrol	CTX-U, F[226)]	0403[226)]
0316	5β-Cholestane-3α, 7α, 12α, 25-tetrol	Alligator[237)]; Rabbit[193)]; Human[172)], -S[157)], -L[200)]; CTX[104, 200, 221, 226)], -S[157)], -U[226, 251)], -F[221, 226, 255)], -L[200)]; HS-U, F[55)]	HoCA[44, 50, 116, 146, 207)]
0317	5β-Cholestane-3β, 7α, 12α, 25-tetrol	—	0319[53)]
0318	5β-Cholestane-3α, 7β, 12α, 25-tetrol	—	1110[226)]
0319	7α, 12α, 25-Trihydroxy-5β-cholestan-3-one	—	0316[116)]
0320	3α, 12α, 25-Trihydroxy-5β-cholestan-7-one	CTX[226)], -F[226)]	0316[226)]
0321	Cholest-5-ene-3β, 7α, 12α, 25-tetrol	HSDD[108)]	—
0322	7α, 12α, 25-Trihydroxycholest-4-en-3-one	—	0319[116)]
0323	5α-Cholestane-3α, 7α, 12α, 26-tetrol (27-Deoxy-5α-cyprinol)	Carp[96)]; Fishes[15)]; Lungfishes[6)]; Toads[97, 257)]; Frogs[14)]; Alligator[237)]; Rat[86)]	ANCY[90)]
0324	(25R)- and (25S)-5β-cholestane-3α, 7α, 12α, 26-tetrols	Toads and frogs[14, 97, 240, 257)]; Rat[86)]; Human[172)]; CHO-U[106, 107)]	0902[13, 51, 63, 130)]; 0406[48)]
0325	5α-Cholest-25-ene-3α, 7α, 12α, 27-tetrol	—	0909[137)]
0326	5β-Cholest-25-ene-3α, 7α, 12α, 27-tetrol	—	0910[136)]
0327	3α, 7α, 12α-Trihydroxy-5β-cholestan-26-al	—	0324[51)]; CAld[203)]
0328	7α, 12α, 26-Trihydroxy-5β-cholestan-3-one	—	0324[51)]
0329	7α, 12α-Dihydroxy-3-oxo-5β-cholestan-26-al	—	0324[51)]
0330	Cholest-5-ene-3β, 7α, 12α, 26-tetrol	HSDD[108)]	—
0331	5α-Cholestane-3α, 7α, 16α, 26-tetrol (3-Epimyxinol)	Hagfish[239)]	—
0332	5α-Cholestane-3β, 7α, 16α, 26-tetrol (Myxinol)	Hagfishes[11, 73, 239)]	—
0333	5β-Cholestane-3α, 7α, 24, 25-tetrol	—	0414[20, 164)]
0334	5β-Cholestane-3α, 7α, 24, 26-tetrol	Human[245)]	0917[245)]
0335	5β-Cholestane-3α, 7α, 25, 26-tetrol	Manatee[173)]; Human[245)]	0414[164)]
0336	Cholest-5-ene-3β, 7α, 25, 26-tetrol	HSDD[108)]	—
0337	5α-Cholestane-3α, 7α, 26, 27-tetrol	—	CY[161)]
0338	5β-Cholestane-3α, 7α, 26, 27-tetrol	Human[245)]	1005[245)]

For abbreviations, see Table 1.

Table 4. Tri-oxygenated C_{27} bile alcohols

No.	Systematic name (Trivial name)	Natural source	Synthetic source
0401	5α-Cholestane-3α, 7α, 12α-triol	—	0403[102)]
0402	5β-Cholestane-3α, 7α, 12α-triol	Human-L[200)]; CTX-F[200, 226)], -L[200)]	CA[26, 127)]; 0313[219, 227)]
0403	5α-Cholest-25-ene-3α, 7α, 12α-triol	—	DECY[98)]
0404	5α-Cholest-25-ene-3β, 7α, 12α-triol	—	0403[142)]
0405	5β-Cholest-24-ene-3α, 7α, 12α-triol	—	0316[44, 48, 91)]
0406	5β-Cholest-25-ene-3α, 7α, 12α-triol	CTX[200)]	0316[44, 48, 91)]
0407	7α, 12α-Dihydroxy-5α-cholestan-3-one	—	0401[102)]
0408	7α, 12α-Dihydroxy-5β-cholestan-3-one	—	0402[27)]
0409	3α, 12α-Dihydroxy-5β-cholestan-7-one	—	0402[63)]
0410	Cholest-4-ene-3α, 7α, 12α-triol	—	0411[102)]
0411	7α, 12α-Dihydroxycholest-4-en-3-one	—	0408[27, 102)]
0412	5β-Cholestane-3α, 7α, 24-triol	Human[172)]	0414[47)]
0413	5α-Cholestane-3α, 7α, 25-triol	—	1113[87)]
0414	5β-Cholestane-3α, 7α, 25-triol	Human[172)]	HoCDCA[40, 116)]
0415	5β-Cholestane-3β, 7α, 25-triol	—	0414[53)]
0416	7α, 25-Dihydroxy-5β-cholestan-3-one	—	0414[116)]
0417	5α-Cholestane-3α, 7α, 26-triol (3-Epi-16-deoxymyxinol)	Hagfish[239)]	DECY[239)]
0418	5β-Cholestane-3α, 7α, 26-triol	Human[172)]	0414[47)]
0419	5α-Cholestane-3β, 7α, 26-triol (16-Deoxymyxinol)	Hagfish[12, 239)]	Kryptogenin[196)]
0420	Cholest-5-ene-3β, 7α, 26-triol	HSDD[108)]	—
0421	7α, 25-Dihydroxycholest-4-en-3-one	—	0416[116)]

For abbreviations, see Table 1.

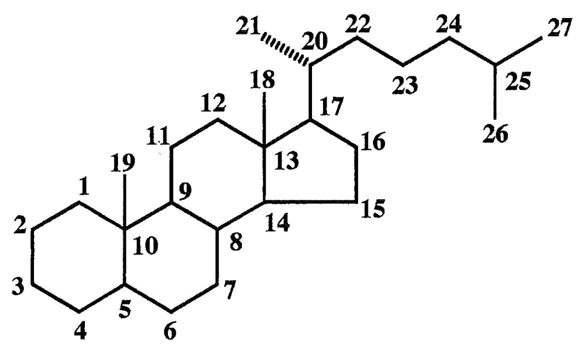

Fig. 1. Cholestane skeleton.

Bile alcohols with a cholestane skeleton are numbered as in Fig. 1. If one of the methyl groups attached to C–25 is substituted, it is assigned the lower number, C–26, as recommended by IUPAC-IUB Joint Commission on Biochemical Nomenclature[191)]. Hence, what is termed, mistakenly, as "5β-cholestane-3α,7α,12α, 27-tetrol" should be correctly called (25R)-5β-cholestane-3α,7α,12α,26-tetrol (III).

The occurrence of bile alcohols in nature was first demonstrated in 1898 by Hammarsten who found that the bile of the northern shark *Scymnus borealis* contains the sulfate ester of a neutral steroid named scymnol as its major constituent[65)]. The structure of scymnol eluded investigators for many years, and was verified by partial synthesis in 1962[32)]. The configuration of 24-hydroxyl group was finally determined in 1991 by means of X-ray diffraction analyses[112)]. Scymnol sulfate has been found in all elasmobranchii (sharks and rays) as their major bile salt, but has not been located in other natural sources[75)].

Table 5. C_{26} Bile alcohols

No.	Systematic name (Trivial name)	Natural source	Synthetic source
0501	24-Nor-5β-cholestane-3α, 7α, 12α, 23, 25-pentol	—	0509[45]
0502	24-Nor-5β-cholestane-3α, 7α, 12α, 23-tetrol	—	0509[49]
0503	24-Nor-5β-cholestane-3α, 7α, 12α, 25-tetrol	Rabbit[193]; Human[172]; CHO[133]	CA[45]
0504	24-Nor-5β-cholestane-3α, 7α, 12α, 26-tetrol	—	0510[49]
0505	(22R)-24-Nor-5β-cholestane-3α, 7α, 22, 25-tetrol	—	22-OH-CDCA[99]
0506	24-Nor-5β-cholestane-3α, 7α, 23, 25-tetrol	—	0513[163]
0507	24-Nor-5β-cholestane-3α, 7α, 25, 26-tetrol	—	0514[163]
0508	24-Nor-5β-cholestane-3α, 7α, 12α-triol	—	0503[45, 49]
0509	24-Nor-5β-cholest-23-ene-3α, 7α, 12α-triol	—	0503[45, 49]
0510	24-Nor-5β-cholest-25-ene-3α, 7α, 12α-triol	—	0503[45, 49]
0511	24-Nor-5β-cholestane-3α, 7α, 25-triol	—	CDCA[163]
0512	24-Nor-5β-cholestane-3α, 7β, 25-triol	—	UDCA[182]
0513	24-Nor-5β-cholest-23-ene-3α, 7α-diol	—	0511[163]
0514	24-Nor-5β-cholest-25-ene-3α, 7α-diol	—	0511[163]
0515	27-Nor-5β-cholestane-3α, 7α, 12α, 24, 25, 26-hexol	Human[172], -S[84], -U[82, 83]; CHO-U[120]; LD-U[83]	0523[172]
0516	27-Norcholestane-3α, 7α, 12α, 24, 25-pentol	Rat[86]; Human[172], -S[84, 85], -U[82, 83, 84, 119, 177]; CTX-U[226]; ZS[57]; CHO-U[107]; LD-U[83, 177]; HS-U, F[55]	CA[55]; 0529[174]
0517	27-Norcholest-5-ene-3β, 7α, 12α, 24, 25-pentol	HSDD[108]	—
0518	27-Nor-5α-cholestane-3α, 7α, 12α, 24, 26-pentol (5α-Ranol)	Frogs[14, 69, 72, 197, 240]	—
0519	(24R)-27-Nor-5β-cholestane-3α, 7α, 12α, 24, 26-pentol (5β-Ranol)	Frogs[14, 132, 161, 197, 240]	1101[132, 167]; 0523[145]
0520	(24S)-27-Nor-5β-cholestane-3α, 7α, 12α, 24, 26-pentol (24-Epi-5β-ranol)	—	1101[167]
0521	(24R)- and (24S)-27-Nor-5α-cholestane-3α, 7α, 12α, 24-tetrols (24-Epi-26-deoxy-5α-ranol and 26-Deoxy-5α-ranol)	Frogs[14, 197, 240]	0525[197]
0522	(24R)- and (24S)-27-Nor-5β-cholestane-3α, 7α, 12α, 24-tetrols (24-Epi-26-deoxy-5β-ranol and 26-Deoxy-5β-ranol)	Frogs[14, 197, 240]	0526[197]; 0523[145]
0523	(24R)- and (24S)-27-Nor-5β-cholest-25-ene-3α, 7α, 12α, 24-tetrols	Human[172]	CAld[145, 172]
0524	27-Nor-5β-cholestane-3α, 7α, 12α, 26-tetrol	—	1102[130]
0525	3α, 7α, 12α-Trihydroxy-27-nor-5α-cholestan-24-one	Bullfrog[198]	ACA[197]
0526	3α, 7α, 12α-Trihydroxy-27-nor-5β-cholestan-24-one	Bullfrog[198]; Human[172]; THD[39]; βOD[39]	CA[197]
0527	3α, 7α, 12α-Trihydroxy-27-nor-5β-cholestan-25-one	—	HoCA[201]
0528	27-Nor-5β-cholestane-3α, 7α, 12α-triol	—	0526[126]
0529	27-Nor-5β-cholest-24-ene-3α, 7α, 12α-triol	—	CAld[174]

For abbreviations, see Table 1.

Table 6. C_{25}, C_{24}, C_{23}, and C_{22} Bile alcohols

No.	Systematic name (Trivial name)	Natural source	Synthetic source
0601	26, 27-Dinor-5β-cholestane-3α, 7α, 12α, 24, 25-pentol	CHO[133]	TADNC[254]
0602	26, 27-Dinor-5α-cholestane-3α, 7α, 12α, 24-tetrol	Frogs[14]	—
0603	26, 27-Dinor-5β-cholestane-3α, 7α, 12α, 24-tetrol	Frogs[14]	0604[134]
0604	3α, 7α, 12α-Trihydroxy-26, 27-dinor-5β-cholestan-24-one	CHO[133]	CA[125]
0605	26, 27-Dinor-5β-cholestane-3α, 7α, 12α, 25-tetrol	—	HoCA[130]
0606	26, 27-Dinor-5β-cholestane-3α, 7α, 24, 25-tetrol	—	CDCA[88]
0607	26, 27-Dinor-5β-cholestane-3α, 7α, 12α-triol	—	0604[125]
0608	26, 27-Dinor-5β-cholestane-3α, 24, 25-triol	—	LCA[189]
0609	3α, 6α, 7α, 12α-Tetrahydroxy-5β-cholan-24-al	—	6-OH-7-ODCA[248]
0610	5α-Cholane-3α, 7α, 12α, 24-tetrol (5α-Petromyzonol)	Lamprey[77]; Lungfishes[6]	ACA[77]
0611	5β-Cholane-3α, 7α, 12α, 24-tetrol (5β-Petromyzonol)	Lungfish[6]; Human[172]	CA[150, 166, 250]
0612	3α, 7α, 12α-Trihydroxy-5α-cholan-24-al	—	DNCT[198]
0613	3α, 7α, 12α-Trihydroxy-5β-cholan-24-al (Cholyl aldehyde)	—	0601[254]; CA[63, 241]
0614	(23R)-5β-Cholane-3α, 7α, 23, 24-tetrol	Human[172]	23-OH-CDCA[172]
0615	5β-Cholane-3α, 6α, 24-triol	—	HDCA[150]
0616	5β-Cholane-3α, 7α, 12α-triol	—	CA[125]
0617	5β-Cholane-3α, 7α, 24-triol	—	CDCA[148]
0618	5β-Cholane-3α, 7β, 24-triol	—	UDCA[148]
0619	5β-Cholane-3α, 12α, 24-triol	—	DCA[150, 250]
0620	3α, 7α-Dihydroxy-5β-cholan-24-al (Chenodeoxycholyl aldehyde)	—	0606[88]
0621	5β-Cholane-3α, 24-diol	—	LCA[150, 250]
0622	3α-Hydroxy-5β-cholan-24-al (Lithocholyl aldehyde)	—	0608[189]
0623	24-Nor-5β-cholane-3α, 7α, 12α, 22, 23-pentol	—	0634[135]
0624	3α, 7α, 12α-Trihydroxy-24-nor-5β-cholan-23-al (Norcholyl aldehyde)	—	NCA[141]; CA[223]
0625	24-Nor-5β-cholane-3α, 7α, 12α, 23-tetrol	—	NCA[150]
0626	24-Nor-5β-cholane-3α, 7α, 22, 23-tetrol	—	0636[139]
0627	24-Nor-5β-cholane-3α, 7β, 22, 23-tetrol	—	0637[143]
0628	24-Nor-5β-cholane-3α, 12α, 22, 23-tetrol	—	0638[143]
0629	24-Nor-5β-cholane-3α, 6α, 23-triol	—	NHDCA[150]
0630	24-Nor-5β-cholane-3α, 7α, 12α-triol	—	NCA[153]
0631	24-Nor-5β-cholane-3α, 7α, 23-triol	—	NCDCA[150]
0632	24-Nor-5β-cholane-3α, 7β, 23-triol	—	NUDCA[150]
0633	24-Nor-5β-cholane-3α, 12α, 23-triol	—	NDCA[150]
0634	24-Nor-5β-chol-22-ene-3α, 7α, 12α-triol	—	CA[36, 135]
0635	24-Nor-5β-chol-22-ene-3α, 6α-diol	—	HDCA[36]
0636	24-Nor-5β-chol-22-ene-3α, 7α-diol	—	CDCA[36, 139]
0637	24-Nor-5β-chol-22-ene-3α, 7β-diol	—	UDCA[36]
0638	24-Nor-5β-chol-22-ene-3α, 12α-diol	—	DCA[36]
0639	3α-Hydroxy-24-nor-5β-cholan-23-al	—	LCA[212, 253]
0640	3α, 7α, 12α-Trihydroxy-23, 24-dinor-5β-cholan-22-al (Bisnorcholyl aldehyde)	—	0623[135]
0641	3α, 7α-Dihydroxy-23, 24-dinor-5β-cholan-22-al (Bisnorchenodeoxycholyl aldehyde)	—	0626[139]
0642	3α, 7β-Dihydroxy-23, 24-dinor-5β-cholan-22-al (Bisnorursodeoxycholyl aldehyde)	—	0627[143]
0643	3α, 12α-Dihydroxy-23, 24-dinor-5β-cholan-22-al (Bisnordeoxycholyl aldehyde)	—	0628[143]
0644	3α-Hydroxy-23, 24-dinor-5β-cholan-22-al	—	LCA[253]

For abbreviations, see Table 1.

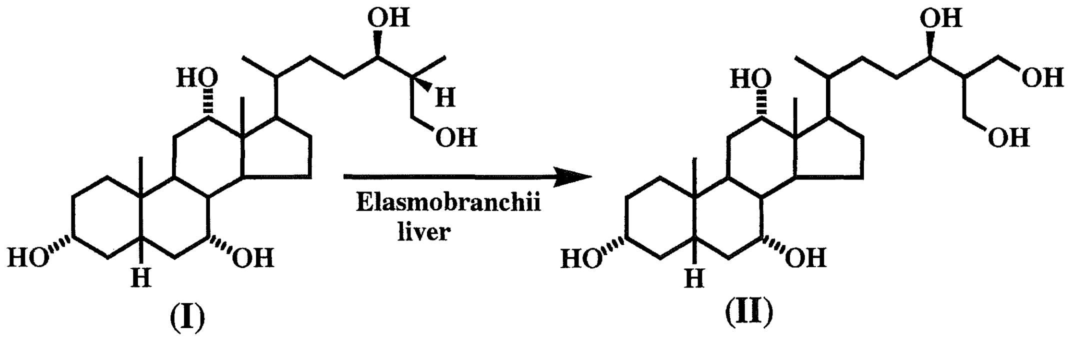

Fig. 2. Postulated structural relationship between 5β-chimaerol (I) and scymnol (II).

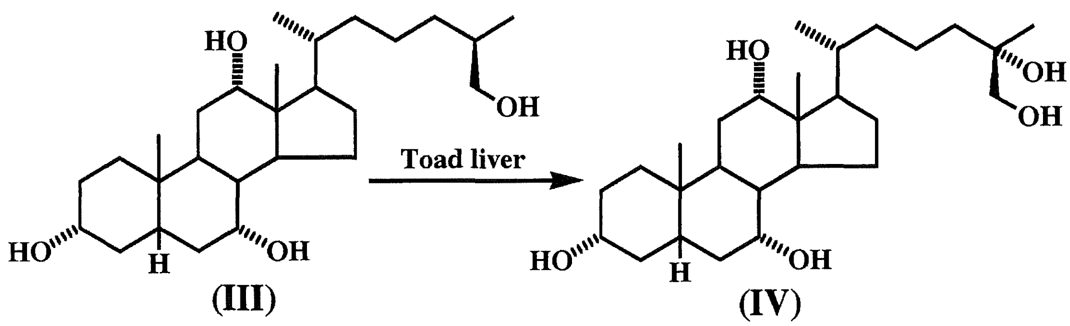

Fig. 3. Postulated structural relationship between (25R)-5β-cholestane-3α,7α,12α,26--tetrol (III) and 5β-bufol (IV).

5β-Chimaerol sulfate is the chief bile salt of *Chimaera monstrosa*[33] and a minor companion of scymnol sulfate in the bile of elasmobranchii[112, 202]. 5β-Chimaerol or its isomer with respect to C–24 and/or C–25 position has also been found in human bile[172] and urine[82, 83]. The stereochemistry of the side chain of 5β-chimaerol remains unresolved, but the configuration at C–25 has been suggested as S on the basis of the data from molecular rotation contribution studies[33]. The structural relationship between scymnol and 5β-chimaerol (the latter is the 27-deoxy derivative of the former) as well as the co-existence of both bile alcohols in elasmobranchii bile and probably also in *Chimaera monstrosa* bile[74] suggests that 5β-chimaerol (I) is the biosynthetic precursor of scymnol (II); hence the configuration at C–24 of 5β-chimaerol (I) should be the same, namely R, as that at C–24 of scymnol (II) (Fig. 2).

A principal bile alcohol of the white sucker *Catostomus commersoni* has the structure 5α-cholestane-3α, 7α, 12α, 24, 26-pentol, whose configuration at C–24 and C–25 was assumed to be the same as those of 5β-chimaerol, and named 5α-chimaerol[13].

A number of 26-hydroxylated and 25, 26-dihydroxylated cholestane derivatives have been found not only in primitive vertebrates but also in mammals including humans. However, the configuration at C–25 of most of these bile alcohols is still undetermined. In biosynthetic experiments using radioactive mevalonate of 5β-bufol in the toad *Bufo vulgaris formosus*, it was shown that the terminal hydroxyl-bearing carbon atom (C–26) of 5β-bufol is derived from C–3′ of mevalonate[162]. This indicates that in the biosynthesis of 5β-bufol the hydroxylation at the end methyl group of the cholesterol side chain is stereospecific, and the configuration at C–25 of 5β-cholestane-3α, 7α, 12α, 26-tetrol, the direct precursor of 5β-bufol, is R. (25R)-5β-Cholestane-3α, 7α, 12α, 26-tetrol (III) has been recognized as an intermediate in the biosynthetic sequence between cholesterol and cholic acid in mammals[28]. Thus, until the formation of (25R)-5β-cholestane-3α, 7α, 12α, 26-tetrol (III), the pathway for the synthesis of 5β-bufol (IV) in the toad is the same as that for the synthesis of cholic acid in mammals. If 25-hydroxylation of (25R)-5β-cholestane-3α, 7α, 12α, 26-tetrol (III) takes place by the direct dis-

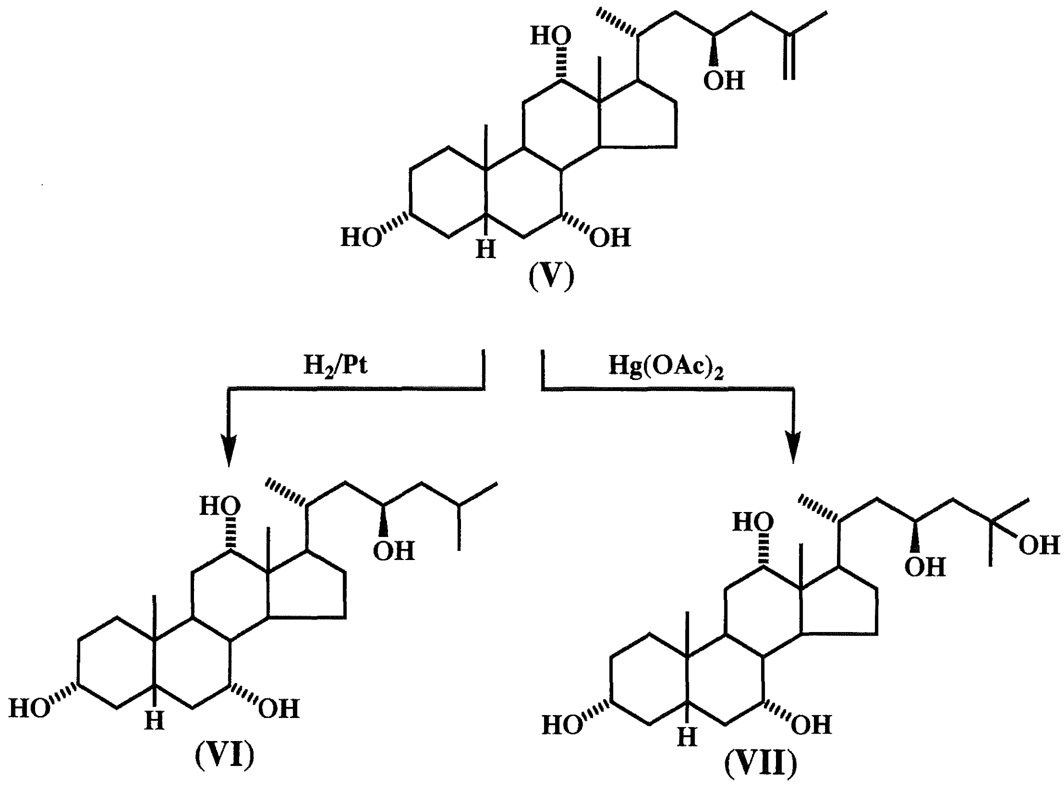

Fig. 4. Structural relationship of (23S)-5β-cholest-25-ene-3α,7α,12α,23-tetrol (V), and (23R)-5β-cholestane-3α, 7α, 12α, 23-tetrol (VI) and (23S)-5β-cholestane-3α,7α,12α,23,25-pentol (VII).

placement mechanism with retention of the configuration, as with hydroxylation of steroids by mixed function oxidases, the configuration at C–25 of 5β-bufol (IV) could be assigned as S (Fig. 3).

Cerebrotendinous xanthomatosis (CTX) is a rare inherited disease caused by an inborn error of cholesterol catabolism and is characterized by accumulation of bile alcohols[221)]. The absolute configuration at C–23 of 5β-cholestane-3α, 7α, 12α, 23-tetrol (VI), one of the bile alcohols isolated from the bile, urine, and feces of patients with CTX, was determined as R by X-ray crystallography[140)]. The 23S-epimer has not yet been detected in nature.

One of two stereoisomers at C–23 of 5β-cholestane-3α, 7α, 12α, 23, 25-pentol is a chief bile alcohol of the urine from CTX patients[226, 251)], and a second or a third bile alcohol of the bile and feces[104, 225, 226)]. The configuration at C–23 of the 23, 25-pentol (VII) was tentatively assigned as S [the same as that at C–23 of the naturally occurring (23R)-5β-cholestane-3α, 7α, 12α, 23-tetrol (VI)] on the basis of optical rotation differences[103)]. However, the opposite configuration at C–23 of the 23, 25-pentol (VII) was assigned by a circular dichroism study[46)]. Definite assignment of the 23S configuration of 5β-cholestane-3α,7α,12α,23,25-pentol (VII) was made by the conversion of a key intermediate, (23S)-5β-cholest-25-ene-3α,7α,12α,23-tetrol (V), to either the 23,25-pentol (VII) or the bile alcohol of known absolute configuration, (23R)-5β-cholestane-3α,7α,12α,23-tetrol (VI) (Fig. 4)[141)]. (23R)-5β-Cholestane-3α,7α,12α,23,25-pentol was detected only in the urine of a CTX patient in a trace amount[226)].

Recently, a bile alcohol isolated from the urine of CTX patients was identified as 5α-cholestane-3α,7α,12α,23,25-pentol[149)]. The configuration at C–23 of the 5α-bile alcohol was deduced as S by the comparison of its ^{13}C-nuclear magnetic resonance spectrum with those of (23R)- and (23S)-5β-cholestane-3α,7α,12α,23,25-pentols.

5β-Ranol, a principal bile alcohol of the bullfrog, *Rana catesbeiana*, was identified as (24R)-27-nor-5β-cholestane-3α,7α,12α,24,26-pentol (XI)[145, 167)]. However, the 24S-epimer (XII) of 5β-ranol (XI) could not be detected in the bullfrog bile, though both stereoisomers at C–24 of 27-nor-5β-cholestane-3α,7α,12α,24-tetrol, 26-deoxy-5β-ranol (IX) and 24-epi-26-deoxy-5β-ranol (X) were found in this bile[197)]. The bile alcohol pattern of the bullfrog bile is consistent with the results from the

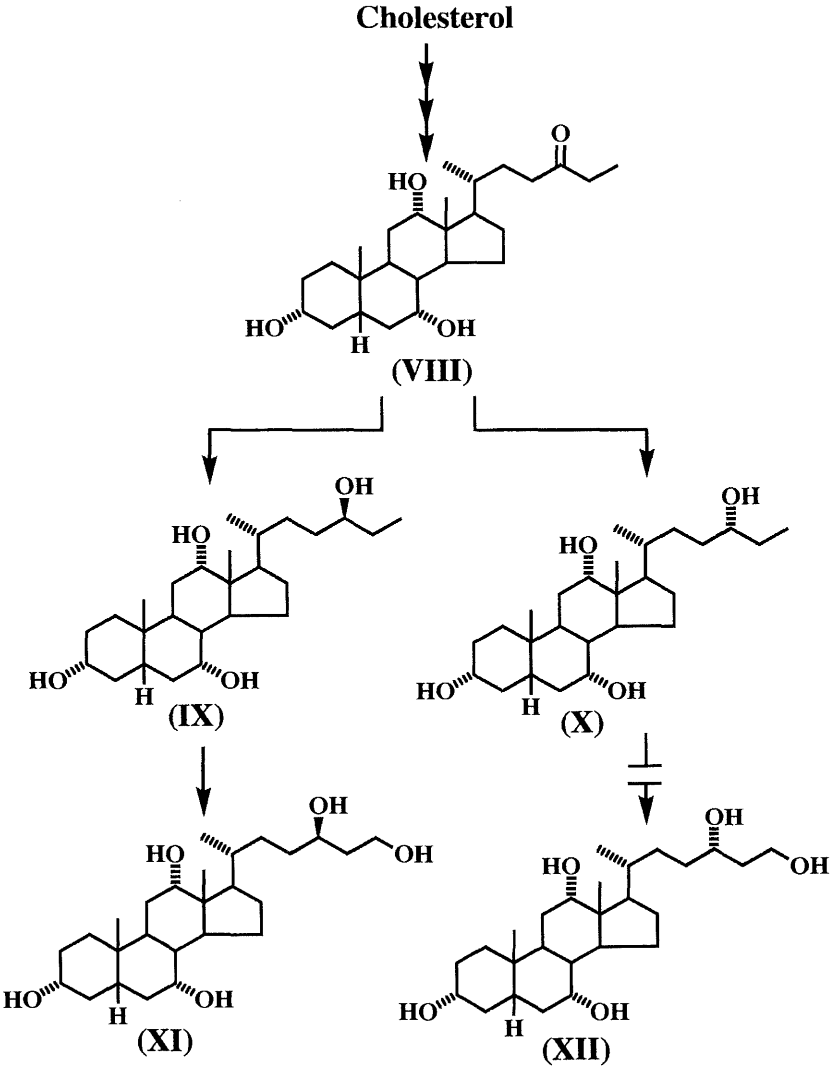

Fig. 5. Biosynthetic route of C_{26} bile alcohols in bullfrog. VIII, 3α,7α,12α-trihydroxy-27-nor-5β-cholestan-24-one; IX, 26-deoxy-5β-ranol [(24S)-27-nor-5β-cholestane-3α,7α,12α,24-tetrol]; X, 24-epi-26-deoxy-5β-ranol [(24R)-27-nor-5β-cholestane-3α,7α,12α,24-tetrol]; XI, 5β-ranol [(24R)-27-nor-5β-cholestane-3α,7α,12α,24,26-pentol]; XII, 24-epi-5β-ranol [(24S)-27-nor-5β-cholestane-3α,7α,12α,24,26-pentol].

biosynthetic experiments of 5β-ranol (XI), which showed that in the bullfrog 3α, 7α, 12α-trihydroxy-27-nor-5β-cholestan-24-one (VIII) formed from cholesterol is converted into both 26-deoxy-5β-ranol (IX) and 24-epi-26-deoxy-5β-ranol (X), and only 26-deoxy-5β-ranol (IX) can be hydroxylated at C–26 to give 5β-ranol (XI), but not 24-epi-26-deoxy-5β-ranol (X) to 24-epi-5β-ranol (XII) (Fig. 5)[199].

Higher Bile Acids

Higher bile acids are here defined as higher homologs with an extended side chain of C_{24} bile acids.

Tables 7–11 list all the naturally occurring higher bile acids of established structure and most chemically derived higher bile acids. Steroidal acids found in natural sources other than vertebrates, e.g. plants and invertebrates, chemically synthesized bile acids carrying no hydroxyl group, and esterified derivatives, are not included in the tables.

Higher bile acids are usually designated their systematic names, because they have no trivial names except with arapaimic acid and varanic acid.

Table 7. C_{29} and C_{28} Bile acids

No.	Systematic name	Natural source	Synthetic source
0701	3α, 7α, 12α, 24-Tetrahydroxy-24-ethyl-5β-cholestan-26-oic acid	—	0526[188]
0702	3α, 7α, 12α-Trihydroxy-24-ethyl-5β-cholestan-26-oic acid	—	0701[188]
0703	3α, 7α, 12α-Trihydroxy-24-carboxymethyl-5β-cholestan-26-oic acid	—	NCA[114]
0704	3α, 7α, 12α-Trihydroxy-27-carboxymethyl-5β-cholestan-26-oic acid	ZS[39, 59, 123, 205], -S[38, 39, 59, 122, 123, 205, 220], -U[39, 59, 205]; RF-S[38]; COA[205], -S[114, 205], -U[115, 205]	CAld[206]
0705	3α, 7α, 12α-Trihydroxy-24-ethyl-5β-cholestane-26, 27-dioic acid	—	NCA[114]
0706	3α, 7α-Dihydroxy-24-ethyl-5β-cholestan-26-oic acid	Sitosterol-fed monkey-F[159]	—
0707	3α-Hydroxy-24-ethyl-5β-cholestan-26-oic acid	Sitosterol-fed monkey-F[159]	—
0708	3β-Hydroxy-24-ethylcholest-5-en-26-oic acid	Sitosterol-fed monkey-F[159]	—
0709	3α, 7α, 12α, 24-Tetrahydroxy-24-methyl-5β-cholestan-26-oic acid	Toad[242]	0604[89]
0710	3α, 7α, 12α-Trihydroxy-24-methyl-5β-cholestan-26-oic acid	Bullfrog[198]	0711[89]
0711	3α, 7α, 12α-Trihydroxy-24-methyl-5β-cholest-23-en-26-oic acid	—	0709[89]
0712	3α, 7α, 12α-Trihydroxy-5β-cholestane-24-carboxylic acid	—	0313[100]
0713	3α, 7α, 12α-Trihydroxy-5α-cholest-22-ene-24-carboxylic acid	Toad[242]	—
0714	3α, 7α, 12α-Trihydroxy-5β-cholest-22-ene-24-carboxylic acid	Toad[228, 242]	—
0715	(25R)-3α, 7α, 12α-Trihydroxy-5β-cholestane-26-carboxylic acid	—	CA[31]
0716	(25S)-3α, 7α, 12α-Trihydroxy-5β-cholestane-26-carboxylic acid	—	CA[31]

For abbreviations, see Table 1.

Table 8. Tetra-oxygenated C_{27} bile acids

No.	Systematic name (Trivial name)	Natural source	Synthetic source
0801	1β, 3α, 7α, 12α-Tetrahydroxy-5β-cholestan-26-oic acid	Alligator[147]; ZS-U[220, 246]	—
0802	2β, 3α, 7α, 12α-Tetrahydroxy-5β-cholestan-26-oic acid (Arapaimic acid)	*Arapaima gigas*[78]	—
0803	3α, 6α, 7α, 12α-Tetrahydroxy-5β-cholestan-26-oic acid	ZS-S[122], -U[246, 248]	0804[248]
0804	3α, 6α, 7α, 12α-Tetrahydroxy-5β-cholest-24-en-26-oic acid	—	0609[248]
0805	(22R)-3α, 7α, 12α, 22-Tetrahydroxy-5β-cholestan-26-oic acid	ZS-U[246, 247]	—
0806	(22S, 25R)-3α, 7α, 12α, 22-Tetrahydroxy-5β-cholestan-26-oic acid	Turtles[4, 62, 79, 252]	—
0807	(23R)-3α, 7α, 12α, 23-Tetrahydroxy-5β-cholestan-26-oic acid	ZS-U[246, 247]	—
0808	3α, 7α, 12α, 24-Tetrahydroxy-5α-cholestan-26-oic acid	Bullfrog[198]	0612[198]
0809	(24R, 25R)-, (24R, 25S)-, (24S, 25R)-, and (24S, 25S)-3α, 7α, 12α, 24-Tetrahydroxy-5β-cholestan-26-oic acids (Varanic acid)	Toad[242]; Frogs[161, 198, 243]; Alligator[147]; Lizards[1, 69]; Human[182]; ZS[39, 205], -S[38, 39, 122, 123, 220], -U[68, 123, 175, 181, 220, 246]; COA[205]; THD[39], -S[39]; βOD[39], -S[39]	CAld[23, 109, 152, 241]
0810	3α, 7α, 12α, 25-Tetrahydroxy-5β-cholestan-26-oic acid	ZS[39], -S[38, 39], -U[175, 220]; RF-U[175]; IO-GC[37]; THD[39], -S[39]; βOD[39], -S[39]	CA[41]
0811	3α, 7α, 12α, 26-Tetrahydroxy-5α-cholestan-27-oic acid	Bullfrog[198]	0909[198]
0812	3α, 7α, 12α, 26-Tetrahydroxy-5β-cholestan-27-oic acid	Toad and frogs[198, 240, 257]; Alligator[147]; Human[182]; ZS[39], -S[38, 39], -U[175, 246]; RF-S[38], -U[175]; THD[39], -S[39]; βOD[39], -S[39]	0910[240]
0813	3α, 7α, 12α, 26-Tetrahydroxy-5β-cholest-23-en-27-oic acid	Toad[257]	—

For abbreviations, see Table 1.

Table 9. Tri-oxygenated C_{27} bile acids

No.	Systematic name	Natural source	Synthetic source
0901	3α, 7α, 12α-Trihydroxy-5α-cholestan-26-oic acid	Coelacanth[142]; Toads and frogs[161, 198, 240, 242, 257]; Alligator[147]; Iguana[204]; Turtle*	DECY[117]
0902	(25R)- and (25S)-3α, 7α, 12α-Trihydroxy-5β-cholestan-26-oic acids	Toads and frogs[14, 154, 161, 171, 178, 198, 240, 242, 243, 257]; Alligator[22, 25, 70, 147]; -F[238]; Crocodile[70, 184]; Lizard[1]; Turtle*; Kite[160]; Baboon[222]; Human[24, 35, 182]; ZS[39, 59, 123, 187, 205], -S[38, 39, 59, 64, 122, 123, 187, 205, 220, 249], -U[68, 123, 181, 205, 220, 246], -F[205], -AF[231]; RF-S[38, 209]; THD[39], -S[39]; NALD-AF[231]; IBDA[58, 67], -S, -U, -F[67]; COA[205], -S, -U, -F[205]; βOD[39], -S[39]; IO-GC[37]	NCA[155]; CA[34]; HoCA[21, 22]; 0908[63]; 0715[31]; 0716[31]
0903	3β, 7α, 12α-Trihydroxy-5α-cholestan-26-oic acid	Coelacanth[142]	0911[142]
0904	3β, 7α, 12α-Trihydroxy-5β-cholestan-26-oic acid	Alligator-F[238]	—
0905	3α, 7β, 12α-Trihydroxy-5β-cholestan-26-oic acid	Alligator[147]	0914[147]
0906	3α, 7α, 12α-Trihydroxy-5α-cholest-23-en-26-oic acid	Toads[242, 257]	—
0907	(25R)-3α, 7α, 12α-Trihydroxy-5β-cholest-23-en-26-oic acid	Toads[80, 81, 242, 257]; Lizard[1]; THD[39]	—
0908	(24E)- and (24Z)-3α, 7α, 12α-Trihydroxy-5β-cholest-24-en-26-oic acids	Lizard[1]; Human[182]; THD[39], -S[39]	CAld[63, 110, 241]
0909	3α, 7α, 12α-Trihydroxy-5α-cholestane-26, 27-dioic acid	—	CY[137, 198]
0910	3α, 7α, 12α-Trihydroxy-5β-cholestane-26, 27-dioic acid	—	CA[136, 240]
0911	7α, 12α-Dihydroxy-3-oxo-5α-cholestan-26-oic acid	Alligator[237]	DECY[142]
0912	7α, 12α-Dihydroxy-3-oxo-5β-cholestan-26-oic acid	Alligator[147, 237]	0902[147]
0913	7β, 12α-Dihydroxy-3-oxo-5β-cholestan-26-oic acid	Alligator[147]	—
0914	3α, 12α-Dihydroxy-7-oxo-5β-cholestan-26-oic acid	Alligator[147, 237]	0902[63, 147]
0915	3α, 7α-Dihydroxy-12-oxo-5α-cholestan-26-oic acid	—	0901[117]
0916	3β, 7α, 12α-Trihydroxycholest-5-en-26-oic acid	HSDD[108]	—
0917	3α, 7α, 24-Trihydroxy-5β-cholestan-26-oic acid	Lizard[1]; ZS-S[122, 123], -U[123]	CDCAld[245]
0918	3α, 12α, 22-Trihydroxy-5β-cholestan-26-oic acid	Turtle[79]	0806*

*. Our unpublished observation. For abbreviations, see in Table 1.

Table 10. Di- and mono-oxygenated C_{27} bile acids

No.	Systematic name	Natural source	Synthetic source
1001	3α, 7α-Dihydroxy-5α-cholestan-26-oic acid	—	0915[117]
1002	3α, 7α-Dihydroxy-5β-cholestan-26-oic acid	Alligator[56, 147], -F[238]; Kite[160]; Human[66]; ZS[58, 59, 123, 187], -S[38, 59, 122, 123, 187, 205, 220, 249], -U[59, 68, 123, 181, 205, 246], -F[205], -AF[231]; NALD-AF[231]; RF-S[38]; COA[205], -S, -U, -F[205]	CDCA[34, 56, 66, 138]; HoCDCA[21]; 0902[25]; 1004[88]
1003	3α, 7α-Dihydroxy-5β-cholest-23-en-26-oic acid	Lizard[1]	—
1004	3α, 7α-Dihydroxy-5β-cholest-24-en-26-oic acid	Lizard[1]	CDCA[88, 110]
1005	3α, 7α-Dihydroxy-5β-cholestane-26, 27-dioic acid	—	CDCA[245]
1006	3β, 7α-Dihydroxy-5α-cholestan-26-oic acid	—	Kryptogenin[192]
1007	7α-Hydroxy-3-oxo-5α-cholestan-26-oic acid	—	Kryptogenin[192]
1008	3β, 7α-Dihydroxycholest-5-en-26-oic acid	Human-S[16, 17]; HSDD[108]; LD-S[18]; IMA-S[17]	—
1009	3α, 7β-Dihydroxy-5β-cholestan-26-oic acid	Alligator[147], -F[238]	1010[147]
1010	3α, 7β-Dihydroxy-5β-cholest-24-en-26-oic acid	—	UDCA[147]
1011	3β, 7β-Dihydroxy-5β-cholestan-26-oic acid	Alligator-F[238]	—
1012	7α-Hydroxy-3-oxocholest-4-en-26-oic acid	Human-S[16, 17]; LD-S[18]; IMA-S[17]; SH-S[194]	—
1013	3α, 12α-Dihydroxy-5β-cholestan-26-oic acid	Alligator[147, 237], -F[238]	DCA[34, 56]; 1014[147]
1014	3α, 12α-Dihydroxy-5β-cholest-24-en-26-oic acid	—	DCA[110, 147]
1015	3β, 12α-Dihydroxy-5β-cholestan-26-oic acid	Alligator-F[238]	—
1016	3α, 7α-Dihydroxy-24-methyl-27-nor-5β-cholestan-26-oic acid	—	CDCA[138]
1017	3α-Hydroxy-5β-cholestan-26-oic acid	Alligator-F[238]; ZS-S[205]; COA-S[114, 205]	LCA[34]; 1019[189]
1018	3β-Hydroxy-5β-cholestan-26-oic acid	Alligator-F[238]	
1019	3α-Hydroxy-5β-cholest-24-en-26-oic acid	—	LCA[110, 189]
1020	3β-Hydroxycholest-5-en-26-oic acid	Human-S[16, 17]; ZS[205], -S[205]; IMA-S[17]; COA[205], -S[114, 205]; LD-S[18]	—

For abbreviations, see Table 1.

Table 11. C_{26} and C_{25} Bile acids

No.	Systematic name (Trivial name)	Natural source	Synthetic source
1101	(24R)- and (24S)-3α, 7α, 12α, 24-Tetrahydroxy-27-nor-5β-cholestan-26-oic acids	—	CAld[167]
1102	3α, 7α, 12α-Trihydroxy-27-nor-5β-cholestan-26-oic acid	—	CA[31, 129]; NCA[128]
1103	3α, 7α, 12α-Trihydroxy-24-nor-5β-cholestan-26-oic acid	—	CA[54]
1104	3α, 7α, 12α, 23-Tetrahydroxy-26, 27-dinor-5β-cholestan-25-oic acid	—	NCAld[103, 146]
1105	3α, 6β, 7α-Trihydroxy-26, 27-dinor-5β-cholestan-25-oic acid	—	1122[256]
1106	3α, 7α, 12α-Trihydroxy-26, 27-dinor-5α-cholestan-25-oic acid (Allohomocholic acid)	Bullfrog*	ANCY[90]
1107	3α, 7α, 12α-Trihydroxy-26, 27-dinor-5β-cholestan-25-oic acid (Homocholic acid)	Bullfrog*	CA[31, 126, 207]
1108	3β, 7α, 12α-Trihydroxy-26, 27-dinor-5β-cholestan-25-oic acid	—	1111[213]
1109	3α, 7β, 12α-Trihydroxy-26, 27-dinor-5α-cholestan-25-oic acid	—	7-EACA[9]
1110	3α, 7β, 12α-Trihydroxy-26, 27-dinor-5β-cholestan-25-oic acid	—	1112[168]
1111	7α, 12α-Dihydroxy-3-oxo-26, 27-dinor-5β-cholestan-25-oic acid	—	HoCA[213]
1112	3α, 12α-Dihydroxy-7-oxo-26, 27-dinor-5β-cholestan-25-oic acid	—	HoCA[168]
1113	3α, 7α-Dihydroxy-26, 27-dinor-5α-cholestan-25-oic acid	—	1117[87]
1114	3α, 7α-Dihydroxy-26, 27-dinor-5β-cholestan-25-oic acid (Homochenodeoxycholic acid)	—	CDCA[40]
1115	3α, 7β-Dihydroxy-26, 27-dinor-5β-cholestan-25-oic acid (Homoursodeoxycholic acid)	—	UDCA[168]
1116	3α, 7β-Dihydroxy-26, 27-dinor-5β-cholest-11-en-25-oic acid	—	1110[168]
1117	7α-Hydroxy-3-oxo-26, 27-dinor-5α-cholestan-25-oic acid	—	HoCDCA[87]
1118	7α-Hydroxy-3-oxo-26, 27-dinor-5β-cholestan-25-oic acid	—	HoCDCA[87, 116]
1119	7α-Hydroxy-3-oxo-26, 27-dinorcholest-4-en-25-oic acid	—	1118[116]
1120	3α-Hydroxy-7-oxo-26, 27-dinor-5β-cholestan-25-oic acid	—	HoCDCA[169]
1121	3α-Hydroxy-26, 27-dinor-5β-cholestan-25-oic acid (Homolithocholic acid)	—	1120[169]
1122	3α-Hydroxy-26, 27-dinor-5β-cholest-6-en-25-oic acid	—	CDCA[256]

*. Our unpublished observation. For abbreviations, see Table 1.

The occurrence of higher bile acids in nature was first demonstrated in 1934 by Shimizu and Oda who isolated a major bile acid from the bile of the toad, *Bufo vulgaris formosus*, to which they assigned the formula $C_{28}H_{46}O_5$, and named it "trihydroxybufosterocholenic acid"[228]. Although the nuclear structure (cholic acid type) and location of the double bond (between C–22 and C–23) of trihydroxybufosterocholenic acid (XIII) were elucidated in 1936 from the fact that it gave bisnorcholic acid (XIV) upon ozonolysis (Fig. 6)[229], the structure of the terminal part of the side

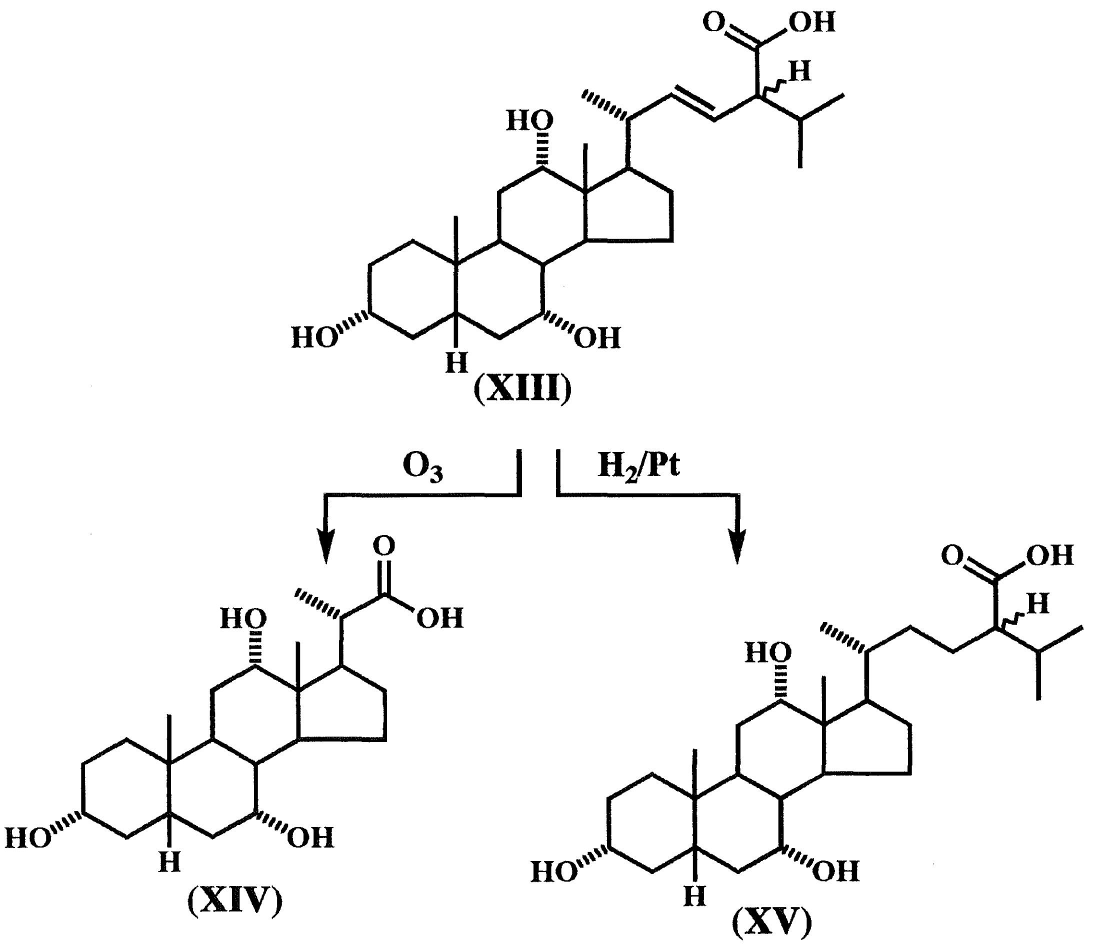

Fig. 6. Structural determination of "trihydroxybufosterocholenic acid". XIII, 3α,7α,12α-trihydroxy-5β-cholest-22-ene-24-carboxylic acid; XIV, bisnorcholic acid; XV, 3α, 7α, 12α-trihydroxy-5β-cholestane-24-carboxylic acid;

chain had not been determined at that time. The structure of trihydroxybufosterocholenic acid was finally described in 1967 by Hoshita et al who synthesized 3α,7α,12α-trihydroxy-5β-cholestane-24-carboxylic acid (XV), which was identical with the hydrogenated derivative of trihydroxybufosterocholenic acid (XIII); hence the major bile acid of the toad was characterized as 3α,7α,12α-trihydroxy-5β-cholest-22-ene-24-carboxylic acid (XIII) (Fig. 6)[100]. The stereochemistry of the side chain is still not yet established.

The natural occurrence of 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid was first demonstrated in 1939 in the bile of the bullfrog, *Rana catesbeiana*[171], and later in various species of amphibians[14, 154, 161, 178, 240, 242, 243, 257], all crocodians examined[75], the kite, *Milvus lineatus lineatus*[160], and even in healthy and diseased humans[35, 58]. This C_{27} homolog of cholic acid has an assymmetric carbon atom at C–25; thus there are two stereoisomers. Most of the above-mentioned vertebrates have only (25R)-3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid (XVIII). However, the bullfrog bile and the crocodile bile contain both 25R and 25S isomers[178, 184]. The occurrence of both 25R and 25S isomers in the same species at once arouses the suspicion that one is an artifact formed from the other. This is especially possible in the case of the crocodile in which the bile acids occur as taurine conjugates. Alkaline conditions necessary to hydrolyze the taurine-conjugated trihydroxy-5β-cholestanoates might cause racemization at C–25. Une et al clearly showed that in the bullfrog both (25R)- and (25S)-3α,7α,12α-trihydroxy-5β-cholestan-26-oic acids are authentic metabolites in this species[243]. Since all bile acids of the bullfrog bile occur in unconjugated form, they could be obtained without use of drastic procedures such as alkaline hydrolysis. High-performance liquid chromatographic analysis of the bile acid mixture of the bullfrog revealed that both 25R and 25S isomers occur in a ratio of about 20:1.

Patients with the cerebrohepatorenal syndorome of Zellweger accumulate 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid and other higher

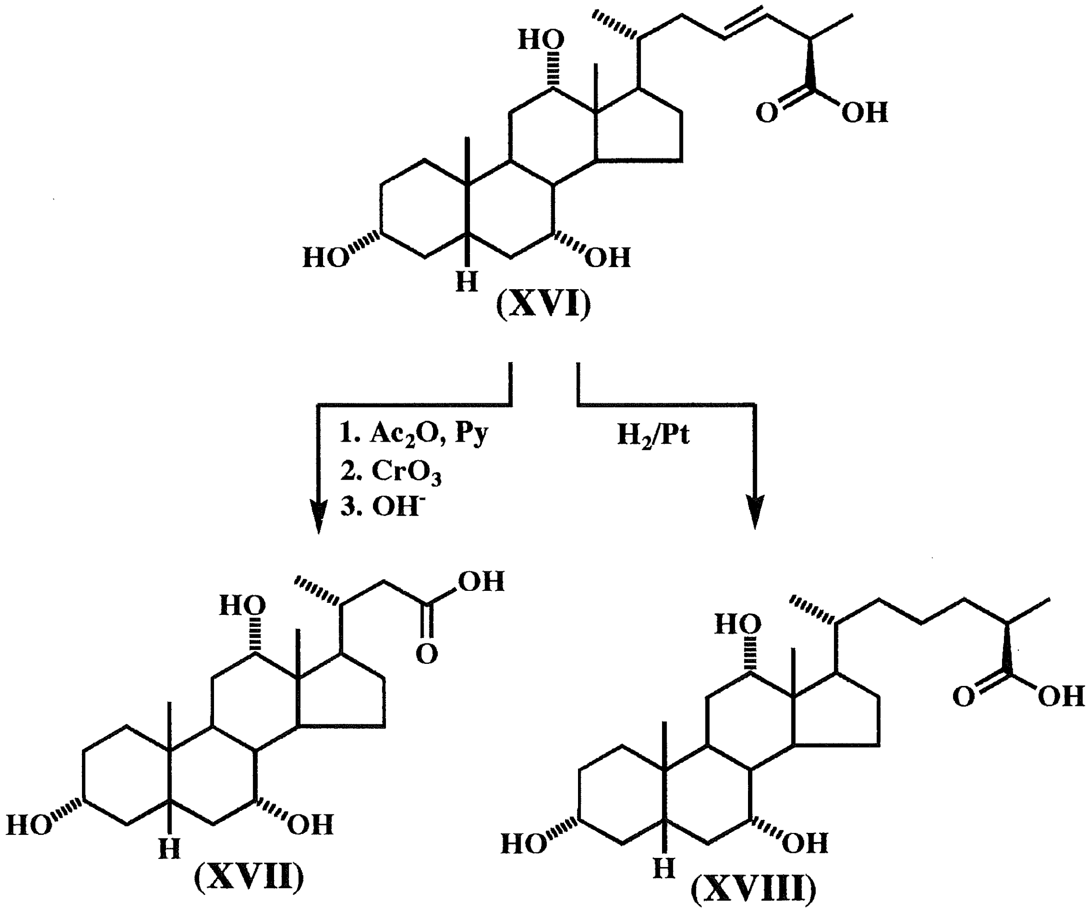

Fig. 7. Structural determination of the second major bile acid of *Bufo vulgaris formosus*. XVI, (25R)-3α,7α,12α-trihydroxy-5β-cholest-23-en-26-oic acid; XVII, norcholic acid; XVIII, (25R)-3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid.

bile acids in their bile, serum, and urine as unusual metabolites of cholesterol[68, 123)]. Une et al have reported that 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid excreted into the urine from an infant with Zellweger syndrome as the unconjugated form consisted of a mixture of the 25R and 25S isomers in the ratio of about 7:3[246)]. Human liver is thought to synthesize only the 25R isomer (XVIII) of 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid as the biosynthetic precursor of cholic acid in normal conditions[28)]. The formation of (25S)-3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid in Zellweger syndrome may reflect the operation of an unusual pathway of cholesterol catabolism in this unusual condition.

Okuda et al isolated a higher bile acid from the bile of the iguana, *Iguana iguana*, as a minor companion of allocholic acid, the major bile acid of this animal[204)]. The structure of the minor bile acid of the iguana was deduced as the C_{27} homolog of allocholic acid, 3α,7α,12α-trihydroxy-5α-cholestan-26-oic acid by lithium aluminum hydride reduction to 5α-cholestane-3α,7α,12α,26-tetrol[204)]. The 5α-C_{27} bile acid was later prepared from 5α-cholestane-3α,7α,12α,26-tetrol[117)], and also found in the bile of some species of amphibians[161,198,240,242)]. The stereochemistry at C–25 of the naturally occurring 3α,7α,12α-trihydroxy-5α-cholestan-26-oic acid remained unknown. Kanemitu isolated a minor bile acid from the bile of the turtle, *Amyda japonica*, and named "heterocholic acid"[118)]. Our own observation has revealed that heterocholic acid is the 2:1 mixture of 3α, 7α, 12α-trihydroxy-5α- and 5β-cholestan-26-oic acids.

A second major bile acid (XVI) from the bile of the toad, *Bufo vulgaris formosus*, was characterized as (25R)-3α,7α,12α-trihydroxy-5β-cholest-23-en-26-oic acid from the fact that the second major bile acid could be converted to norcholic acid (XVII) by oxidation and to (25R)-3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid (XVIII) by hydrogenation (Fig. 7)[80,81)]. This unsaturated C_{27} bile acid also occurs in the bile of another species of the toad, *Bufo marinus*, as a major bile acid[257)], and in the bile of the monitor lizard, *Varanus monitor*, as a minor constituent[1)].

In 1936, Yamasaki and Yuuki isolated a major

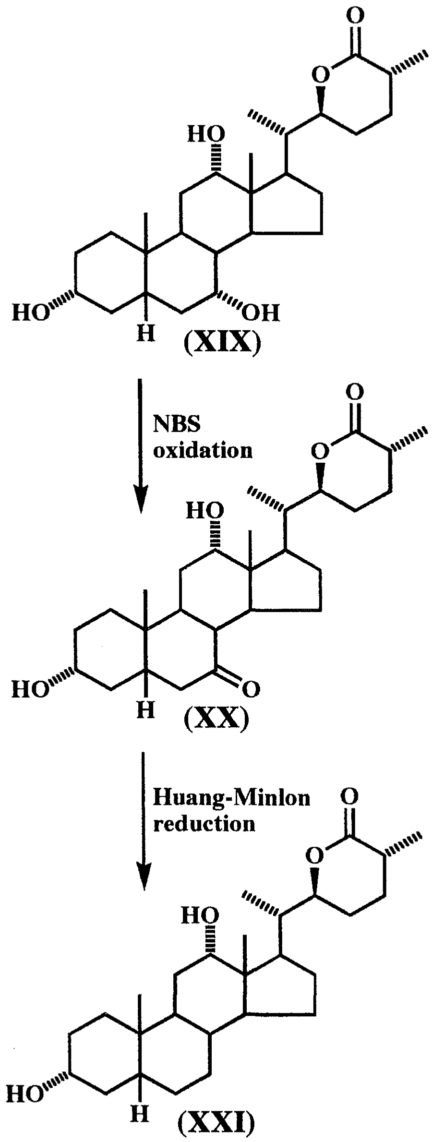

Fig. 8. Chemical conversion of the major bile acid of the turtle into a minor bile acid. XIX, (22S, 25R)-3α,7α,12α-trihydroxy-5β-cholestano-26,22-lactone; XX, (22S,25R)-3α,12α-dihydroxy-7-oxo-5β-cholestano-26,22-lactone; XXI, (22S,25R)-3α,12α-dihydroxy-5β-cholestano-26,22-lactone. NBS, *N*-Bromosuccinimide.

bile acid of the turtle, *Amyda japonica*, as the lactone form, and named it "tetrahydroxysterocholanic lactone"[252]. The structure of tetrahydroxysterocholanic lactone was characterized as (22S,25R)-3α,7α,12α-trihydroxy-5β-cholestano-26, 22-lactone (XIX) by ^{1}H-nuclear magnetic resonance spectrometry comparison with the reference compounds, four possible stereoisomers with respect to the C–22 and C–25 positions of 6β-methyl-3α,5-cyclo-5α-cholestano-26,22-lactones[62]. Thus, the native higher bile acid of the turtle should be formulated as (22S,25R)-3α,7α, 12α,22-tetrahydroxy-5β-cholestan-26-oic acid, which was found in all turtles and tortoises examined as their major biliary constituent but not in any other vertebrate, and is now recognized as the characteristic component of the bile of the chelonians[75].

3α,12α,22-Trihydroxy-5β-cholestan-26-oic acid was found in the bile of the green turtle, *Chelonia mydas* along with (22S, 25R)-3α,7α,12α, 22-tetrahydroxy-5β-cholestan-26-oic acid[79]. Our own observation has also revealed that 3α,12α, 22-trihydroxy-5β-cholestan-26-oic acid is a minor companion of (22S,25R)-3α,7α,12α,22-tetrahydrox-5β-cholestan-26-oic acid in the bile of the turtle, *Amyda japonica*. The stereochemistry of the side chain of 3α,12α,22-trihydroxy-5β-cholestan-26-oic acid is believed to be the same as that of (22S,25R)-3α,7α,12α,22-tetrahydroxy-5β-cholestan-26-oic acid because the lactone (XXI) of the former can be derived from the lactone (XIX) of the latter by the selective oxidation of 7α-hydroxyl group followed by Huang-Minlon reduction of the resultant 7-oxo group to the methylene group (our unpublished observation) (Fig. 8).

Une et al have found two novel taurine-conjugated higher bile acids in urine from a patient with Zellweger syndrome[246,247]. These higher bile acids were obtained as the lactone form after alkaline hydrolysis followed by the extraction with ether of the acidified hydrolysate. The two steroidal lactones (XXIV, XXV) were treated with lithium aluminum hydride and the resultant reduction products (XXVI, XXVII) were identified as (22R,25R)-5β-cholestane-3α,7α,12α,22, 26-pentol and (23R)-5β-cholestane-3α,7α,12α,23, 26-pentol by comparison with authentic compounds. These results indicate that the two native higher bile acids (XXII, XXIII) are (22R,25R)-3α,7α, 12α, 22- and (23R)-3α,7α,12α,23-tetrahydroxy-5β-cholestan-26-oic acids, respectively (Fig. 9)[247].

Varanic acid was isolated from the lizard, *Varanus niloticus*, from which the bile acid received its name, and characterized as a 3α,7α,12α,24-tetrahydroxy-5β-cholestan-26-oic acid[41,69,109]. Varanic acid or its diastereoisomers at C–24 and/or C–25 was found in the bile of several species of amphibians[242,243] and in the biological fluids of healthy and diseased humans[175,205]. Une et al synthesized all four stereoisomers at C–24 and C–25 of 3α,7α,12α,24-tetrahydroxy-5β-cholestan-26-oic acid[241]. Comparison with the synthetic varanic acids of known absolute configuration revealed that the varanic acid of the frog, *Bombina orientalis*, has the 24R, 25S configuration[243]. It is, however, still necessary to continue study of the stereochemistry of varanic acids; since Kinoshita et al also examined the stereochemistry of all four isomers at C–24 and C–25 of varanic acid and claimed the 24R, 25R configuration for the *Bombina* varanic acid[152].

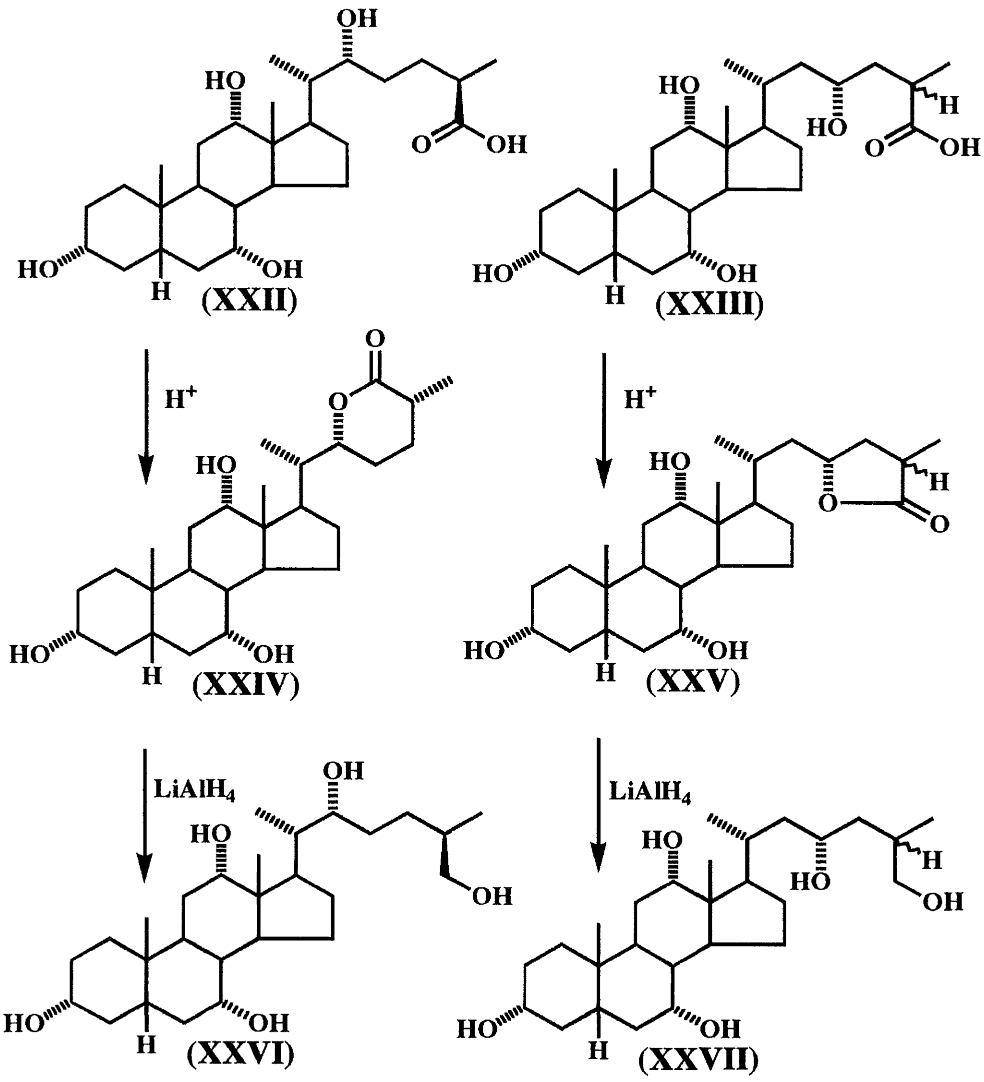

Fig. 9. Structural determination of two novel higher bile acids found in urine from patients with Zellweger syndrome. XXII, (22R,25R)-3α,7α,12α,22-tetrahydroxy-5β-cholestan-26-oic acid; XXIII, (23R)-3α,7α,12α, 23-tetrahydroxy-5β-cholestan-26-oic acid; XXIV, (22R,25R)-3α,7α,12α-trihydroxy-5β-cholestano-26, 22-lactone; XXV, (23R)-3α, 7α,12α-trihydroxy-5β-cholestano-26,23-lactone; XXVI, (22R,25R)-5β-cholestane-3α,7α,12α,22,26-pentol; XXVII, (23R)-5β-cholestane-3α,7α,12α,23,26-pentol.

According to current concepts, the major pathway for the biosynthesis of cholic acid (XXXI) in mammals involves a 3α,7α,12α-trihydroxy-5β-cholest-24-en-26-oic acid and a 3α,7α,12α,24-tetrahydroxy-5β-cholestan-26-oic acid as the intermediates[28,244]. By direct comparison with the compounds of known absolute configuration, these intermediary higher bile acids were identified as (24E)-3α,7α,12α-trihydroxy-5β-cholest-24-en-26-oic acid (XXIX) and the 3α,7α,12α,24-tetrahydroxy-5β-cholestan-26-oic acid assigned by us to have the 24R, 25S configuration (Fig. 10)[244].

3α,7α,12α-Trihydroxy-5β-cholest-24-en-26-oic acid has been detected in the bile of the lizard, *Varanus monitor*, as its minor constituent[1] and in the bile of healthy and diseased humans[39,182]. The stereochemistry of the Δ^{24}-double bond of the C_{27} bile acid found in healthy human bile was determined as Z[182], while a patient with thiolase deficiency contained both the 24E and 24Z isomers[39].

An unusual C_{29}-dicarboxylic bile acid, 3α,7α, 12α-trihydroxy-27-carboxymethyl-5β-cholestan-26-oic acid (3α,7α,12α-trihydroxy-27a,27b-dihomo-5β-cholestane-26,27b-dioic acid) (XXXII) was found in the serum of patients with Zellweger syndrome (Fig. 11)[205]. The structure has recently been confirmed by partial synthesis[206].

Short Side Chain Bile Acids

Lester et al have claimed that the term "bile acids" should be applied to the steroids with a

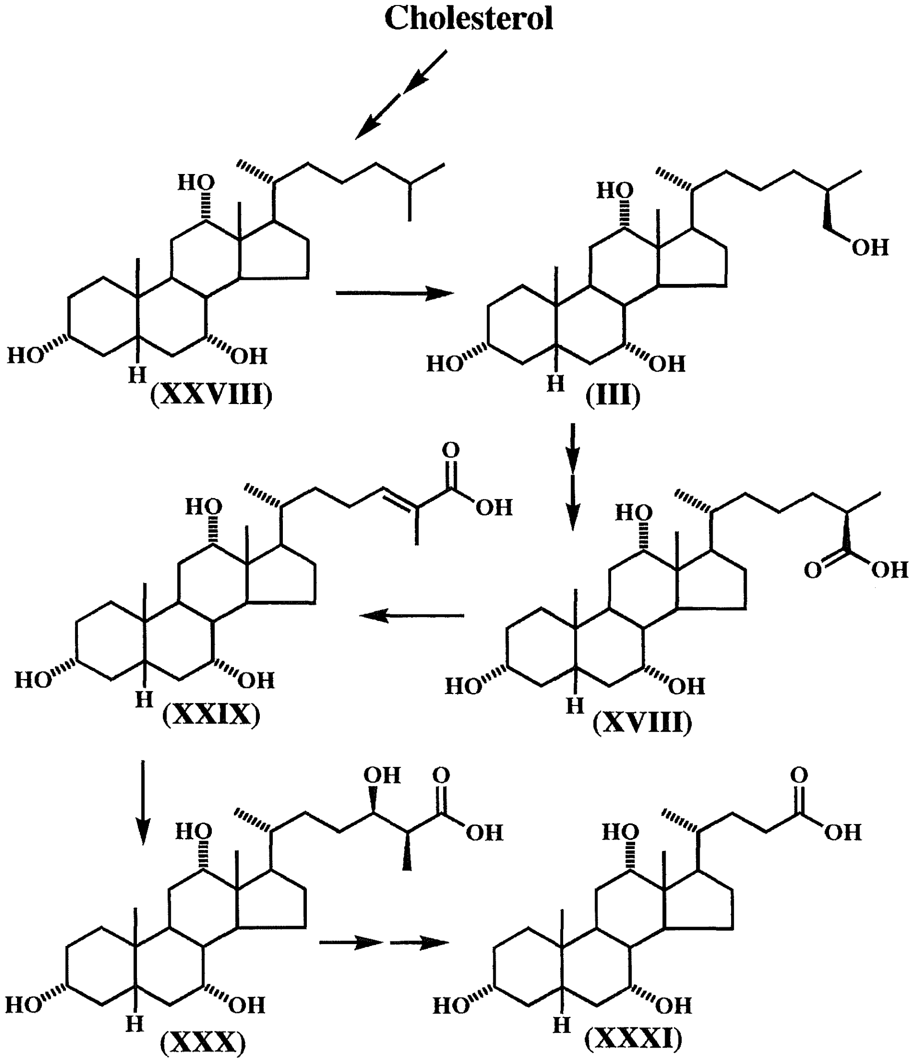

Fig. 10. Postulated pathway for the biosynthesis of cholic acid. XXVIII, 5β-cholestane-3α,7α,12α-triol; III, (25R)-5β-cholestane-3α,7α,12α,26-tetrol; XVIII, (25R)-3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid; XXIX, (24E)-3α,7α,12α-trihydroxy-5β-cholest-24-en-26-oic acid; XXX, (24R,25S)-3α,7α,12α,24-tetrahydroxy-5β-cholestan-26-oic acid; XXXI, cholic acid.

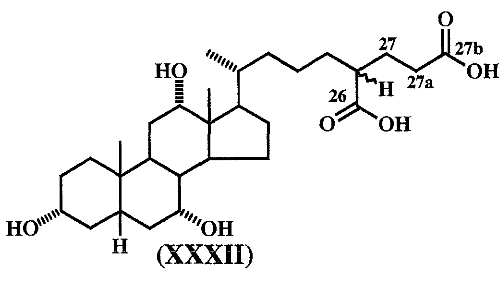

Fig. 11. 3α,7α,12α-Trihydroxy-27-carboxymethyl-5β-cholestan-26-oic acid (XXXII).

side chain at C–17 ending in a carboxylic acid group[176]. However, etianic acid derivatives and pregnanoic acid derivatives are not termed "bile acids" in this review, since these C_{20} and C_{21} steroidal acids are biochemically related to steroid hormones rather than common C_{24} bile acids. Thus, short side chain bile acids are here defined as C_{23} and C_{22} steroidal acids with one and two less carbon atoms in the side chain than common C_{24} bile acids.

The prefixes "nor" and "dinor" are used for systematic names of C_{23} and C_{22} bile acids, respectively, while the prefix "bisnor" is used only for the trivial name of C_{22} bile acids.

Tables 12 and 13 list most of the naturally occurring and chemically derived C_{23} and C_{22} bile acids with the shortened side chain. Specifically

Table 12. C_{23} Bile acids

No.	Systematic name (Trivial name)	Natural source	Synthetic source
1201	1β, 3α, 7α, 12α-Tetrahydroxy-24-nor-5β-cholan-23-oic acid	CTX-U[170]	—
1202	2β, 3α, 7α, 12α-Tetrahydroxy-24-nor-5β-cholan-23-oic acid	CTX-U[170]	—
1203	3α, 7α, 12α-Trihydroxy-24-nor-5α-cholan-23-oic acid (Allonorcholic acid)	Human[182]; CTX[144, 182], -U[144, 170]	1207[224]
1204	3α, 7α, 12α-Trihydroxy-24-nor-5β-cholan-23-oic acid (Norcholic acid)	Human[182], -U[2], -M[19], -AF[230], -UCB[230]; CTX[144, 182], -U[144, 156, 170]; LD-U[2, 7, 29, 230], -S[30, 230]; IMA-U[3]; CHO-U[236]	CA[190, 217, 223, 224, 229, 233]
1205	3β, 7α, 12α-Trihydroxy-24-nor-5α-cholan-23-oic acid	—	1207[224]
1206	3β, 7α, 12α-Trihydroxy-24-nor-5β-cholan-23-oic acid	—	1208[224]
1207	7α, 12α-Dihydroxy-3-oxo-24-nor-5α-cholan-23-oic acid	—	NCA[224]
1208	7α, 12α-Dihydroxy-3-oxo-24-nor-5β-cholan-23-oic acid	—	NCA[195, 224]
1209	7α, 12α-Dihydroxy-3-oxo-24-norchol-4-en-23-oic acid	—	NCA[224]
1210	3α, 12α-Dihydroxy-7-oxo-24-nor-5β-cholan-23-oic acid	CTX[182], -U[170]	NCA[195]
1211	3α, 7α-Dihydroxy-12-oxo-24-nor-5β-cholan-23-oic acid	CTX-U[170]	NCA[233]
1212	3α-Hydroxy-7, 12-dioxo-24-nor-5β-cholan-23-oic acid	—	NCA[233]
1213	3α, 6α-Dihydroxy-24-nor-5β-cholan-23-oic acid (Norhyodeoxycholic acid)	—	HDCA[151, 186, 217]
1214	3α, 7α-Dihydroxy-24-nor-5β-cholan-23-oic acid (Norchenodeoxycholic acid)	Human[182]	CDCA[71, 113, 217]
1215	3α, 7β-Dihydroxy-24-nor-5β-cholan-23-oic acid (Norursodeoxycholic acid)	Human[182]; CTX-U[156]	UDCA[156, 217]; 0512[182]
1216	3α, 12α-Dihydroxy-24-nor-5β-cholan-23-oic acid (Nordeoxycholic acid)	—	DCA[217]; 1210[195]
1217	3α-Hydroxy-12-oxo-24-nor-5β-cholan-23-oic acid	—	NDCA[218]
1218	3α-Hydroxy-24-nor-5β-cholan-23-oic acid (Norlithocholic acid)	—	LCA[212, 215, 217]; 1217[218]
1219	3β-Hydroxy-24-nor-5β-cholan-23-oic acid	—	NLCA[212]
1220	3β-Hydroxy-24-norchol-5-en-23-oic acid	—	1313[232]

For abbreviations, see Table 1.

Table 13. C_{22} Bile acids

No.	Systematic name (Trivial name)	Natural source	Synthetic source
1301	1β, 3α, 7α, 12α-Tetrahydroxy-23, 24-dinor-5β-cholan-22-oic acid	CTX-U[170]	—
1302	2β, 3α, 7α, 12α-Tetrahydroxy-23, 24-dinor-5β-cholan-22-oic acid	CTX-U[170]	—
1303	3α, 7α, 12α-Trihydroxy-23, 24-dinor-5β-cholan-22-oic acid (Bisnorcholic acid)	CTX[182], -U[170]	NCA[190, 229, 234]
1304	3α, 12α-Dihydroxy-7-oxo-23, 24-dinor-5β-cholan-22-oic acid	CTX-U[170]	BNCA[170]
1305	3α, 7α-Dihydroxy-12-oxo-23, 24-dinor-5β-cholan-22-oic acid	CTX-U[170]	BNCA[170, 234]
1306	3α, 6α-Dihydroxy-23, 24-dinor-5β-cholan-22-oic acid (Bisnorhyodeoxycholic acid)	—	NHDCA[151, 186]
1307	3α, 7α-Dihydroxy-23, 24-dinor-5β-cholan-22-oic acid (Bisnorchenodeoxycholic acid)	—	NCDCA[113]; 1305[99]
1308	3α, 12α-Dihydroxy-23, 24-dinor-5β-cholan-22-oic acid (Bisnordeoxycholic acid)	—	NDCA[124]
1309	3α-Hydroxy-12-oxo-23, 24-dinor-5β-cholan-22-oic acid	—	BNDCA[218]
1310	3α-Hydroxy-23, 24-dinor-5α-cholan-22-oic acid or 3β-Hydroxy-23, 24-dinor-5β-cholan-22-oic acid	Human-S[211]	1313[210]
1311	3α-Hydroxy-23, 24-dinor-5β-cholan-22-oic acid (Bisnorlithocholic acid)	Human-M[210]	1313[210]
1312	3β-Hydroxy-23, 24-dinor-5α-cholan-22-oic acid	Human-S[211]	1313[210]
1313	3β-Hydroxy-23, 24-dinorchol-5-en-22-oic acid	Human-S[211], -M[210]	Stigmasterol[60]

For abbreviations, see Table 1.

excluded are 11-oxygenated derivatives and $\Delta^{20(22)}$-norcholenoic acids, which had some passing importance in the manufacture of steroid hormones. It has been known that some microorganisms degraded cholesterol and C_{24} bile acids to bisnorcholanoic acid derivatives. However, these microbial metabolites are not included in the tables.

The first recognition of the natural occurrence of bile acids with the shortened side chain came from the studies, in 1977, of Alme et al who found a trace amount of unconjugated norcholic acid (XVII) in urine from healthy and liver diseased humans[2]. In healthy humans, the C_{23} bile acid (XVII) is thought to be formed from the corresponding C_{24} bile acid, cholic acid (XXXI), by shortening of the side chain by one carbon atom (α-oxidation) (Fig. 12). Matoba et al[182] and Kuramoto et al[170] have found a relatively large amount of C_{23} and C_{22} bile acids in the bile and urine from patients with CTX, respectively. It seems unlikely that these short side chain bile acids are derived from common C_{24} bile acids by α- and β-oxidations, since the production of C_{24} bile acids is below normal in this disease. We postulate, therefore, that the increased formation of the short side chain bile acids in CTX is ascribed to the degradation of some 22- and 23-hydroxylated bile alcohols (e.g. VI) which are synthesized unusually in patients with CTX (Fig. 12).

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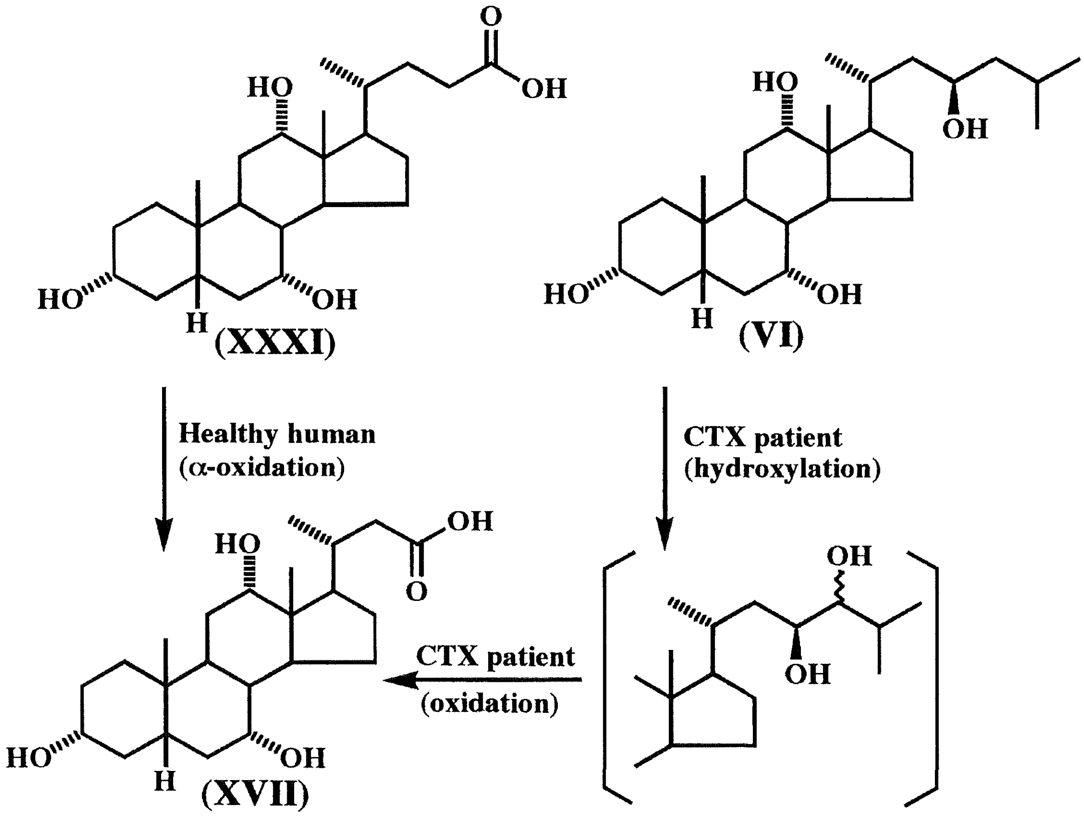

Fig. 12. Postulated pathways for the formation of norcholic acid in healthy persons and in patients with CTX. XXXI, cholic acid; XVII, norcholic acid; VI, (23R)-5β-cholestane-3α,7α,12α,23-tetrol.

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