SYNTHESIS OF SEVERAL HYDROXYLATED 23-(BENZIMIDAZOL-2-YL-, BENZOXAZOL-2-YL AND BENZOTHIAZOL-2-YL)NORCHOLANES AND SOME RELATED COMPOUNDS

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The bile acids *Ia – Id* (lithocholic, chenodeoxycholic, deoxycholic, cholic) and their derivatives (*O*-acetylated acids and *O*-acetylated acid chlorides) reacted under various conditions with 1,2-diaminobenzene, 2-aminophenol and 2-aminothiophenol and afforded the title benzimidazoles *II* and *VII*, benzoxazoles *V* and benzothiazoles *VI*. Alkylation of the benzimidazole derivative *IIa* with 2-dimethylaminoethyl chloride resulted in 3α-hydroxy-23-[1-(2-dimethylaminoethyl)benzimidazol-2-yl]-norcholane (*IVa*). The use of 1,2-diamino-4-methylbenzene enabled the preparation of 3α-acetoxy-23-[5(6)-methylbenzimidazol-2-yl]norcholane (*VIII*). Reactions of the 3α-hydroxy compounds *IVa*, *Va* and *VIa* with succinic anhydride resulted in the hemisuccinates *IVi – VIi*. The boric acid mediated condensation of *O*-acetyllithocholic acid (*Ie*) with 3,4-diaminopyridine gave compound *X* which was transformed to 3α-acetoxy-23-[1*H*-imidazo(4,5-*c*)pyridin-2-yl]norcholane (*IX*). The structure of the products was corroborated by the mass, IR, ^{1}H NMR and ^{13}C NMR spectra. Some of the compounds were tested for antileukemic and for the anti-HIV activity in vitro.

In spite of the fact that benzimidazole is one of the oldest[1] and most thoroughly studied nitrogen heterocyclic systems, its systematic use as a versatile "carrier" system for building of molecules of compounds with potential biological activities started only at the end of the 50th. Since that time, many benzimidazoles were tested and some of them found practical use as analgetics, anthelmintics, antiulcer and antihistamine agents etc. (refs[2–4]). The very recent international list[5] of organic drug substances

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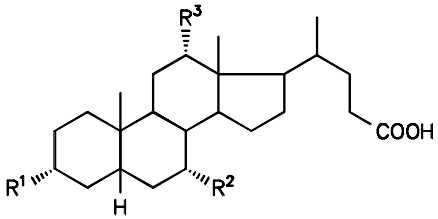
quotes 105 benzimidazole derivatives out of the total 12 111. We mentioned that until now, molecular combinations of the benzimidazole and steroid fragments are not known and this paper represents our first effort at filling up the gap in the knowledge. At the same time we are aware of the fact that benzimidazole cannot be considered only a "carrier system"; it also may function as the pharmacophore. The present study was further extended to some steroidal benzoxazoles and benzothiazoles.

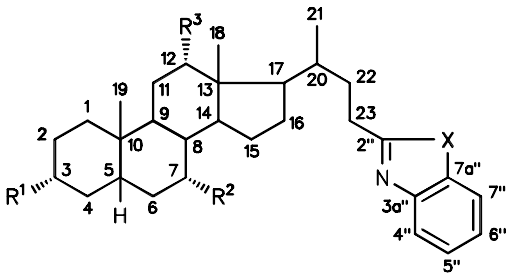
The most common way of preparing benzimidazoles is the Ladenburg's method consisting in reactions of carboxylic acids and their derivatives with 1,2-diaminobenzene[6–8]. Our starting materials were lithocholic (*Ia*), chenodeoxycholic (*Ib*), deoxycholic (*Ic*) and cholic acid (*Id*) which did not react with 1,2-diaminobenzene under mild conditions and were thus heated with excess of the diamine for 30 min to 240 – 250 °C (for analogy cf. refs[9,10]) and gave in reasonable yields the benzimidazoles *IIa*, *IIc* and *IId*. In series *a* and *d*, small amounts of insoluble by-products were isolated which were identified as the esters *VIIa* and *VIId*. In series *b*, the starting acid *Ib* gave under similar conditions two products (evidently *IIb* and *VIIb*) which did not crystallize. The crude products were, therefore, acetylated by refluxing with acetic anhydride in presence of 4-dimethylaminopyridine[11] (DMAP) which resulted in the two expected diacetoxy benzimidazoles *IIf* and *VIIf*. A similar procedure with acetylation with acetic anhydride in boiling pyridine gave in addition to *IIf* (main product) the *N*-acetylated by-product *IIIf*. Heating *O*-acetyllithocholic acid[12] (*Ie*) with 1,2-diaminobenzene to 170 – 190 °C gave the acetoxy benzimidazole *IIe* as the only product in moderate yield. The same reaction, carried out at 250 °C, led to a complex mixture which was separated by chromatography; the main products were *IIa* and *VIIa* and the minor products were identified as *IIe* and *VIIe*. The third similar experiment was carried out using the boric acid catalyzed reaction (for analogy cf. refs[13,14]): 34% of *IIe* were obtained.

It was clear that combination of the benzimidazole fragment – being with regard to its polarity rather well balanced – with the highly hydrophobic steroid moiety (unless its lipophilicity is compensated by presence of a number of polar groups) must result in hydrophobic substances whose biological testing would be difficult. These considerations led us to model experiments aiming at the introduction of further polar groups which could equilibrate the disproportion in the balance of lipophilic and hydrophilic fragments of the molecules under study. The first was the *N*-alkylation of the benzimidazole *IIa*, treated initially with sodium hydride, and then with 2-dimethylaminoethyl chloride in a mixture of aprotic solvents, which resulted in the amino alcohol *IVa* (the free hydroxyl group did not interfere). Reaction of the product with succinic anhydride in boiling pyridine gave the hemisuccinate *IVi*. 1,2-Diamino-4-methylbenzene was used instead of 1,2-diaminobenzene; its heating with *Ie* (ref.[12]) and catalytic amount of boric acid in xylene afforded the 5(6)-methylbenzimidazole *VIII*.

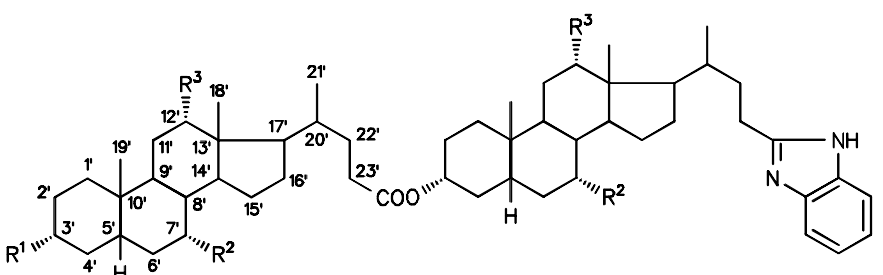
As already mentioned, the present work was extended to similar steroidal benzoxazoles and benzothiazoles. Benzoxazoles were mostly prepared by heating 2-aminophenols



I



II, X = NH
III, X = NAc
IV, X = $NCH_2CH_2N(CH_3)_2$ (1* 2*)
V, X = O
VI, X = S



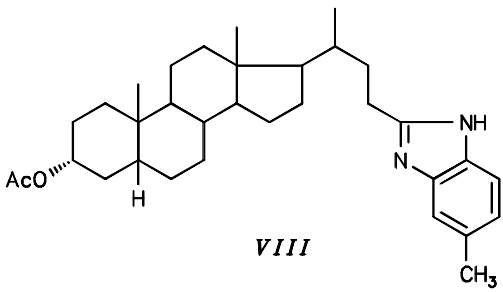
VII

In formulae *I* – *VII* :

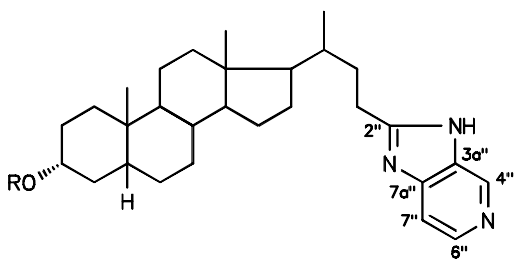
a, R^1 = OH; R^2 = R^3 = H
b, R^1 = R^2 = OH; R^3 = H
c, R^1 = R^3 = OH; R^2 = H
d, R^1 = R^2 = R^3 = OH
e, R^1 = OAc; R^2 = R^3 = H
f, R^1 = R^2 = OAc; R^3 = H
g, R^1 = R^3 = OAc; R^2 = H
h, R^1 = R^2 = R^3 = OAc
i, R^1 = $OCOCH_2CH_2COOH$ (1+ 2+ 3+ 4+); R^2 = R^3 = H

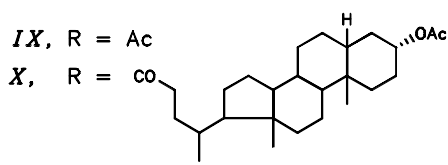
with carboxylic acids, their chlorides and further reactive derivatives[15–17]. In our case, lithocholic (*Ia*) and deoxycholic acid (*Ic*) were heated for 1 h with 2-aminophenol to 230 – 270 °C and gave the benzoxazoles *Va* and *Vc*. Cholic acid (*Id*) gave similarly an amorphous product which was acetylated by refluxing with acetic anhydride in presence of a small amount of DMAP; the product was the triacetoxy benzoxazole *Vh*. *O*-Acetyllithocholic acid[12] (*Ie*) was refluxed with 2-aminophenol in xylene in presence of a small amount of boric acid and afforded the acetoxy benzoxazole *Ve*. Reaction of *Va* with succinic anhydride in boiling pyridine gave the hemisuccinate *Vi*.

Benzothiazoles are usually synthesized by reaction of carboxylic acids and derivatives (especially acid chlorides) with 2-aminothiophenol[18]. We used the acid chloride approach and started from the *O*-acetylated bile acids *Ie* (ref.[12]), *If* (ref.[19]), *Ig* (ref.[19]) and *Ih* (refs[20,21]) which were transformed by treatment with thionyl chloride in benzene to the acid chlorides (only the chlorides of *Ie* and *Ig* were mentioned in the literature[22–25]). These were used as crude products and reacted with 2-aminothiophenol in boiling benzene; the *O*-acetylated benzothiazoles *VIe* – *VIh* were obtained in high yields. Compound *VIe* was hydrolyzed with sodium hydroxide in aqueous methanol and the obtained crude *VIa* was transformed by treatment with succinic anhydride to the hemi-



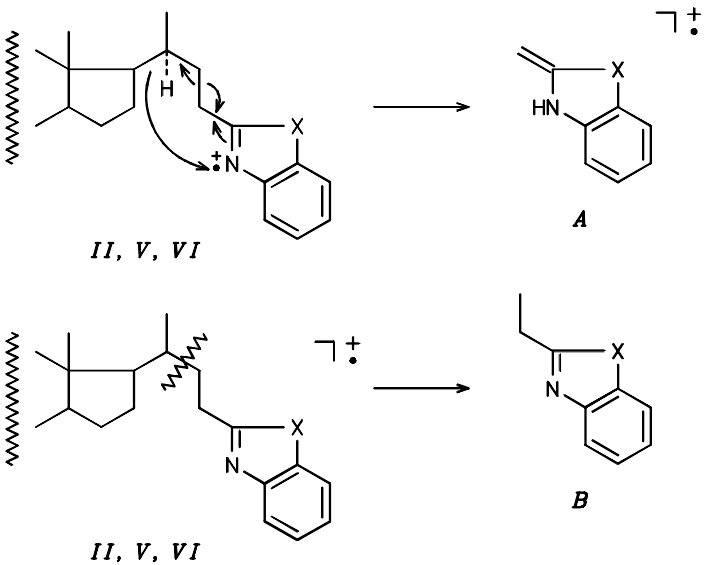
VIII





succinate *VIi*. The last experiment aimed at the 1*H*-imidazo(4,5-*c*)pyridine derivative *IX* in the *O*-acetyllithocholic acid series. The boric acid-catalyzed reaction of the acid[12] *Ie* with 3,4-diaminopyridine in xylene resulted, however, in the amorphous "quasi dimer" *X* whose identity was corroborated by spectra. Its hydrolysis with sodium hydroxide in aqueous methanol afforded the crude hydroxy compound which was acetylated with acetic anhydride to give the desired *O*-acetylated imidazo(4,5-*c*)pyridine *IX*.

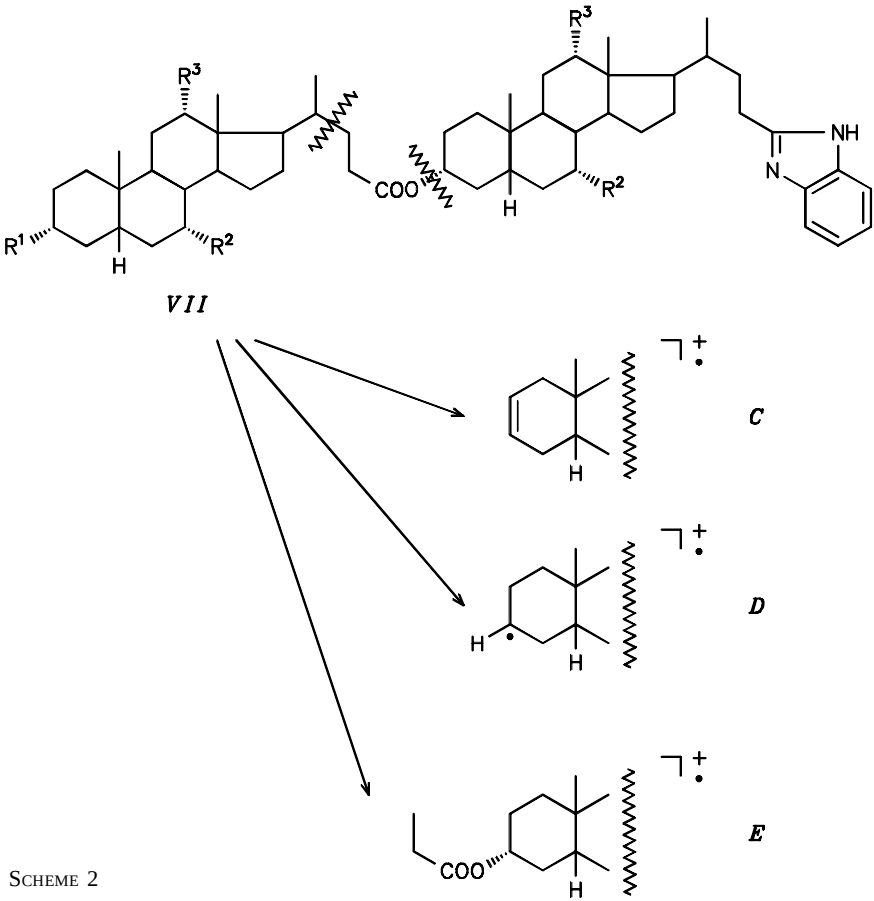
All the compounds prepared were characterized on the basis of spectral data analysis. In the benzimidazoles *II*, *VII*, *VIII*, there appears a tautomeric proton exchange whose rate is so high that their ^{1}H NMR spectra show two symmetrical two-proton multiplets at about 7.1 – 7.7 ppm corresponding to hydrogens in positions 4″,7″ and 5″,6″ of the benzimidazole nucleus. In the ^{13}C NMR spectra, the indicated symmetry (common signals for 3a″,7a″, 4″,7″ and 5″,6″ benzimidazole carbons) was found with compounds which do not contain free hydroxyl groups in the steroid moiety. On the other hand, the hydroxy derivatives show for each of the seven benzimidazole carbons separated signals in the region of 110 – 160 ppm. This is evidently the result of hydrogen bonds which slow down the mentioned tautomeric exchange. The solvent used (deuteriochloroform or hexadeuteriodimethyl sulfoxide) did not influence the phenomenon observed. With benzoxazoles and benzothiazoles, a similar tautomerism is not possible: in the ^{1}H NMR spectra of these compounds, the aromatic protons appear as three symmetric multiplets between 7.3 and 8.0 ppm where protons in positions 4″ and 7″ were completely distinguished; in the ^{1}H NMR spectra of benzoxazoles, two one-proton multiplets with one two-proton multiplet were apparent; ^{1}H NMR spectra of benzothiazoles showed two one-proton doublets and one two-proton multiplet.



SCHEME 1

The mass spectra of the benzimidazoles *IIa – IId* are very clean-cut and clearly reflect the known fragmentation of the steroid part of the molecules as well as the fragmentation belonging to the heterocyclic substituent. For benzimidazoles, the most typical ions were those with *m*/*z* 132 and *m*/*z* 145, for benzoxazoles with *m*/*z* 133 and *m*/*z* 146, and for benzothiazoles with *m*/*z* 149 and *m*/*z* 162. Structures *A* and *B* could correspond to these fragments (Scheme 1); their formation could be explained[8,26] by rearrangement and cleavage.

With the "quasi dimeric" by-products *VII*, the ^{1}H NMR spectra showed the 18-, 18′-, 19- and 19′-methyls either as four singlets (3 + 3 + 3 + 3 H) or three singlets (3 + 3 + 6 H) and the integration of protons indicated the 2 : 1 ratio of the steroid skeleton and the aromatic system. The ^{13}C NMR spectra had most of the carbon signals doubled. Their mass spectra display in addition to the already shown typical fragments some further fragments with atypical masses *C*, *D* and *E* whose formation is explained by cleavage indicated in Scheme 2.



SCHEME 2

Most of the compounds prepared were tested for inhibition of the growth of leukemia or carcinoma cells in the concentration of 10 μmol l^{-1}: in the mouse leukemia L 1210 cell culture, compound *IVa* inhibited the growth to 32% of the control value (100%); the murine L 929 cell growth was inhibited by *IIc* to 18%; the human cervix carcinoma HeLa S3 cell growth was inhibited by *IIc* to 25% and by *VIg* to 37%. The compounds were also evaluated for in vitro anti-HIV activity in the testing system in which the protection of T4 lymphocytes from the human immunodeficiency virus (HIV) infection was determined (concentration of the tested compound in mol l^{-1} and percent of protection are given): *IIf*: 1.58 . 10^{-5}, 10.72%; *Vh*: 5.00 . 10^{-6}, 31.45%. These values mean very low activity which does not indicate practical utility. The other compounds, which were tested in 8 different concentrations, practically did not show any protection.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured with the automatic instrument ETL-NPL (Bendix–Ericson) with the accuracy of ± 2 °, solvent chloroform (unless stated otherwise), *c* in mg ml^{-1}, *t* = 20 °C. IR spectra (ν, cm^{-1}) were taken with a Perkin–Elmer 684 instrument, solvent chloroform (unless otherwise stated). ^1H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were recorded on a Varian Unity 200 spectrometer (200 MHz for ^1H and 50.3 MHz for ^{13}C). Deuteriochloroform (unless otherwise stated) was used as solvent and tetramethylsilane as internal standard. Mass spectra were run with an Incos 50 instrument, energy of the ionizing electrons 70 eV, ionizing current 800 mA, temperature of the ionic source 150 °C; the samples were evaporated from a direct exposer probe with a temperature gradient of 5 or 10 mA s^{-1}. Preparative chromatographic separations were carried out on columns of silica gel (0.03 – 0.06 mm). The extracts were dried with Na_2SO_4 and evaporated under reduced pressure.

General Procedure for Preparation of Benzimidazoles *IIa*, *IIc* and *IId*

A mixture of the bile acid (*Ia*, *Ic*, *Id*; 2 mmol) and 1,2-diaminobenzene (10 mmol) was heated with stirring for 30 min to 240 – 250 °C under nitrogen. After cooling, the mixture was dissolved in a 1 : 1 mixture of chloroform and methanol, the undissolved solid was filtered off and washed with the same mixture of solvents. The filtrate was evaporated with 5 g silica gel and the residue was chromatographed on 80 g silica gel. The by-products *VIIa* and *VIId* were obtained from the insoluble solids.

23-(Benzimidazol-2-yl)norcholan-3α-ol (IIa). General procedure was used for reacting lithocholic acid (*Ia*, 2.45 g, 6.5 mmol) and 1,2-diaminobenzene (2.2 g, 20 mmol). After the removal of the undissolved product (0.17 g), the soluble portion was chromatographed on silica gel (120 g) using elution with benzene–ether and chloroform–acetone giving 2.56 g (88%) of *IIa*, m.p. 292 – 295 °C (chloroform–ethyl acetate), $[\alpha]_D$ + 29° (*c* 0.27, pyridine). IR spectrum: 1 621, 1 534 (Ar); 1 056 (s-OH); 737 (4 adjacent Ar-H). ^1H NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulfoxide): 0.65 s, 3 H (18-CH_3); 0.91 s, 3 H (19-CH_3); 1.04 d, 3 H, *J* = 5.37 (21-CH_3); 1.04 – 2.01 m, ca 26 H (skeletal CH_2 and CH); 3.48 bs, 1 H (OH); 3.57 m, 1 H (H-3β); 7.15 m, 2 H (H-5″, H-6″); 7.49 m, 2 H (H-4″, H-7″). Mass spectrum, *m*/*z* (%): 448 (M^+, $C_{30}H_{44}N_2O$, 7.5), 433 (6.0), 391 (6.9), 199 (3.7), 185 (5.0), 173 (9.7), 171 (6.7), 157 (3.0), 145 (100), 132 (85), 119 (4.6), 107 (3.7), 105 (3.7), 95 (5.7), 93 (9.0), 91 (8.0), 81 (8.0), 79 (9.0), 67 (9.0), 55 (11.5), 43 (7.4), 41 (11.3). For $C_{30}H_{44}N_2O$ (448.7) calculated: 80.30% C, 9.89% H, 6.24% N; found: 80.37% C, 10.00% H, 6.17% N.

The insoluble solid melting at 266 – 268 °C, which could not be recrystallized, was identified as *23-(benzimidazol-2-yl)-3α-(lithocholoyloxy)norcholane* (VIIa). IR spectrum (Nujol): 1 733 (R–COO–R′); 1 623, 1 537 (Ar); 738 (4 adjacent Ar-H). ^{1}H NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulfoxide): 0.64 and 0.66 2 s, 3 + 3 H (18-CH_3 and 18′-CH_3); 0.94 s, 6 H (19-CH_3 and 19′-CH_3); 0.92 d, 6 H, J = 6.89 (21-CH_3 and 21′-CH_3); 1.02 – 1.98 m, ca 52 H (skeletal CH_2 and CH); 2.24 m, 4 H (2 H-23 and 2 H-23′); 3.51 bs, 1 H (OH); 4.67 m, 2 H (H-3β and H-3′β); 6.89 m, 2 H (H-5″ and H-6″); 7.25 m, 2 H (H-4″ and H-7″). Mass spectrum, *m*/*z* (%): 503 (0.6), 447 (1.1), 431 (8.7), 215 (8.0), 201 (5.7), 185 (4.9), 173 (11.5), 159 (6.9), 145 (100), 132 (72.4), 119 (9.1), 107 (11.5), 105 (11.4), 81 (14.0), 79 (13.8), 67 (12.6), 55 (23.0), 41 (20.7). For $C_{54}H_{82}N_2O_3$ (807.3) calculated: 80.35% C, 10.24% H, 3.47% N; found: 80.33% C, 10.40% H, 3.53% N.

23-(Benzimidazol-2-yl)norcholane-3α,12α-diol (IIc). A mixture of deoxycholic acid (*Ic*, 1.30 g, 3.3 mmol) and 1,2-diaminobenzene (1.02 g, 9.4 mmol) was similarly processed and the crude product was chromatographed on silica gel (130 g). Elution with mixtures of benzene, chloroform and methanol gave 1.16 g (76%) of *IIc*, m.p. 301 – 302 °C (benzene–methanol), $[\alpha]_D$ +34° (*c* 0.42, pyridine). IR spectrum (Nujol): 3 621 (OH and NH); 1 617, 1 535 (Ar); 1 044 (s-OH); 733 (4 adjacent Ar-H). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 0.58 s, 3 H (18-CH_3); 0.84 s, 3 H (19-CH_3); 1.02 d, 3 H, J = 6.8 (21-CH_3); 0.98 – 1.84 m, ca 24 H (skeletal CH_2 and CH); 2.76 m, 2 H (2 H-23); 3.33 m, 1 H (H-3β); 3.81 d, 1 H, J = 3.4 (H-12β); 4.25 d, 1 H, J = 4.15 (12-OH); 4.48 d, 1 H, J = 4.4 (3-OH); 7.08 dd, 2 H, J = 2.9; 6.1 (H-5″ and H-6″); 7.36 m, 2 H (H-4″ and H-7″). ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide): 12.6 (C-18); 17.3 (C-21); 23.3 (C-19); 23.7 (C-15); 25.7 (C-23); 26.3 (C-16); 27.2 (C-7); 27.4 (C-6); 28.8 (C-11); 30.4 (C-2); 33.1 (C-9); 34.0 (C-10); 34.4 (C-22); 35.3 (C-1); 35.4 (C-20); 36.5 (C-4); 41.8 (C-5); 46.2 (C-13); 46.3 (C-17); 47.7 (C-14); 70.1 (C-3); 71.2 (C-12); 110.8 (C-7″); 118.2 (C-4″); 120.9 and 121.4 (C-5″ and C-6″); 134.5 (C-3a″); 143.5 (C-7a″); 155.8 (C-2″). Mass spectrum, *m*/*z* (%): 464 (M^+, $C_{30}H_{44}N_2O_2$, 0.6), 173 (4.4), 145 (100), 132 (78.9), 119 (4.2), 105 (4.2), 93 (4.9), 91 (4.9), 81 (7.6), 79 (5.6), 67 (5.6), 55 (10.6), 41 (8.5). For $C_{30}H_{44}N_2O_2$ (464.7) calculated: 77.54% C, 9.54% H, 6.03% N; found: 77.54% C, 9.54% H, 6.06% N.

23-(Benzimidazol-2-yl)norcholane-3α,7α,12α-triol (IId). Similar reaction of cholic acid (*Id*, 2.0 g, 4.9 mmol) with 1,2-diaminobenzene (1.0 g, 9.3 mmol) gave 0.15 g of the minor product (insoluble solid) and the main soluble product which was chromatographed on silica gel (100 g). Elution with ethyl acetate afforded 1.65 g (70%) of *IId*, m.p. 299 – 301 °C (benzene–methanol). IR spectrum (Nujol): 3 511 (OH and NH); 1 624, 1 538 (Ar); 1 080 (s-OH); 739 (4 adjacent Ar-H). ^{1}H NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulfoxide): 0.58 s, 3 H (18-CH_3); 0.80 s, 3 H (19-CH_3); 1.04 d, 3 H, J = 5.6 (21-CH_3); 0.92 – 2.20 m, ca 22 H (skeletal CH_2 and CH); 2.77 m, 2 H (2 H-23); 3.39 bs, 1 H (H-3β); 3.62 bs, 1 H (H-7β); 3.82 bs, 1 H (H-12β); 4.05 d, 1 H, J = 2.7 (3-OH); 4.18 d, 1 H, J = 2.9 (7-OH); 4.36 d, 1 H, J = 2.9 (12-OH); 7.09 dd, 2 H, J = 2.9; 5.9 (H-5″ and H-6″); 7.41 m, 2 H (H-4″ and H-7″). ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide): 12.5 (C-18); 17.3 (C-21); 22.8 (C-19); 23.0 (C-15); 25.7 (C-23); 26.4 (C-9); 27.5 (C-16); 28.7 (C-11); 30.6 (C-2); 34.5 (C-6, C-10 and C-22); 35.0 (C-1); 35.5 (C-20); 39.3 (C-4); 39.7 (C-8); 41.6 and 41.7 (C-5 and C-14); 45.9 (C-13); 46.2 (C-17); 66.4 (C-7); 70.6 (C-3); 71.2 (C-12); 110.8 (C-7″); 118.1 (C-4″); 120.9 and 121.4 (C-5″ and C-6″); 134.6 (C-3a″); 143.7 (C-7a″); 155.8 (C-2″). Mass spectrum, *m*/*z* (%): 480 (M^+, $C_{30}H_{44}N_2O_3$, 2.8), 185 (5.1), 173 (10.1), 145 (100), 132 ((90.1), 119 (7.7), 105 (8.5), 93 (10), 91 (9.2), 81 (9.0), 79 (10), 67 (9.5), 55 (14.1), 41 (10). For $C_{30}H_{44}N_2O_3$ (480.7) calculated: 74.96% C, 9.23% H, 5.83% N; found 74.94% C, 9.28% H, 5.82% N.

The solid (insoluble in chloroform–methanol) was recrystallized from a mixture of chloroform and ethyl acetate; 0.15 g (7%) of *23-(benzimidazol-2-yl)-3α-(choloyloxy)norcholane-7α,12α-diol* (VIId), m.p. 305 – 310 °C. IR spectrum (Nujol): 3 596 (OH); 3 520 (NH); 1 625, 1 538 (Ar); 1 022 (s-OH); 736 (4 adjacent Ar-H). ^{1}H NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulfoxide): 0.65 and 0.67 2 s, 3 + 3 H (18-CH_3 and 18′-CH_3); 0.86 and 0.90 2 s, 3 + 3 H (19-CH_3 and 19′-CH_3);

0.97 and 1.10 2 × d, 3 + 3 H, J = 5.61; 5.86 (21-CH_3 and 21′-CH_3); 1.16 – 2.38 m, ca 44 H (skeletal CH_2 and CH); 2.87 m, 4 H (2 H-23 and 2 H-23′); 3.26 m, 2 H (H-3β and H-3′β); 3.42 bs, 2 H (H-7β and H-7′β); 3.53 m, 2 H (H-12β and H-12′β); 3.74 bs, 2 H (12-OH and 12′-OH); 3.87 and 3.91 2 bs, 1 + 1 H (7-OH and 7′-OH); 4.52 bs, 1 H (3′-OH); 7.13 dd, 2 H, J = 1.6; 2.95 (H-5″ and H-6″); 7.49 dd, 2 H, J = 1.6; 2.95 (H-4″ and H-7″). ^{13}C NMR spectrum (deuteriochloroform–hexadeuteriodimethyl sulfoxide): 11.3 (C-18 and C-18′); 16.0 and 16.2 (C-21 and C-21′); 21.3 and 21.4 (C-19 and C-19′); 21.8 (C-15 and C-15′); 25.2 (C-9 and C-9′); 26.3 and 27.3 (C-16 and C-16′); 29.3 (C-11 and C-11′); 29.8 and 30.3 (C-2 and C-2′); 33.4 (C-6 and C-6′); 33.6 and 33.7 (C-10 and C-10′); 34.0 (C-20 and C-20′); 34.4 (C-8 and C-8′); 37.9 (C-23 and C-23′); 38.4 (C-22 and C-22′); 38.8 (C-1 and C-1′); 39.2 (C-4 and C-4′); 40.2 (C-14 and C-14′); 40.4 (C-5 and C-5′); 45.0 (C-13 and C-13′); 45.3 (C-17 and C-17′); 65.9 and 66.1 (C-7 and C-7′); 70.0 (C-3 and C-3′); 70.8 (C-12 and C-12′); 113.5 (C-5″ and C-6″); 120.2 (C-4″ and C-7″); 143.7 (C-3a″ and C-7a″); 154.9 (C-2″); 172.2 (COO). Mass spectrum, m/z (%): 463 (1.0), 462 (2.4), 255 (4.8), 199 (4.6), 185 (4.9), 145 (100), 132 (91.5), 119 (8.5), 105 (11.3), 95 (7.0), 93 (11.3), 91 (14.1), 81 (12.0), 79 (14.1), 67 (11.2), 55 (16.9), 41 (15.5). For $C_{54}H_{82}N_2O_7$ (871.3) calculated: 74.44% C, 9.49% H, 3.22% N; found: 74.40% C, 9.44% H, 3.26% N.

3α,7α-Diacetoxy-23-(benzimidazol-2-yl)norcholane (*IIf*)

A mixture of chenodeoxycholic acid (*Ib*, 1.36 g, 3.5 mmol) and 1,2-diaminobenzene (1.1 g, 10 mmol) was stirred and heated to 250 °C for 30 min under nitrogen. After cooling, it was dissolved in 20 ml mixture of chloroform and methanol, the solution was evaporated with 5 g silica gel and chromatographed on 100 g silica gel. Elution with chloroform and chloroform–ethyl acetate gave two products which did not crystallize: crude *IIb*, 0.10 g (7%) and crude *VIIb*, 1.40 g (86%). The main product was refluxed for 2 h with 10 ml acetic anhydride in presence of DMAP (0.2 g). Similar processing like in the preparation of *IIa* gave 1.6 g (97%) of *IIf*, m.p. 213 – 215 °C (chloroform–hexane), $[\alpha]_D$ +12° (*c* 0.22). IR spectrum: 3 667 (NH); 1 724 (RCOOR′); 1 625 (Ar); 819 (Ar-H). ^{1}H NMR spectrum: 0.58 s, 3 H (18-CH_3); 0.92 s, 3 H (19-CH_3); 0.93 d, 3 H, J = 7.6 (21-CH_3); 0.88 – 2.01 m, ca 24 H (skeletal CH_2 and CH); 2.04 and 2.05 2 s, 3 + 3 H (2 CH_3COO); 2.86 m, 2 H (2 H-23); 4.59 m, 1 H (H-3β); 4.86 d, 1 H, J = 1.8 (H-7β); 7.19 dd, 2 H, J = 3.2; 6.1 (H-5″ and H-6″); 7.53 dd, 2 H, J = 3.2; 6.1 (H-4″ and H-7″); 7.61 bs, 1 H (NH). ^{13}C NMR spectrum: 11.6 (C-18); 18.3 (C-21); 20.5 (C-11); 21.4 and 21.5 (2 CH_3 in 3- and 7-OAc); 22.6 (C-19); 23.4 (C-15); 25.8 (C-23); 26.7 (C-2); 28.0 (C-16); 31.2 (C-6); 34.0 (C-9); 34.3 (C-1); 34.5 (C-4); 34.7 (C-10); 35.5 (C-20); 37.8 (C-8); 39.4 (C-12); 40.8 (C-5); 42.6 (C-13); 50.2 (C-14); 55.6 (C-17); 71.3 (C-7); 74.1 (C-3); 114.4 (C-4″ and C-7″); 122.2 (C-5″ and C-6″); 137.8 (C-3a″ and C-7a″); 155.6 (C-2″); 170.5 and 170.7 (2 CO in 3- and 7-OAc). Mass spectrum, m/z (%): 548 (M^+, $C_{34}H_{48}N_2O_4$, 2.0), 533 (2.3), 491 (2.0), 214 (11.5), 199 (5.4), 185 (7.0), 173 (13.8), 171 (7.6), 145 (98.6), 132 (100), 119 (5.6), 105 (7.9), 93 (6.3), 91 (6.3), 81 (6.3), 79 (6.3), 67 (5.6), 55 (6.8), 43 (49.3). For $C_{34}H_{48}N_2O_4$ calculated: 74.42% C, 8.82% H, 5.10% N; found: 74.45% C, 8.86% H, 5.02% N.

The minor product was similarly acetylated (2 ml acetic anhydride) in presence of DMAP and after crystallization from chloroform–hexane gave 0.10 g (87%) of *7α-acetoxy-3α-[3,7-di(O-acetyl)-chenodeoxycholoyloxy]-23-(benzimidazol-2-yl)norcholane* (VIIf), m.p. 162 – 165 °C, $[\alpha]_D$ +12° (*c* 0.33). IR spectrum: 3 463 (NH); 1 725 (RCOOR′); 1 600, 1 536 (Ar). ^{1}H NMR spectrum: 0.65 s, 6 H (18-CH_3 and 18′-CH_3); 0.92 d, 6 H, J = 4.9 (21-CH_3 and 21′-CH_3); 0.93 s, 6 H (19-CH_3 and 19′-CH_3); 1.01 – 2.01 m, ca 48 H (skeletal CH_2 and CH); 2.03 and 2.04 2 s, 3 + 3 H (2 CH_3 in 7- and 7′-OAc); 2.06 s, 3 H (CH_3 in 3′-OAc); 2.25 m, 2 H (2 H-23′); 2.89 m, 2 H (2 H-23); 4.59 m, 2 H (H-3β and H-3′β); 4.88 s, 2 H (H-7β and H-7′β); 7.23 dd, 2 H, J = 2.9; 4.4 (H-5″ and H-6″); 7.56 dd, 2 H, J = 2.9; 4.4 (H-4″ and H-7″). ^{13}C NMR spectrum: 11.7 (C-18 and C-18′); 18.3 and 18.4 (C-21 and C-21′); 20.6 (C-11 and C-11′); 21.5 (CH_3 in 3′-OAc); 21.6 (2 CH_3 on 7- and 7′-OAc); 22.7 (C-19 and C-19′);

23.5 (C-15 and C-15′); 25.9 (C-23 and C-23′); 26.8 (C-2 and C-2′); 28.0 (C-16 and C-16′); 31.1 (C-6 and C-6′); 31.3 and 31.7 (C-4 and C-4′); 34.1 (C-9 and C-9′); 34.7 (C-10 and C-10"); 34.8 (C-1 and C-1′); 34.9 (C-22 and C-22′); 35.3 and 35.6 (C-20 and C-20′); 37.9 (C-8 and C-8′); 39.5 (C-12 and C-12′); 40.9 (C-5 and C-5′); 42.7 (C-13 and C-13′); 50.4 (C-14 and C-14′); 55.7 and 55.8 (C-17 and C-17′); 71.3 (C-7 and C-7′); 73.9 and 74.2 (C-3 and C-3′); 114.8 (C-4″ and C-7″); 122.5 (C-5″ and C-6″); 137.8 (C-3a″ and C-7a″); 170.4 (2 CO in 7- and 7′-OAc); 170.6 and 173.8 (2 CO in 3- and 3′-OCOR). Mass spectrum, *m/z* (%): 429 (13.8), 356 (8.2), 255 (8.2), 213 (11.8), 199 (8.6), 185 (8.4), 173 (15.0), 159 (9.6), 145 (85.9), 132 (100), 119 (8.5), 105 (9.8), 93 (8.7), 81 (7.0), 67 (4.6), 55 (7.0), 43 (38.0). For $C_{60}H_{88}N_2O_8$ (965.4) calculated: 74.65% C, 9.19% H, 2.98% N; found: 74.70% C, 9.25% H, 2.78% N.

3α,7α-Diacetoxy-23-(1-acetylbenzimidazol-2-yl)norcholane (*IIIf*)

A mixture of *Ib* (2.0 g, 5.1 mmol) and 1,2-diaminobenzene (1.10 g, 10.2 mmol) was processed similarly as in the preceding experiment. The crude product was chromatographed on 100 g silica gel (elution with chloroform and chloroform–methanol), crude eluate (1.2 g of mixture) was treated with acetic anhydride (5 ml) and pyridine (5 ml) and the mixture was refluxed for 2 h. After decomposition with ice and extraction with ethyl acetate, the mixture (1.18 g) obtained was chromatographed on 80 g silica gel (elution with benzene, benzene–ether and chloroform–ethyl acetate). The first to be eluated was the minor product (0.36 g, 22%) which was identified as *IIIf*, m.p. 100 – 102 °C (ether–heptane), $[\alpha]_D$ +5° (*c* 0.36). IR spectrum: 1 723 (RCOOR′); 1 622, 1 536 (Ar); 1 024 (RCOOR′); 908 (Ar-H). ^{1}H NMR spectrum: 0.68 s, 3 H (18-CH_3); 0.94 s, 3 H (19-CH_3); 1.07 d, 3 H, *J* = 5.9 (21-CH_3); 0.88 – 2.07 m, ca 24 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in 3-OAc); 2.06 s, 3 H (CH_3 in 7-OAc); 2.81 s, 3 H (CH_3 in NAc); 3.14 m, 2 H (2 H-23); 4.59 m, 1 H (H-3β); 4.88 d, 1 H, *J* = 2.9 (H-7β); 7.33 m, 2 H (H-5″ and H-6″); 7.69 m, 2 H (H-4″ and H-7″). ^{13}C NMR spectrum: 11.6 (C-18); 18.5 (C-21); 20.6 (C-11); 21.3 and 21.5 (2 CH_3 in 3- and 7-OAc); 22.6 (C-19); 23.5 (C-15); 26.7 (C-23); 27.0 (CH_3 in NAc); 28.0 (C-2); 28.7 (C-16); 31.2 (C-6); 33.6 (C-22); 34.0 (C-9); 34.5 (C-1); 34.7 (C-10); 34.8 (C-4); 35.8 (C-20); 37.8 (C-8); 39.4 (C-12); 40.9 (C-5); 42.6 (C-13); 50.3 (C-14); 55.6 (C-17); 71.1 (C-7); 74.0 (C-3); 113.5 (C-7″); 119.9 (C-4″); 124.1 and 124.2 (C-5″ and C-6″); 132.5 (C-3a″); 142.7 (C-7a″); 157.7 (C-2″); 168.9 (CO in NAc); 170.3 and 170.4 (2 CO in 3- and 7-OAc). Mass spectrum, *m/z* (%): 590 (M^+, $C_{36}H_{50}N_2O_5$, 6.7), 214 (6.0), 199 (7.2), 187 (44.2), 174 (46.5), 145 (76.7), 132 (88.4), 119 (8.8); 105 (10.5), 93 (9.3), 91 (9.0), 81 (8.8), 79 (8.8), 65 (6.5), 55 (8.5), 47 (8.6), 43 (100). For $C_{36}H_{50}N_2O_5$ (590.8) calculated: 73.19% C, 8.53% H, 4.74% N; found: 73.19% C, 8.55% H, 4.73% N. The next to be eluted was the main product *IIf* (0.78 g, 51%), m.p. 213 – 215 °C (cyclohexane–chloroform), $[\alpha]_D$ +12° (c 0.22).

3α-Acetoxy-23-(benzimidazol-2-yl)norcholane (*IIe*)

A. O-Acetyllithocholic acid[12] (*Ie*, 2.0 g, 4.8 mmol) and 1,2-diaminobenzene (1.0 g, 9.3 mmol) were stirred and heated to 170 – 190 °C for 45 min under nitrogen and after cooling, the reaction mixture was chromatographed on 100 g silica gel. Elution with benzene–ether 4 : 1 and chloroform with 5% acetone afforded 0.58 g (25%) of *IIe*, m.p. 130 – 133 °C (chloroform–heptane), $[\alpha]_D$ +33° (*c* 0.48). IR spectrum: 3 666 (NH); 1 719 (RCOOR′); 1 624, 1 536 (Ar); 819 (Ar-H). ^{1}H NMR spectrum: 0.64 s, 3 H (18-CH_3); 0.93 s, 3 H (19-CH_3); 1.02 d, 3 H, *J* = 6.1 (21-CH_3); 0.93 – 2.02 m, ca 26 H (skeletal CH_2 and CH); 2.02 s, 3 H (CH_3 of OAc); 2.85 m, 2 H (2 H-23); 4.69 m, 1 H (H-3β); 7.15 dd, 2 H, *J* = 3.2; 6.1 (H-5″ and H-6″); 7.51 dd, 2 H, *J* = 3.2; 6.1 (H-4″ and H-7″); 7.61 bs, 1 H (NH). ^{13}C NMR spectrum: 11.4 (C-18); 17.9 (C-21); 20.2 (C-11); 20.8 (CH_3 of OAc); 22.7 (C-19); 23.5 (C-15); 25.5 (C-23); 25.6 (C-2); 25.9 (C-7); 26.4 (C-6); 27.6 (C-16); 31.6 (C-4); 33.9 (C-10); 34.4 (C-1); 35.1 (C-20); 39.4 (C-12); 39.7 (C-9); 41.2 (C-5); 42.1 (C-13); 55.3 (C-17); 55.8 (C-14); 73.6 (C-3);

114.0 (C-5″ and C-6″); 120.8 (C-4″ and C-7″); 138.6 (C-3a″ and C-7a″); 155.8 (C-2″); 170.8 (CO of OAc). Mass spectrum, *m*/*z* (%): 490 (M^+, $C_{32}H_{46}N_2O_2$, 1.5), 475 (1.5), 433 (1.5), 415 (1.3), 214 (3.7), 199 (2.1), 185 (3.0), 173 (8.5), 145 (100), 132 (87), 119 (2.8), 107 (3.3), 105 (2.9), 95 (2.9), 93 (5.9), 91 (5.0), 81 (5.6), 79 (6.9), 67 (4.0), 55 (5.8), 43 (13.0). For $C_{32}H_{46}N_2O_2$ (490.7) calculated: 78.32% C, 9.45% H, 5.71% N; found: 78.31% C, 9.40% H, 5.73% N.

B. A mixture of *Ie* (100 mg, 0.2 mmol), 1,2-diaminobenzene (80 mg, 0.7 mmol), H_3BO_3 (10 mg) and xylene (7 ml) was refluxed for 40 h. After evaporation in vacuo, the residue was dissolved in ether (100 ml), the solution was washed with water, dried, and evaporated. The residue was processed by preparative TLC using silica gel G (Merck) on a plate (19 × 27 cm) and elution with a system of benzene–ether 4 : 1. It was obtained 40 mg (34%) of the compound *IIe*, m.p. 130 – 133 °C (heptane–chloroform).

3α-(*O*-Acetyllithocholoyloxy)-23-(benzimidazol-2-yl)norcholane (*VIIe*)

A mixture of *Ie* (ref.[12]) (2.0 g, 4.8 mmol) and 1,2-diaminobenzene (1.0 g, 9.3 mmol) was heated for 30 min to 250 °C under nitrogen, after cooling dissolved in chloroform (20 ml), the undissolved solid was filtered off and washed with a boiling mixture of chloroform and methanol; 0.33 g (11%) of *VIIa*, m.p. 266 – 268 °C. The filtrate was evaporated and the residue was chromatographed on 100 g silica gel with successive elution with benzene–ether and chloroform containing 10% of acetone. The first eluted compound was identified as *VIIe* (0.26 g, 13%), m.p. 164 – 166 °C (chloroform–methanol), $[\alpha]_D$ +36° (*c* 0.3). IR spectrum: 3 461 (NH); 1 716 (RCOOR′); 1 600, 1 535 (Ar). ^{1}H NMR spectrum: 0.62 and 0.64 2 s, 3 + 3 H (18-CH_3 and 18′-CH_3); 0.92 s, 6 H (19-CH_3 and 19′-CH_3); 0.97 d, 6 H, *J* = 5.95 (21-CH_3 and 21′-CH_3); 0.90 – 1.99 m, ca 52 H (skeletal CH_2 and CH); 2.04 s, 3 H (CH_3 of OAc); 2.27 m, 2 H (2 H-23′); 2.89 m, 2 H (2 H-23); 4.73 m, 2 H (H-3β and H-3′β); 5.26 bs, 1 H (NH); 7.21 m, 2 H (H-5″ and H-6″); 7.55 m, 2 H (H-4″ and H-7″). ^{13}C NMR spectrum: 12.0 (C-18 and C-18′); 18.3 and 18.4 (C-21 and C-21′); 20.8 (C-11 and C-11′); 21.5 (CH_3 in OAc); 23.3 (C-19 and C-19′); 24.2 (C-15 and C-15′); 26.3 (C-23 and C-23′); 26.6 (C-2 and C-2′); 27.0 (C-6 and C-6′); 28.2 (C-7 and C-7′); 31.0 (C-16 and C-16′); 31.7 (C-4 and C-4′); 32.3 (C-1 and C-1′); 34.6 (C-10 and C-10′); 35.0 (C-22 and C-22′); 35.3 (C-20 and C-20′); 35.8 (C-8 and C-8′); 40.1 (C-13 and C-13′); 40.4 (C-9 and C-9′); 41.9 (C-5 and C-5′); 42.7 (C-12 and C-12′); 56.0 (C-17 and C-17′); 56.5 (C-14 and C-14′); 74.1 and 74.4 (C-3 and C-3′); 114.5 (C-4″ and C-7″); 122.1 (C-5″ and C-6″); 138.3 (C-3a″ and C-7a″); 155.5 (C-2″); 170.7 (COO); 173.9 (CO in 3′-OAc). Mass spectrum, *m*/*z* (%): 503 (0.9), 447 (1.3), 413 (12.4), 215 (6.4), 173 (12.0), 145 (100), 132 (80.4), 119 (6.9), 107 (9.2), 105 (6.9), 95 (8.0), 93 (9.2), 81 (9.0), 79 (8.0), 67 (6.9), 55 (9.2), 43 (11.5). For $C_{56}H_{84}N_2O_4$ (849.9) calculated: 79.20% C, 9.97% H, 3.30% N: found: 79.17% C, 9.95% H, 3.32% N. The last two compounds eluted were *IIe* (90 mg, 4%), m.p. 130 – 133 °C (chloroform–heptane), and *IIa* (0.69 g, 32%), m.p. 292 – 295 °C (chloroform–methanol), $[\alpha]_D$ +29° (*c* 0.27, pyridine).

3α-Hydroxy-23-(1-(2-dimethylaminoethyl)benzimidazol-2-yl)norcholane (*IVa*)

The suspension of NaH (100 mg) in mineral oil was washed with heptane, dimethyl sulfoxide (20 ml) and *IIa* (300 mg) were added and the mixture was refluxed for 2 h. After cooling, the mixture was treated with 2-dimethylaminoethyl chloride (released from 300 mg hydrochloride) in ether (10 ml) and the resulting mixture was refluxed for 3 h. Ether was evaporated, the residue mixed with water (200 ml) and extracted with ethyl acetate (100 ml). Processing of the extract and crystallization of the residue from ether gave 210 mg (60%) of *IVa*, m.p. 167 – 168 °C, $[\alpha]_D$ +14° (*c* 0.28). IR spectrum: 3 609 (OH); 1 613, 1 508 (Ar); 1 030 (C-OH). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide–tetradeuteriomethanol): 0.66 s, 3 H (18-CH_3); 0.89 s, 3 H (19-CH_3); 1.04 d, 3 H, *J* = 5.6 (21-CH_3); 1.16 – 2.01 m, 26 H (skeletal CH_2 and CH); 2.23 s, 6 H ($N(CH_3)_2$); 2.59 t, 2 H, *J* = 7.0

(2^*-CH_2); 2.86 m, 2 H (2 H-23); 3.42 m, 1 H (H-3β); 4.26 t, 2 H, J = 7.0 (1^*-CH_2); 7.18 m, 2 H (H-5″ and H-6″); 7.50 m, 2 H (H-4″ and H-7″). ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide–tetradeuterio- methanol): 13.1 (C-18); 19.8 (C-21); 21.9 (C-11); 24.5 (C-19); 24.9 (C-15); 25.4 (C-7); 27.7 (C-6); 28.4 (C-16); 29.3 (C-23); 31.7 (C-2); 35.1 (C-1); 35.7 (C-10); 36.6 (C-4); 36.95 (C-20); 37.01 (C-8); 37.6 (C-22); 41.3 (C-12); 41.6 (C-9); 42.9 (C-1^*); 43.2 (C-5); 43.9 (C-13); 46.7 ($N(CH_3)_2$); 57.1 (C-17); 57.7 (C-14); 59.5 (C-2^*); 71.6 (C-3); 111.3 (C-7″); 119.5 (C-4″); 122.9 (C-6″); 123.2 (C-5″); 136.3 (C-3a″); 143.4 (C-7a″); 157.4 (C-2″). Mass spectrum, *m/z* (%): 519 (M^+, $C_{34}H_{53}N_3O$, 10.9), 449 (12.6), 216 (24.1), 203 (11.3), 188 (6.9), 187 (6.9), 171 (24.1), 159 (20.7), 146 (25.3), 145 (25.2), 133 (9.2), 132 (8.0), 119 (5.7), 109 (8.0), 95 (9.2), 91 (9.2), 83 (11.5), 82 (11.5), 72 (45.9), 71 (66.7), 58 (100), 57 (41.3), 55 (36.8), 43 (39.0), 41 (32.2). For $C_{34}H_{53}N_3O$ (519.8) calculated: 78.56% C, 10.28% H, 8.08% N; found: 78.58% C, 10.27% H, 8.10% N.

23-(1-(2-Dimethylaminoethyl)benzimidazol-2-yl)-3α-(succinyloxy)norcholane (*IVi*)

A mixture of *IVa* (100 mg, 0.2 mmol), succinic anhydride (100 mg, 1 mmol) and pyridine (8 ml) was refluxed for 14 h, decomposed with water (20 ml) and extracted with ethyl acetate. The extract was washed with water and evaporated. The residue was processed by preparative TLC (silica gel G (Merck), plate 19 × 27 cm). Elution with mixture of ethyl acetate–methanol 7 : 3 gave 80 mg (67%) of *IVi* which did not crystallize, $[\alpha]_D$ +20° (*c* 0.25). IR spectrum: 3 613, 3 539, 2 400 (COOH); 1 723 (COOH and RCOOR′); 1 614, 1 511 (Ar); 839 (Ar-H). ^{1}H NMR spectrum: 0.67 s, 3 H (18-CH_3); 0.92 s, 3 H (19-CH_3); 1.07 d, 3 H, J = 5.4 (21-CH_3); 0.88 – 2.01 m, 26 H (skeletal CH_2 and CH); 2.40 s, 6 H (($N(CH_3)_2$); 2.63 s, 4 H (2^+,3^+-CH_2CH_2); 2.73 t, 2 H, J = 7.7 (2^*-CH_2); 2.89 m, 2 H (2 H-23); 4.28 t, 2 H, J = 7.7 (1^*-CH_2); 4.74 m, 1 H (H-3β); 7.24 m, 2 H (H-5″ and H-6″); 7.34 m, 1 H (H-7″); 7.74 dd, 1 H, J = 3.6; 6.0 (H-4″); 10.19 bs, 1 H (COOH). ^{13}C NMR spectrum: 12.1 (C-18); 18.6 (C-21); 20.8 (C-11); 23.3 (C-19); 24.1 (C-23); 24.2 (C-15); 26.3 (C-2); 26.6 (C-7); 27.0 (C-6); 28.3 (C-16); 30.0 (C-2^+ and C-3^+); 32.2 (C-4); 34.3 (C-1); 34.5 (C-10); 35.0 (C-22); 35.9 (C-8); 40.1 (C-12); 40.4 (C-9); 41.1 (C-1^*); 41.8 (C-5); 42.8 (C-13); 45.0 ($N(CH_3)_2$); 55.9 (C-17); 56.4 (C-14); 57.5 (C-2^*); 74.5 (C-3); 109.0 (C-7″); 119.0 (C-4″); 122.2 (C-6″); 122.3 (C-5″); 134.4 (C-3a″); 141.9 (C-7a″); 155.5 (C-2″); 172.2 (C-1^+ in COO); 175.7 (C-4^+ in COOH). Mass spectrum, *m/z* (%): 619 (M^+, $C_{38}H_{57}N_3O_4$, 1.8), 549 (5.3), 519 (2.1), 216 (36.6); 203 (9.2), 188 (13.8), 171 (35.6), 162 (26.4), 159 (26.7), 146 (34.5), 145 (35.6), 133 (9.2), 132 (12.9), 119 (6.9), 107 (7.3), 105 (7.3), 95 (9.4), 93 (9.4), 81 (13.8), 72 (82.7), 71 (82.8), 59 (100), 58 (100), 55 (32.2), 45 (20.7), 43 (34.5), 41 (25.3). For $C_{38}H_{57}N_3O_4$ (619.9) calculated: 73.63% C, 9.27% H, 6.78% N; found: 73.68% C, 9.17% H, 6.82% N.

3α-Acetoxy-23-[5(6)-methylbenzimidazol-2-yl]norcholane (*VIII*)

From a mixture of *Ie* (ref.[12]) (2.0 g, 4.8 mmol), 1,2-diamino-4-methylbenzene (0.80 g, 6.6 mmol), H_3BO_3 (0.2 g) and xylene (50 ml), 10 ml of the solvent were slowly distilled off for removing water. The remaining solution was then refluxed for 40 h. After evaporation in vacuo, the residue was dissolved in 150 ml ether, the solution was washed with water, dried, and evaporated. The residue was chromatographed on 100 g silica gel using elution with benzene and benzene–ether; 1.40 g (58%) of *VIII*, m.p. 134 – 137 °C (chloroform–methanol), $[\alpha]_D$ +27° (c 0.4). IR spectrum: 3 462 (NH); 1 710 (RCOOR′); 1 600, 1 536 (Ar); 1 026 (RCOOR′); 810 (Ar-H). ^{1}H NMR spectrum: 0.58 s, 3 H (18-CH_3); 0.91 s, 3 H (19-CH_3); 0.92 d, 3 H, J = 6.1 (21-CH_3); 0.98 – 1.95 m, 26 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in OAc); 2.45 s, 3 H ($ArCH_3$); 2.88 m, 2 H (2 H-23); 3.51 s, 1 H (NH); 4.73 m, 1 H (H-3β); 7.02 dd, 1 H, J = 7.8; 0.9 (H-5″); 7.32 bs, 1 H (H-7″); 7.43 d, 1 H, J = 7.8 (H-4″). ^{13}C NMR spectrum: 11.9 (C-18); 18.3 (C-21); 20.8 (C-11); 21.4 (CH_3 of OAc); 21.6 (5″(6″)-CH_3); 23.3 (C-19); 24.1 (C-15); 26.1 (C-23); 26.2 (C-2); 26.6 (C-7); 27.0 (C-6); 28.1 (C-16); 32.2 (C-4); 34.5 (C-10 and

C-22); 35.0 (C-1); 35.6 (C-20); 35.7 (C-8); 40.1 (C-12); 40.3 (C-9); 41.8 (C-5); 42.6 (C-13); 55.8 (C-17); 56.3 (C-14); 74.4 (C-3); 123.3 (C-4″, C-6″(C-5″) and C-7″); 131.6 (C-3a″, C-5″(C-6″) and C-7a″); 155.6 (C-2″); 170.8 (CO of OAc). Mass spectrum, *m/z* (%): 504 (M^+, $C_{33}H_{48}N_2O_2$, 5.2), 489 (2.5), 447 (2.7), 228 (4.1), 199 (1.9), 187 (7.5), 159 (100), 146 (49.3), 95 (2.8), 81 (2.8), 71 (2.8), 57 (4.9), 43 (6.1). For $C_{33}H_{48}N_2O_2$ (504.7) calculated: 78.52% C, 9.59% H, 5.55% N; found: 78.51% C, 9.62% H, 5.53% N.

23-(Benzoxazol-2-yl)norcholan-3α-ol (*Va*)

A mixture of *Ia* (1.76 g, 4.7 mmol) and 2-aminophenol (1.5 g, 13.8 mmol) was stirred for 1 h and heated to 240 – 270 °C under nitrogen. After cooling, the mixture was dissolved in chloroform, the solution was filtered through a layer of silica gel (10 g) and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (130 g), eluent benzene and benzene–ether 9 : 1; 1.72 g (82%) of *Va*, m.p. 135 – 136 °C (ether), $[\alpha]_D$ +20° (*c* 0.47). IR spectrum: 3 608 (OH); 1 613, 1 570 (Ar); 1 030 (C-OH); 849 (Ar-H). ^{1}H NMR spectrum: 0.65 s, 3 H (18-CH_3); 0.92 s, 3 H (19-CH_3); 1.02 d, 3 H, *J* = 6.35 (21-CH_3); 0.92 – 2.00 m, ca 26 H (skeletal CH_2 and CH); 2.92 m, 2 H (2 H-23); 3.63 m, 1 H (H-3β); 7.29 m, 2 H (H-5″ and H-6″); 7.48 dd, 1 H, *J* = 3.0; 6.2 (H-4″); 7.78 dd, 1 H, *J* = 2.7; 5.9 (H-7″). ^{13}C NMR spectrum: 12.0 (C-18); 18.3 (C-21); 20.8 (C-11); 23.3 (C-19); 24.2 (C-15); 25.6 (C-23); 26.4 (C-7); 27.2 (C-6); 28.2 (C-16); 30.5 (C-2); 33.0 (C-22); 34.5 (C-10); 35.3 (C-1); 35.5 (C-20); 35.8 (C-8); 36.4 (C-4); 40.1 (C-12); 40.4 (C-9); 42.1 (C-5); 42.7 (C-13); 55.8 (C-17); 56.4 (C-14); 71.8 (C-3); 110.2 (C-4″); 119.4 (C-7″); 124.0 (C-5″); 124.3 (C-6″); 141.3 (C-7a″); 150.7 (C-3a″); 167.8 (C-2″). Mass spectrum, *m/z* (%): 449 (M^+, $C_{30}H_{43}NO_2$, 15.8), 202 (47.9), 174 (11.3), 162 (12.7), 146 (85.9), 133 (100), 119 (5.6), 109 (16.9). 93 (14.8), 91 (11.3), 85 (44.4), 81 (14.1), 79 (15.1), 67 (16.7), 55 (16.7), 47 (15.5), 41 (9.2). For $C_{30}H_{43}NO_2$ (449.7) calculated: 80.13% C, 9.64% H, 3.12% N; found: 80.14% C, 9.65% H, 3.12% N.

23-(Benzoxazol-2-yl)norcholane-3α,12α-diol (*Vc*)

Acid *Ic* (1.5 g, 3.8 mmol) and 2-aminophenol (1.25 g, 11.5 mmol) were similarly processed (230 – 250 °C) and the crude product was chromatographed on silica gel (80 g). Elution with benzene and benzene-acetone 19 : 1 gave 1.50 g (85%) of *Vc*, m.p. 99 – 100 °C (ether), $[\alpha]_D$ +33° (*c* 0.45). IR spectrum: 3 611 (OH); 1 614, 1 570 (Ar and C=N); 1 039 (C-OH); 843 (Ar-H). ^{1}H NMR spectrum: 0.68 s, 3 H (18-CH_3); 0.90 s, 3 H (19-CH_3); 1.07 d, 3 H, *J* = 6.35 (21-CH_3); 0.85 – 1.84 m, ca 24 H (skeletal CH_2 and CH); 2.35 s, 2 H (3- and 12-OH); 2.92 m, 2 H (2 H-23); 3.62 m, 1 H (H-3β); 4.01 s, 1 H (H-12β); 7.28 m, 2 H (H-5″ and H-6″); 7.47 dd, 1 H, *J* = 3.0; 5.8 (H-4″); 7.67 dd, 1 H, *J* = 3.4; 5.8 (H-7″). ^{13}C NMR spectrum: 12.7 (C-18); 17.3 (C-21); 23.1 (C-19); 23.7 (C-15); 25.8 (C-23); 26.1 (C-16); 27.1 (C-7); 27.5 (C-6); 28.6 (C-11); 30.4 (C-2); 32.8 (C-22); 33.6 (C-9); 34.1 (C-10); 35.2 (C-1); 36.0 (C-8); 36.4 (C-4); 42.0 (C-5); 46.5 (C-13); 47.0 (C-17); 48.2 (C-14); 71.7 (C-3); 73.1 (C-12); 110.2 (C-4″); 119.4 (C-7″); 124.0 (C-5″); 124.3 (C-6″); 141.2 (C-7a″); 150.7 (C-3a″); 167.8 (C-2″). Mass spectrum, *m/z* (%): 465 (M^+, $C_{30}H_{43}NO_3$, 6.5), 356 (7.6), 339 (12.4), 256 (7.0), 202 (11.3), 159 (6.2), 146 (74.6), 133 (100), 119 (5.6), 105 (11.3), 93 (15.5), 81 (12.7), 79 (12.7), 67 (11.3), 55 (16.2), 41 (12.4). For $C_{30}H_{43}NO_3$ (465.5) calculated: 77.38% C, 9.31% H, 3.01% N; found: 77.40% C, 9.35% H, 3.00% N.

3α,7α,12α-Triacetoxy-23-(benzoxazol-2-yl)norcholane (*Vh*)

Acid *Id* (1.5 g, 3.7 mmol) and 2-aminophenol (1.2 g, 11 mmol) were processed similarly to the case of *Va*. The crude product, which did not crystallize, was treated with acetic anhydride (10 ml) and refluxed in presence of DMAP (0.1 g) for 1 h. The mixture was decomposed with ice and extracted

with ethyl acetate. The residue, obtained by processing of the extract, was chromatographed on silica gel (100 g) using elution with benzene–ether 9 : 1; 1.45 g (65%) of *Vh*, m.p. 150 – 152 °C (chloroform–hexane), $[\alpha]_D$ + 62° (*c* 0.49). IR spectrum: 1 724, 1 024 (RCOOR); 1 614, 1 570 (Ar). ^{1}H NMR spectrum: 0.74 s, 3 H (18-CH_3); 0.92 s, 3 H (19-CH_3); 0.93 d, 3 H, *J* = 6.0 (21-CH_3); 0.85 – 2.00 m, ca 22 H (skeletal CH_2 and CH); 2.05 s, 3 H (CH_3 in 3-OAc); 2.09 s, 3 H (CH_3 in 7-OAc); 2.16 s, 3 H (CH_3 in 12-OAc); 2.90 m, 2 H (2 H-23); 4.58 m, 1 H (H-3β); 4.91 d, 1 H, *J* = 2.3 (H-7β); 5.11 t, 1 H, *J* = 2.5 (H-12β); 7.29 m, 2 H (H-5″ and H-6″); 7.48 dd, 1 H, *J* = 3.0; 5.7 (H-4″); 7.66 dd, 1 H, *J* = 3.5; 6.0 (H-7″). ^{13}C NMR spectrum: 12.1 (C-18); 17.5 (C-21); 21.3 and 21.5 (3 CH_3 in 3,7,12-$(OAc)_3$); 22.7 (C-15); 25.3 (C-11); 25.5 (C-23); 26.8 (C-2); 27.2 (C-18); 28.8 (C-9); 31.1 (C-6); 32.6 (C-22); 34.2 (C-4 and C-10); 34.5 (C-1); 34.7 (C-20); 37.6 (C-8); 40.8 (C-5); 43.3 (C-14); 45.0 (C-13); 47.1 (C-17); 70.6 (C-7); 74.0 (C-3); 75.3 (C-12); 110.1 (C-4″); 119.4 (C-7″); 124.0 (C-5″); 124.3 (C-6″); 141.2 (C-7a″); 150.7 (C-3a″); 167.4 (C-2″); 170.2 and 170.4 (3 CO in 3,7,12-$(OAc)_3$). Mass spectrum, *m*/*z* (%): 607 (M^+, $C_{36}H_{49}NO_7$, 1.2), 174 (9.6), 159 (3.9), 146 (70.6), 133 (100), 119 (5.9), 105 (8.2), 93 (7.3), 91 (5.9), 81 (7.1), 67 (4.7), 55 (5.9), 43 (35.3). For $C_{36}H_{49}NO_7$ (607.8) calculated: 71.13% C, 8.14% H, 2.30% N; found: 71.13% C, 8.15% H, 2.31% N.

3α-Acetoxy-23-(benzoxazol-2-yl)norcholane (*Ve*)

A mixture of *Ie* (ref.[12]) (100 mg, 0.2 mmol), 2-aminophenol (80 mg, 0.7 mmol), H_3BO_3 (10 mg) and xylene (7 ml) was refluxed for 10 h and evaporated in vacuo. The residue was dissolved in ether (100 ml), the solution was washed with water, dried, and evaporated. The residue was processed by preparative TLC (silica gel G (Merck), plate 19 × 27 cm); elution with benzene–ether 7 : 3 gave 90 mg (75%) of *Ve*, m.p. 99 – 101 °C (chloroform–heptane). IR spectrum: 1 718, 1 030 (RCOOR′); 1 613, 1 570 (Ar). ^{1}H NMR spectrum: 0.65 s, 3 H (18-CH_3); 0.93 s, 3 H (19-CH_3); 1.02 d, 3 H, *J* = 6.11 (21-CH_3); 0.97 – 1.97 m, 26 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in 3-OAc); 2.91 m, 2 H (2 H-23); 4.73 m, 1 H (H-3β); 7.29 m, 2 H (H-5″ and H-6″); 7.48 m, 1 H (H-4″); 7.67 m, 1 H (H-7″). ^{13}C NMR spectrum: 12.0 (C-18); 18.4 (C-21); 20.8 (C-11); 21.4 (CH_3 in OAc); 23.3 (C-19); 24.2 (C-15); 25.6 (C-23); 26.6 (C-7); 27.0 (C-6); 28.2 (C-16); 32.2 (C-2); 33.0 (C-22); 34.5 (C-10); 35.0 (C-1); 35.5 (C-20); 35.8 (C-8); 40.1 (C-12); 40.4 (C-9); 41.9 (C-5); 42.8 (C-13); 55.9 (C-17); 56.5 (C-14); 74.4 (C-3); 110.2 (C-4″); 119.4 (C-7″); 124.0 (C-5″); 124.3 (C-6″); 141.4 (C-7a″); 150.8 (C-3a″); 167.8 (C-2″); 170.6 (CO in OAc). Mass spectrum, *m*/*z* (%): 491 (M^+, $C_{32}H_{45}NO_3$, 0.3), 432 (9.0), 215 (8.7), 202 (28.0), 174 (10.0), 162 (7.0), 146 (100), 133 (76), 119 (5.6), 109 (9.9), 93 (14.1), 81 (15.5), 67 (9.9), 55 (9.9), 43 (8.5). For $C_{32}H_{45}NO_3$ (491.7 calculated: 78.16% C, 9.23% H, 2.85% N; found: 78.14% C, 9.23% H, 2.88% N.

23-(Benzoxazol-2-yl)-3α-(succinyloxy)norcholane (*Vi*)

A mixture of *Va* (100 mg, 0.22 mmol), succinic anhydride (100 mg, 1 mmol) and pyridine (7 ml) was refluxed for 3 h, cooled, diluted with 20 ml water and extracted with ether. Processing of the extract including filtration through a layer of silica gel (5 g) gave after evaporation 100 mg (81.8%) of *Vi*, m.p. 126 – 128 °C (ether), $[\alpha]_D$ +28° (*c* 0.32). IR spectrum: 3 521, 3 342, 2 354 (OH of COOH); 1 717 (COOH); 1 613, 1 570 (Ar); 1 019 (C–O of RCOOR′); 841 (Ar-H). ^{1}H NMR spectrum: 0.65 s, 3 H (18-CH_3); 0.93 s, 3 H (19-CH_3); 1.02 d, 3 H, *J* = 6.1 (21-CH_3); 1.08 – 2.01 m, 26 H (skeletal CH_2 and CH); 2.64 m, 4 H (2^+, 3^+-CH_2CH_2); 2.92 m, 2 H (2 H-23); 4.76 m, 1 H (H-3β); 7.29 m, 2 H (H-5″ and H-6″); 7.48 dd, 1 H, *J* = 3.3; 6.6 (H-4″); 7.69 dd, 1 H, *J* = 3.1; 6.0 (H-7″). ^{13}C NMR spectrum: 12.1 (C-18); 18.4 (C-21); 20.8 (C-11); 23.3 (C-10); 24.2 (C-15); 25.5 (C-23); 26.3 (C-2); 26.6 (C-7); 27.0 (C-6); 28.2 (C-16); 29.0 and 29.3 (C-2^+ and C-3^+); 32.1 (C-4); 33.0 (C-22); 34.6 (C-10); 35.0 (C-1); 35.6 (C-20); 35.8 (C-8); 40.1 (C-12); 40.4 (C-9); 41.9 (C-5); 42.8 (C-13); 55.9 (C-17); 56.4 (C-14); 74.9 (C-3); 110.2 (C-4″); 119.4 (C-7″); 124.1 (C-5″); 124.4 (C-6″);

141.1 (C-7a″); 150.7 (C-3a″); 167.9 (C-2″); 171.7 (1^+-CO); 177.2 (4^+-COOH). Mass spectrum, *m/z* (%): 549 (M^+, $C_{34}H_{47}NO_5$, 3.2), 534 (0.9), 492 (0.5), 432 (1.1), 416 (0.9), 323 (2.2), 216 (3.4), 215 (6.2), 202 (46.5), 189 (5.6), 174 (11.3), 162 (10.2), 146 (100), 133 (95.8), 119 (5.6), 107 (8.5), 93 (12.7), 81 (13.2), 67 (12.7), 55 (21.1), 43 (9.9), 41 (9.9). For $C_{34}H_{47}NO_5$ (549.7) calculated: 74.28% C, 8.62% H, 2.55% N; found: 74.28% C, 8.64% H, 2.54% N.

General Procedure for Preparation of Benzothiazoles *VIe – VIh*

O-Acetylated bile acids *Ie – Ih* (3 mmol) were dissolved in benzene (15 ml), the solution was treated with $SOCl_2$ (3 ml) and the mixture was allowed to stand for 2 h at room temperature. It was then evaporated in vacuo and the remaining $SOCl_2$ was removed by repeated evaporation with benzene. The residue (the crude acid chloride) was dissolved in benzene (10 ml), the solution was treated under stirring with 2-aminothiophenol (0.93 g, 7.5 mmol) and the mixture was refluxed for 2 h. After cooling, benzene was evaporated in vacuo, the residue was dissolved in ether, the solution was washed with water, dried, and evaporated. The residue was chromatographed on 50 g silica gel using elution with light petroleum and light petroleum–ethyl acetate mixtures.

3α-Acetoxy-23-(benzothiazol-2-yl)norcholane (VIe). The general procedure was applied to *Ie* (ref.[12]) and $SOCl_2$ in 10 ml benzene. The crude acid chloride (mentioned in refs[22–24]) was reacted with 2-aminothiophenol (0.93 g, 7.5 mmol) and after chromatography (80 g silica gel) gave 0.97 g (80%) of *VIe*, m.p. 103 – 105 °C (chloroform–hexane). IR spectrum: 1 719 (COOH); 1 517 (Ar), 1 020 (C-O of RCOOR′). ^{1}H NMR spectrum: 0.65 s, 3 H (18-CH_3); 0.95 s, 3 H (19-CH_3); 1.04 d, 3 H, J = 6.1 (21-CH_3); 1.02 – 2.04 m, ca 26 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in OAc); 3.10 m, 2 H (2 H-23); 4.73 m, 1 H (H-3β); 7.39 m, 2 H (H-5″ and H-6″); 7.84 dd, 1 H, J = 0.6; 7.4 (H-4″); 7.97 dd, 1 H, J = 0.6; 8.0 (H-7″). ^{13}C NMR spectrum: 12.1 (C-18); 18.5 (C-21); 20.8 (C-11); 21.5 (CH_3 in OAc); 23.3 (C-19); 24.2 (C-15); 26.3 (C-2); 26.6 (C-7); 27.0 (C-6); 28.3 (C-16); 31.3 (C-22); 32.2 (C-4); 34.6 (C-10); 35.0 (C-1); 35.6 (C-20); 35.8 (C-8); 36.0 (C-23); 40.2 (C-12); 40.4 (C-9); 41.9 (C-5); 42.8 (C-13); 56.0 (C-17); 56.5 (C-14); 74.4 (C-3); 121.4, 122.5, 124.6 and 125.8 (C-4″, C-5″, C-6″ and C-7″); 135.4 (C-3a″); 153.5 (C-7a″); 170.6 (CO of OAc); 172.9 (C-2″). Mass spectrum, *m/z* (%): 507 (M^+, $C_{32}H_{45}NO_2S$, 4.4), 190 (6.0), 162 (100), 149 (100), 107 (6.6), 93 (7.7), 81 (7.0), 79 (7.7), 67 (6.9), 55 (7.0), 43 (13.4). For $C_{32}H_{45}NO_2S$ (507.8) calculated: 75.69% C, 8.93% H, 2.76% N, 6.31% S; found: 75.70% C, 8.95% H, 2.73% N, 6.31% S.

3α,7α-Diacetoxy-23-(benzothiazol-2-yl)norcholane (VIf). According to the general procedure, *If* (refs[19,28]) (1.2 g, 2.5 mmol) and $SOCl_2$ (3 ml) gave the crude acid chloride which was reacted with 2-aminothiophenol (0.93 g, 7.5 mmol) and the crude product was chromatographed on 100 g silica gel giving 1.17 g (82%) of amorphous *VIf*, $[\alpha]_D$ +7° (*c* 0.5). IR spectrum: 1 724 (COOH); 1 517 (Ar); 1 024 (C–O in RCOOR′). ^{1}H NMR spectrum: 0.65 s, 3 H (18-CH_3); 0.93 s, 3 H (19-CH_3); 1.05 d, 3 H, J = 6.1 (21-CH_3); 0.92 – 2.07 m, 24 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in 3-OAc); 2.06 s, 3 H (CH_3 in 7-OAc); 3.12 m, 2 H (2 H-23); 4.60 m, 1 H (H-3β); 4.88 d, 1 H, J = 2.7 (H-7β); 7.39 m, 2 H (H-5″ and H-6″); 7.84 dd, 1 H, J = 1.1; 7.9 (H-4″); 7.96 dd, 1 H, J = 1.1; 7.9 (H-7″). ^{13}C NMR spectrum: 11.7 (C-18); 18.4 (C-21); 20.6 (C-11); 21.4 and 21.5 (2 CH_3 in 3,7-$(OAc)_2$); 22.6 (C-19); 23.5 (C-15); 26.7 (C-2); 28.0 (C-16); 31.1 (C-22); 31.2 (C-6); 34.0 (C-9); 34.7 (C-10); 34.8 (C-1); 35.4 (C-20); 35.6 (C-23); 35.9 (C-4); 37.8 (C-8); 39.4 (C-12); 40.9 (C-5); 42.7 (C-13); 50.3 (C-14); 55.6 (C-17); 71.1 (C-7); 74.1 (C-3); 121.4, 122.4, 124.5 and 125.8 (C-4″, C-5″, C-6″ and C-7″); 135.0 (C-3a″); 153.1 (C-7a″); 170.3 and 170.5 (2 CO in 3,7-$(OAc)_2$); 172.7 (C-2″). Mass spectrum, *m/z* (%): 565 (M^+, $C_{34}H_{47}NO_4S$, 4.4), 232 (7.2), 190 (6.2), 162 (81.7), 149 (100), 105 (7.0), 93 (7.1), 79 (5.6), 67 (4.2), 55 (4.9), 42 (19.0). For $C_{34}H_{47}NO_4S$ (565.8) calculated: 72.18% C, 8.37% H, 2.48% N, 5.67% S; found: 72.19% C, 8.40% H, 2.45% N, 5.66% S.

3α,12α-Diacetoxy-23-(benzothiazol-2-yl)norcholane (VIg). The acid *Ig* (refs[19,29]) (1.86 g, 3.9 mmol) was transformed by treatment with $SOCl_2$ (6 ml) to the crude acid chloride (mentioned in ref.[25]) which reacted with 2-aminothiophenol (1.3 ml). The crude product was chromatographed on 100 g silica gel and gave 1.72 g (78%) of *VIg*, m.p. 155 – 158 °C (chloroform–methanol), $[\alpha]_D$ +60° (*c* 0.38). IR spectrum: 1 719 (COOH); 1 517 (Ar); 1 027 (C–O in RCOOR′). ^{1}H NMR spectrum: 0.73 s, 3 H (18-CH_3); 0.91 s, 3 H (19-CH_3); 0.94 d, 3 H, *J* = 6.35 (21-CH_3); 0.95 – 2.02 m, 24 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in 3-OAc); 2.12 s, 3 H (CH_3 in 12-OAc); 3.08 m, 2 H (2 H-23); 4.71 m, 1 H (H-3β); 5.11 t, 1 H, *J* = 2.3 (H-12β); 7.40 m, 2 H (H-5″ and H-6″); 7.84 dd, 1 H, *J* = 8.7; 1.1 (H-4″); 7.96 dd, 1 H, *J* = 8.6; 1.1 (H-7″). ^{13}C NMR spectrum: 12.4 (C-18); 17.7 (C-21); 21.4 (2 CH_3 in 3,12-$(OAc)_2$); 23.0 (C-19); 23.4 (C-15); 25.6 (C-11); 25.8 (C-16); 26.6 (C-7); 26.8 (C-2); 27.4 (C-6); 31.2 (C-22); 32.2 (C-4); 34.0 (C-10); 34.4 (C-9); 34.7 (C-23); 34.9 (C-20); 35.6 (C-8); 35.8 (C-1); 41.8 (C-5); 45.0 (C-13); 47.6 (C-17); 49.4 (C-14); 74.1 (C-3); 75.9 (C-12); 121.4, 122.4, 124.6 and 125.8 (C-4″, C-5″, C-6″ and C-7″); 135.2 (C-3a″); 153.3 (C-7a″); 170.4 and 170.5 (2 CO in 3,12-$(OAc)_2$); 172.6 (C-2″). Mass spectrum, *m/z* (%): 565 (M^+, $C_{34}H_{47}NO_4S$, 4.4), 190 (6.2), 162 (50.5), 149 (100), 105 (3.9), 90 (4.0), 81 (4.6), 69 (4.6), 55 (9.2), 43 (20.7). For $C_{34}H_{47}NO_4S$ (565.8) calculated: 72.18% C, 8.37% H, 2.48% N, 5.67% S; found: 72.18% C, 8.35% H, 2.49% N, 5.67% S.

3α,7α,12α-Triacetoxy-23-(benzothiazol-2-yl)norcholane (VIh) The acid *Ih* (refs[20,21]) (1.3 g, 2.5 mmol) was transformed by treatment with $SOCl_2$ (3 ml) to the crude acid chloride which was reacted with 2-aminothiophenol (0.93 g, 7.5 mmol) according to the general procedure. The crude product was chromatographed on 100 g silica gel; 1.3 g (85%) of *VIh*, m.p. 139 – 142 °C (chloroform–methanol), $[\alpha]_D$ +62° (*c* 0.4). IR spectrum: 1 724 (COOH); 1 517 (Ar); 1 024 (C–O in RCOOR′); 823, 813 (Ar-H). ^{1}H NMR spectrum: 0.73 s, 3 H (18-CH_3); 0.91 s, 3 H (19-CH_3); 0.94 d, 3 H, *J* = 6.1 (21-CH_3); 1.06 – 2.00 m, 22 H (skeletal CH_2 and CH); 2.05 s, 3 H (CH_3 in 3-OAc); 2.09 s, 3 H (CH_3 in 7-OAc); 2.16 s, 3 H (CH_3 in 12-OAc); 3.09 m, 2 H (2 H-23); 4.58 m, 1 H (H-3β); 4.91 d, 1 H, *J* = 2.9 (H-7β); 5.12 s, 1 H (H-12β); 7.39 m, 2 H (H-5″ and H-6″); 7.84 dd, 1 H, *J* = 7.5; 1.6 (H-4″); 7.96 dd, 1 H, *J* = 7.5; 1.4 (H-7″). ^{13}C NMR spectrum: 12.1 (C-18); 17.6 (C-21); 21.3 and 21.5 (3 CH_3 in 3,7,12-$(OAc)_3$); 22.4 (C-19); 22.7 (C-15); 25.5 (C-11); 26.8 (C-2); 27.2 (C-16); 28.8 (C-9); 30.9 (C-23); 31.1 (C-6); 34.2 (C-10); 34.5 (C-4 and C-22); 34.7 (C-20); 35.6 (C-1); 37.6 (C-8); 40.8 (C-5); 43.3 (C-14); 45.0 (C-13); 47.1 (C-17); 70.5 (C-7); 73.9 (C-3); 75.3 (C-12); 121.4, 122.3, 124.5 and 125.8 (C-4″, C-5″, C-6″ and C-7″); 135.0 (C-3a″); 153.0 (C-7a″); 170.2, 170.4 and 172.4 (3 CO in 3,7,12-$(OAc)_3$ and C-2″). Mass spectrum, *m/z* (%): 623 (M^+, $C_{36}H_{49}NO_6S$, 3.4), 442 (2.7), 382 (1.8), 313 (4.1), 190 (6.2), 162 (46.0), 149 (100), 119 (4.1), 105 (4.8), 93 (4.6), 69 (4.7), 55 (9.2), 43 (27.6). For $C_{36}H_{49}NO_6S$ (623.8) calculated: 69.31% C, 7.92% H, 2.25% N, 5.14% S; 69.32% C, 7.90% H, 2.26% N, 5.14% S.

23-(Benzothiazol-2-yl)-3α-(succinyloxy)norcholane (*VIi*)

A solution of *VIe* (150 mg, 0.3 mmol) in methanol (15 ml) was treated with NaOH (0.1 g) in water (0.5 ml) and the mixture was refluxed for 4 h. Most of the organic solvent was evaporated in vacuo, the residue was diluted with water (50 ml) and slightly acidified with dilute hydrochloric acid. The precipitated crude *VIa* (0.13 g, 95%) was washed with water and dried. It was dissolved in 8 ml pyridine, the solution was treated with succinic anhydride (0.15 g, 1.5 mmol) and the mixture was refluxed for 4 h. After cooling, it was diluted with water (20 ml) and extracted with ether. Processing of the extract gave 0.13 g (82%) of *VIi*, m.p. 160 – 161 °C (ether), $[\alpha]_D$ +28° (*c* 0.35). IR spectrum: 3 514, 3 346 (OH of COOH); 1 717 (COOH); 1 516 (Ar). ^{1}H NMR spectrum: 0.64 s, 3 H (18-CH_3); 0.92 s, 3 H (19-CH_3); 1.03 d, 3 H, *J* = 5.6 (21-CH_3); 0.90 – 2.01 m, 26 H (skeletal CH_2 and CH); 2.65 m, 4 H (2^+,3^+-CH_2CH_2); 3.11 m, 2 H (2 H-23); 4.75 m, 1 H (H-3β); 7.36 m, 2 H (H-5″ and H-6″); 7.83 d, 1 H, *J* = 7.4 (H-4″); 8.00 d, 1 H, *J* = 8.2 (H-7″); 10.76 bs, 1 H (COOH). ^{13}C NMR

spectrum: 12.0 (C-18); 18.4 (C-21); 20.8 (C-11); 23.3 (C-19); 24.1 (C-15); 26.2 (C-2); 26.5 (C-7); 26.9 (C-6); 28.2 (C-16); 29.1 and 29.3 (C-2$^+$ and C-3$^+$); 31.0 (C-23); 32.1 (C-4); 34.5 (C-10); 35.0 (C-1); 35.6 (C-20); 35.7 (C-8); 36.0 (C-22); 40.1 (C-12); 40.3 (C-9); 41.8 (C-5); 42.7 (C-13); 55.9 (C-17); 56.4 (C-14); 74.8 (C-3); 121.4 (C-4″); 122.3 (C-5″); 124.6 (C-6″); 125.9 (C-7″); 134.8 (C-3a″); 152.7 (C-7a″); 173.5 (C-2″); 177.1 (COOH). Mass spectrum, *m*/*z* (%): 565 (M^+, $C_{34}H_{47}NO_4S$, 5.5), 508 (1.8), 231 (3.0), 202 (4.0); 190 (8.8); 175 (1.9); 162 (100); 149 (93.3); 136 (7.5); 105 (4.6); 93 (6.9); 81 (6.9); 67 (6.9), 55 (13.8), 43 (6.9), 41 (9.2). For $C_{34}H_{47}NO_4NO_4S$ (565.8) calculated: 72.18% C, 8.37% H, 2.48% N, 5.67% S; found: 72.19% C, 8.33% H, 2.49% N, 5.67% S.

3α-(*O*-Acetyllithocholoyloxy)-23-(1*H*-imidazo(4,5-*c*)pyridin-2-yl)norcholane (*X*)

From a mixture of *Ie* (ref.[12]) (2.0 g, 4.8 mmol), 3,4-diaminopyridine (0.5 g, 4.6 mmol), H_3BO_3 (0.2 g) and xylene (50 ml), a part of xylene (10 ml) was distilled off at normal pressure for removing the formed H_2O and the residue was refluxed for 10 days. 3,4-Diaminopyridine (0.2 g, 0.9 mmol) and xylene (15 ml) were added, xylene (10 ml) were again distilled off and the residue was refluxed for further 10 days. The mixture was evaporated in vacuo, the residue was dissolved in chloroform (170 ml), the solution was washed with water, dried, and evaporated. The residue was chromatographed on 100 g silica gel using elution with benzene–ethyl acetate 9 : 1; 1.83 g (98%) of the amorphous solid *X*, $[\alpha]_D$ +26° (*c* 0.63, pyridine). IR spectrum: 3 627 (NH); 1 725, 1 713 (C–O of RCOOR′); 1 631 (Ar); 1 023 (C–O of RCOOR′). ^{1}H NMR spectrum: 0.64 s, 6 H (18- and 18′-CH_3); 0.92 s, 6 H (19- and 19′-CH_3); 0.91 d, 6 H, *J* = 5.8 (21- and 21′-CH_3); 0.90 – 2.05 m, 52 H (skeletal CH_2 and CH); 2.03 s, 3 H (CH_3 in 3′-OAc); 2.24 m, 2 H (2 H-23′); 2.96 m, 2 H (2 H-23); 4.72 m, 2 H (H-3β and H-3′β); 7.47 d, 1 H, *J* = 5.3 (H-7″); 8.37 d, 1 H, J = 5.3 (H-6″); 8.92 s, 1 H (H-4″). ^{13}C NMR spectrum: 11.3 (C-18 and C-18′); 17.5 and 17.6 (C-21 and C-21′); 20.1 (C-11 and C-11′); 20.3 (CH_3 in 3′-OAc); 20.4 (C-19 and C-19′); 23.5 (C-15 and C-15′); 25.5 (C-23); 25.6 (C-2 and C-2′); 25.9 (C-7 and C-7′); 27.5 (C-6 and C-6′); 28.0 (C-16 and C-16′); 30.4 (C-23′); 30.9 and 31.6 (C-4 and C-4′); 33.6 (C-10 and C-10′); 33.9 (C-22 and C-22′); 34.3 (C-1 and C-1′); 34.6 (C-8 and C-8′); 35.0 and 35.1 (C-20 and C-20′); 39.4 (C-12 and C-12′); 39.7 (C-9 and C-9′); 41.2 (C-5 and C-5′); 42.1 (C-13 and C-13′); 55.4 (C-17 and C-17′); 55.6 and 55.8 (C-14 and C-14′); 73.2 and 73.4 (C-3 and C-3′); 140.6 (C-4″); 159.0 (C-2″); 170.0 and 170.6 (2 CO in 3- and 3′-OCO). Mass spectrum, *m*/*z* (%): 849 (M^+, $C_{55}H_{83}N_3O_4$, 0.08), 504 (1.6), 448 (1.5), 432 (7.8), 215 (4.2), 174 (6.9), 146 (100), 133 (29.6), 107 (3.6), 95 (4.2), 81 (4.2), 69 (4.9), 57 (7.9), 55 (5.6), 43 (7.7). For $C_{55}H_{83}N_3O_4$ (850.3) calculated: 77.69% C, 9.84% H, 4.94% N; found: 77.67% C, 9.89% H, 4.92% N.

3α-Acetoxy-23-(1*H*-imidazo(4,5-*c*)pyridin-2-yl)norcholane (*IX*)

A mixture of *X* (1.8 g, 2.1 mmol) and methanol (50 ml) was treated with NaOH (0.5 g) in water (1 ml) and the mixture was refluxed for 2 h, partly evaporated in vacuo, and the residue was diluted with 100 ml water. The precipitated solid was filtered, washed with water and methanol, and dried. This intermediate was dissolved in pyridine (10 ml), the solution was treated with acetic anhydride (5 ml) and the mixture was allowed to stand overnight at room temperature. Then it was poured on ice and extracted with chloroform. The extract was washed with an aqueous solution of Na_2CO_3 and with water, filtered through a layer of Al_2O_3 (10 g) and evaporated; 0.80 g (80%) of amorphous *IX*, $[\alpha]_D$ +27° (*c* 0.98). IR spectrum: 3 451 (NH); 1 719 (RCOOR′); 1 622, 1 589 (Ar); 1 091 (C–O in ester); 823, 813 (Ar-H). ^{1}H NMR spectrum: 0.59 s, 3 H (18-CH_3); 0.91 s, 3 H (19-CH_3); 0.95 d, 3 H, *J* = 5.86 (21-CH_3); 1.01 – 1.96 m, 26 H (skeletal CH_2 and CH); 2.04 s, 3 H (CH_3 in OAc); 3.01 m, 2 H (2 H-23); 4.72 m, 1 H (H-3β); 7.52 d, 1 H, *J* = 5.6 (H-7″); 8.39 d, 1 H, *J* = 5.7 (H-6″); 8.97 s, 1 H (H-4″). ^{13}C NMR spectrum: 11.9 (C-18); 18.3 (C-21); 20.7 (C-11); 21.4 (CH_3 in OAc); 23.2 (C-19); 24.0 (C-15); 26.2 (C-2); 26.3 (C-7); 26.5 (C-23); 26.8 (C-6); 28.1 (C-16); 32.1 (C-4); 34.4 (C-10 and

C-22); 34.9 (C-1); 35.6 (C-8 and C-20); 40.0 (C-12); 40.2 (C-9); 41.7 (C-5); 42.6 (C-13); 55.7 (C-17); 56.3 (C-14); 138.2 and 138.3 (C-3a″ and C-7a″); 159.6 (C-2″); 170.6 (CO in OAc). Mass spectrum, *m/z* (%): 491 (M^+, $C_{31}H_{45}N_3O_2$, 1.9), 476 (2.2), 434 (3.8), 431 (3.0), 416 (2.1), 374 (1.3), 215 (4.4), 202 (3.9), 186 (2.7), 159 (2.8), 146 (100), 133 (66.1), 107 (2.5), 93 (2.8), 81 (2.9), 79 (3.8), 67 (4.2), 55 (6.0), 43 (8.5). For $C_{31}H_{45}N_3O_2$ (491.7) calculated: 75.72% C, 9.23% H, 8.55% N; found: 75.72% C, 9.25% H, 8.54% N.

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REFERENCES

1. Ladenburg A.: Ber. Dtsch. Chem. Ges. *8*, 677 (1875).
2. Hunger A., Kebrle J., Rossi A., Hoffmann K.: Helv. Chim. Acta *43*, 800, 1032 (1960).
3. Sharma S., Abuzar S. in: *Prog. Drug Res.* (E. Jucker, Ed.), Vol. 27, p. 85. Birkhauser, Basel 1983.
4. Janssens F., Torremans J., Janssen P., Stokbroekx R. A., Luyckx M., Janssen P. A. J.: J. Med. Chem. *28*, 1925, 1934, 1943 (1985).
5. Negwer M.: *Organic-Chemical Drugs and Their Synonyms* (*An International Survey*), 7th ed., Vol. I – IV. Akademie-Verlag, Berlin 1994.
6. Phillips M. A.: J. Chem. Soc. *1928*, 172, 2393; *1929*, 2820.
7. Wright J. B.: Chem. Rev. *48*, 397 (1951).
8. Preston P. N.: Chem. Rev. *74*, 279 (1974).
9. Porai-Koshits B. A., Ginzburg O. F., Efros L. S.: J. Gen. Chem. (U.S.S.R.) *17*, 1768 (1947); Chem. Abstr. *42*, 5903 (1948).
10. Porai-Koshits B. A., Efros L. S., Ginzburg O. F.: Zh. Obshch. Khim. *19*, 1545 (1949); Chem. Abstr. *44*, 1100 (1950).
11. Scriven E. F. V.: Chem. Soc. Rev. *12*, 129 (1983).
12. Reindel F., Niederlander K.: Ber. Dtsch. Chem. Ges. *68*, 1969 (1935).
13. Barton D. H. R., Motherwell W. B., Wozniak J., Zard S. Z.: J. Chem. Soc., Perkin Trans. 1 *1985*, 1865.
14. Banerjee S., Dessai U. R., Trivedi G. K.: Tetrahedron *48*, 133 (1992).
15. Ladenburg A.: Ber. Dtsch. Chem. Ges. *9*, 1524 (1876).
16. Phillips M. A.: J. Soc. Chem. Ind. *56*, 474 (1937).
17. Wiley R. H.: Chem. Rev. *37*, 401 (1945).
18. Hofmann A. E.: Ber. Dtsch. Chem. Ges. *13*, 8 (1880).
19. Bergstrom S., Rottenberg M., Voltz J.: Acta Chem. Scand. *7*, 481 (1953); Chem. Abstr. *48*, 2736 (1954).
20. Jovanovic S., Djokovic D., Misic-Vukovic N., Djordjevic L., Ugljesic-Kilibarda D.: J. Serb. Chem. Soc. *53*, 339 (1988); Chem. Abstr. *111*, 233343 (1989).
21. Gargiulo D., Blizzard T. A., Nakanishi L.: Tetrahedron *45*, 5423 (1989).
22. Barton D. H. R., Boivin L., Lelandais P.: J. Chem. Soc., Perkin Trans. 1 *1989*, 463.

23. Ercoli A., De Rugieri P.: Farmaco, Ed. Sci. Tec. (Pavia) *6*, 438 (1951); Chem. Abstr. *46*, 8131 (1952).
24. Tsuchida E., Komatsu T., Babe I., Nakata T., Nishide H., Inoue H.: Bull. Chem. Soc. Jpn. *63*, 2323 (1990); Chem. Abstr. *114*, 23635 (1991).
25. Barton D. H. R., Crich D., Motherwell W. B.: J. Chem. Soc., Chem. Commun. *1984*, 242.
26. Lawesson S.-O., Schroll G., Bowie J. H., Cooks R. G.: Tetrahedron *24*, 1875 (1968).
27. Weislow O. W., Kiser R., Fine D., Bader J., Shoemaker R. H., Boyd M. R.: J. Natl. Cancer Inst. *81*, 577 (1989).
28. Miyazi S., Isaka J.: J. Biochem. (Tokyo) *30*, 297 (1939); Chem. Zentralbl. *1940* I, 2165.
29. Brink N. G., Clark D. M., Wallis E. S.: J. Biol. Chem. *162*, 695 (1946); Chem. Abstr. *40*, 7224 (1946).