6. A. G. Gonzalez, J. Bermejo, J. M. Amaro, G. M. Massanet, A. Galido, and J. Cabrera, Can. J. Chem., 56, No. 4, 491 (1979).
7. R. I. Evstratova, K. S. Rybalko, and I. V. Sheichenko, Khim. Prir. Soedin., 451 (1972).
8. J. Harley-Masson, A. T. Hewson, O. Kennard, and R. C. Petterson, Chem. Commun., 460 (1972).
9. R. I. Evstratova, V. I. Sheichenko, and K. S. Rybalko, Khim. Prir. Soedin., 161 (1973).
10. E. Caspi, J. Wicha, and A. Mandelbaum, Chem. Commun., 1161 (1976).

TRANSFORMED STEROIDS.

123. SYNTHESIS OF 5α(H)- AND 5α(OH)-6-KETOSTEROIDS WITH AN ADDITIONAL 17α,20ξ-DIHYDROXYTETRAHYDROPYRAN RING E

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The paper is devoted to the synthesis of 3,17α,20-trihydroxy-16β,23-epoxy-21,24-dinor-5αH-cholan-6-one and 3,5α,17α,20-tetrahydroxy-16β,23-epoxy-21,24-dinorcholan-6-one and derivatives of them. It has been shown that the reduction of 3,17α-dihydroxy-16β,23-epoxy-21,24-dinorchol-5-en-20-one with sodium tetrahydroborate and with diborane takes place stereospecifically with different spatial directivities: in the products of diborane reduction, ring E exists in the boat form, as has been shown by ^1H and ^{13}C NMR methods. The trans linkage of rings A/B in the modified steroids has been confirmed by their circular dichroism spectra.

Continuing investigations into the "structure-function" relationship of polyhydroxysteroids with a tetrahydropyran ring at E, we have synthesized 5α(H)-6-keto and 5α(OH)-6-keto derivatives of 17α,20-diols. The initial compounds for the transformation of ring E and the introduction of the oxygen-containing functions into ring B were the pyranones (I) and (II) [1]. In (I) and (II), ring E was modified by the reduction of the 20-carbonyl group with sodium tetrahydroborate or with diborane. The reduction of (I) and (II) with $NaBH_4$ formed the same 17α,20β-dihydroxy derivative, which was isolated and characterized in the form of the monoacetate (IIIa), the triol (IIIb), the 3,20-diacetate (IIIc), and the 3β,17α,20β-trimethyl ether (IIId). In addition to the saturated diol (IIIa), the reduction of (I) formed as a minor product the allyl alcohol (IV). The position of the C=C double bond in ring E of (IV) was confirmed by its PMR and ^{13}C NMR spectra. The PMR spectrum contained three signals relating to the 20-H, 22-H, and 23-H protons (AMX spin system) and having the following parameters: δ 5.54 ppm, $J_{20,23}$ = 2.6 Hz, $J_{20,23}$ = 2.0 Hz [H(20)], δ 4.65 ppm, $J_{22,20}$ = 2.6 Hz, $J_{22,23}$ = 6 Hz [H(22)], and δ 6.33 ppm, $J_{23,22}$ = 6 Hz, $J_{23,20}$ = 2.0 Hz [H-(23)]. In the ^{13}C NMR spectrum doublets with δ 99.9 and 140.0 ppm corresponded to the C(22) and C(23) carbons.

The introduction of a 5α-hydroxy-6-keto function into ring B of compound (II) and that of (IIIc) was effected by a method which we have developed previously using steroid δ-lactones as examples [2]: by the opening of 5α,6α-epoxides to form 5α,6β-diols and the oxidation of the latter to the desired ketones (VII) and (VIII). See next page for scheme a.

For the synthesis of 6-ketones of the 5-(H) series we used the hydroboration of the tetrahydropyranyl derivative (IIc), obtained by the method of Miashita et al. [3], or of the trimethoxy derivative (IIId). The hydroboration of (IIId) and subsequent oxidation led to the trimethoxy ketone (IX). In the case of (IIc), however, reaction took place at two reaction centers: at the Δ^5 bond and at the 20-keto group, and, as a result, after the elimination of tetrahydropyranyl protection at C-3, oxidation with chromium trioxide in pyridine, and acetylation, the 3β,20α-diacetate (X) was obtained. The axial nature of the proton at C-20 in each of compounds (III), (VIII), and (X) was deduced on the basis of the results of PMR spectroscopy. In all these compounds the 20-H signal has the form of a doublet of dou-

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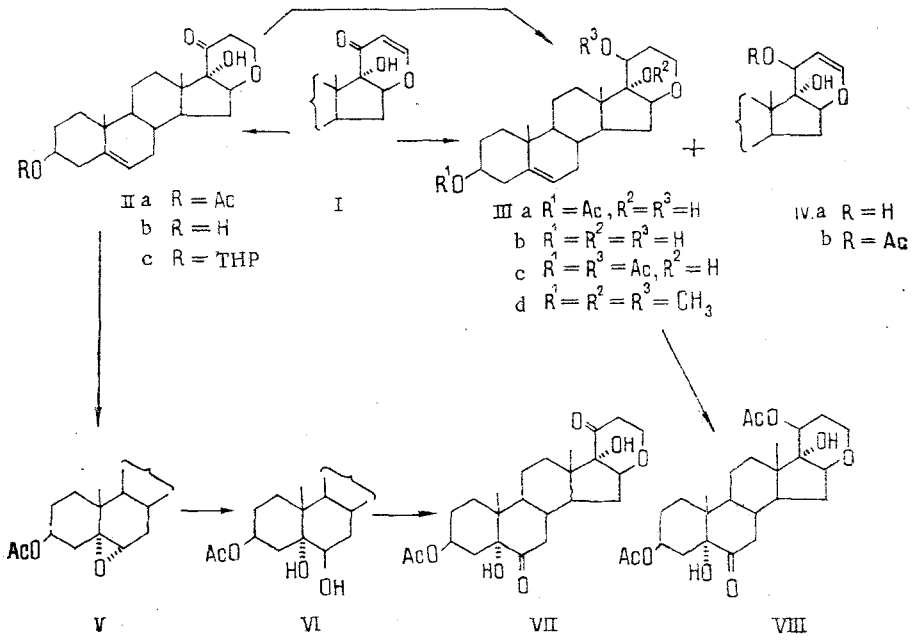
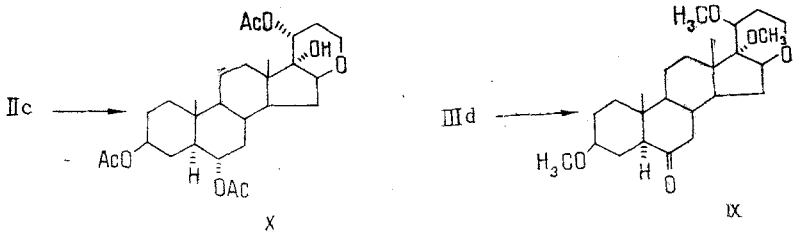


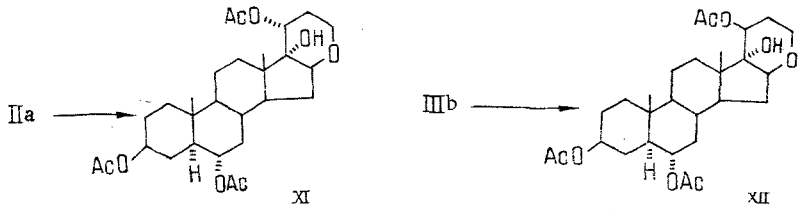
blets [4]: in (IIIc) at δ 5.12 ppm (in $CDCl_3$) with spin-spin coupling constants of 12 Hz (a,a) and 7 Hz (a,e), and for (X) at δ 5.30 ppm (in $CDCl_3$) or 5.40 ppm (in C_6D_6) with spin–spin coupling constants of 11 Hz (a,a), and 6 Hz (a,e).

The resonance signals of the protons of the acetyl groups at C-3 and C-20 in the diacetate (X) shifted upfield (from δ 2.08 to δ 1.66 ppm and from δ 2.03 to δ 1.75 ppm, respectively) on passing from solution in $CDCl_3$ to solution in C_6D_6, which confirms their 3,20-di-equatorial nature [5].



Thus, judging from spectral characteristics, the 20-hydroxy groups in compounds (VIII) and (X) have an equatorial nature and should possess identical configurations. However, their ^{13}C NMR spectra differ substantially, which indicates the possibility of the existence of ring E in (X) in the boat form with the 20β-H (a) and 20α-OAc (e) configurations of the substituent.*

To confirm this hypothesis, we performed the hydroboration of the 20-ketone (IIa) and of the 20β-acetate (IIIc) with their subsequent acetylation.

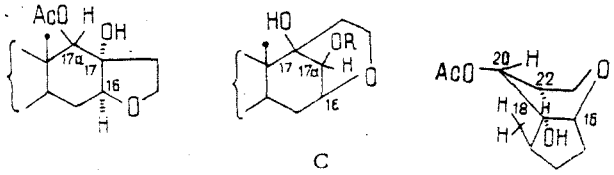


Compounds (XI) and (XII) obtained in this way also differed in relation to their ^{13}C NMR spectra. In compound (XII), the ^{13}C δ values of the carbon atoms of ring E coincided (within the limits of experimental error) with the ^{13}C δ values in compounds (IIIc) and (VIII) (in which, according to x-ray structural analysis, the pyran ring has the chair conformation [6]). In compound (XI), the ^{13}C δ values of the corresponding carbon atoms differed substantially from the chemical shifts of the carbon atoms of rings E in compounds (IIIc), (VIII), and (XII). The greatest differences were observed for C-20 and C-22, the signals of which in (X) are shifted upfield by 12 and 6.6 ppm [81.9 and 69.9 ppm for C(20);

*The ^{13}C NMR spectra of (X) and other compounds will be published in a separate communication.

30.3 and 23.7 ppm for C(22)]. Since the mass spectra of (XI) and (XII) are practically identical, compound (XI) cannot be the analog with the opened ring E. In this case, two other possibilities remained to be considered: 1) the expansion of D through the cleavage of the C(16)—C(17) or the C(13)—C(17) bond and the contraction of ring E to a tetrahydrofuran ring, or 2) the passage of ring E from the "chair" conformation into the "boat" conformation by the inversion of the C(17)—C(20)—C(22) fragment. The realization of the first of these probabilities would lead to structures of type B or C. However, in structural fragment B the protons closest to 17a-H are separated from it by four δ bonds and ^4J for 5- and 6-membered rings does not exceed 6 Hz even with the favorable W arrangement of the H—C—C—C—H bonds [7]. The same thing applies to fragment C, since only one spin—spin coupling of 17a-H through three bonds with 16-H (e) is possible. Furthermore, in the substituted bicyclo[3,3,1]nonanes [8] and borabicyclo[3,3,1]nonanes [9] closest in structure to fragment C, the values of $^4J_{HH}$, including those for the W configuration of the bonds, are between 1.5 and 2.5 Hz.

Thus, in the structural fragments B and C the splitting of the 17a-H signal with J = 6 and 10 Hz is unlikely. However, the passage of ring E from the "chair" conformation into the "boat" conformation with inversion of the C(17)—C(20)—C(22) fragment agrees well with the changes in the ^{13}C spectrum. In actual fact, in this case there should be an upfield shift of the C(20) and C(22) signals as the result of 1,3-diaxial interaction between C(20)—H_a and 18-CH_3, on the one hand, and between 17-OH and 22-H_a, on the other hand, i.e., through the gauche γ-effects of the γ substituents [18-CH_3 for C(20) and 17-OH for C(22)].



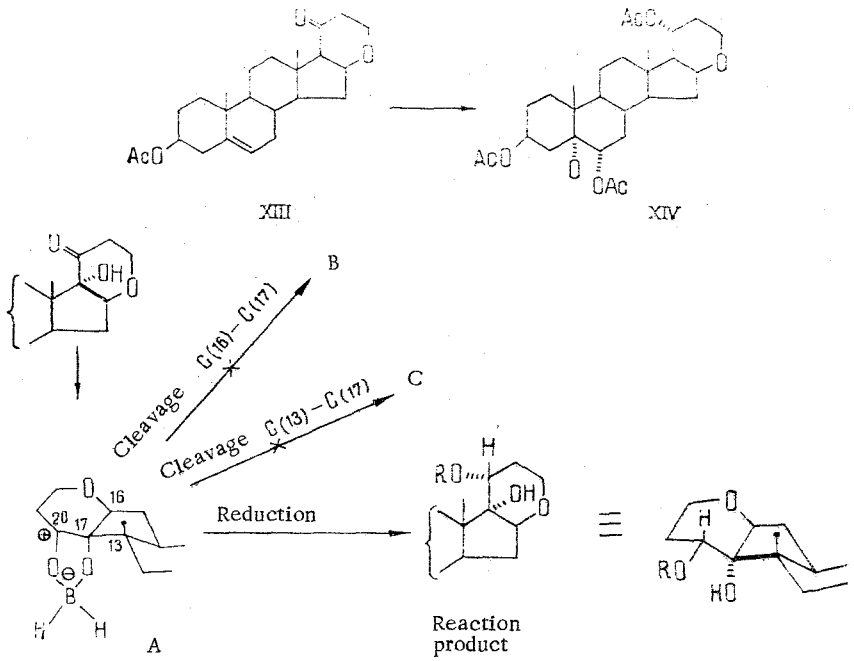
C

Then the proton at C(20) remains in the axial position, and therefore the spin—spin coupling constants between this proton and the protons at C(22) change little ($J_{H,H}$: 11 and 7 Hz in (XII), and 10 and 6 Hz in (XI)). A comparison of the ^{13}C spectra of compounds (XI) and (X) shows that in the latter the pyran ring is also present in the "boat" conformation: δ ^{13}C — 69.9, 69.7 [C(20)], 23.7, 23.7 [C(22)], 32.4, 32.3 [C(15)], 84.8, 84.6 [C(16)], and 80.9, 80.8 [C(17)], respectively. Apparently, of considerable importance for the "chair"—"boat" conformational transition with the simultaneous re-orientation of the 20-OAc group is the presence of the 17α-OH group, since on the hydroboration and subsequent acetylation of the 17-deoxypyranone (XIII), ring E in the triacetate (XIV) formed has the chair conformation, according to its ^{13}C NMR spectrum. According to the generally accepted mechanism of the reduction of ketones by diborane [10], the latter attacks the 20-CO group of compounds (IIa), (IIc), and (XIII) at the least hindered α region of the molecule with the formation of an intermediate complex. Intramolecular hydride transfer with the subsequent decomposition of the borate in the case of (XIII) leads to the formation of the 20α (a) alcohol (XIV). When a 17α-hydroxy group is present, the formation of a cyclic intermediate of type (A) is possible which may subsequently either rearrange into a compound with the D-homo structure (B or C) [11] or be converted into the 20α (e) alcohol, while the presence of the vicinal 17α-hydroxy group in (IIa) and (IIc) makes the "chair" conformation in the reduction products thermodynamically unfavorable, which leads to the "chair" into "boat" rearrangement. See next page for scheme A.

TABLE 1

Compound	CD (in CH_3CN)		UV (in CH_3CN)	
	λ_{max}	Δε	λ_{max}	ε
VII	302	—6.80	215	1630
	230	—1,65	304	146
VIII	316 sh.	—1,03	212	612
	306	—1,41	233	290
	297 sh.	—1,21		
IX	307 sh.	—0,84	203	1485
	298	—1,27	229 sh.	203
	290 sh.	—1,21	282	89
X	296	—1,26	207	1313
			227 sh.	445
			275	142

In the reduction of the 20-ketone (IIa) with $NaBH_4$, the hydride ion attacks the molecule from the α region, which explains the formation of the 20β-hydroxy derivatives (III) with an unchanged conformation of ring E in the "chair" form.



The trans linkage of rings A/B in compounds (VII-X) was confirmed by their CD spectra. In the region of the n → π* transition of the carbonyl group in the CD spectra, a negative Cotton effect (CE) is observed (Table 1). Compounds (IX) and (X) have negative CEs at 298 nm with close Δε values, which is in complete agreement with literature information for 5αH-6-ketosteroids [12]. In compound (VIII), the observed value of the CE of the n–π* transition of the C(6) carbonyl and its bathochromic shift to some extent in comparison with the CD of compound (X) correspond to the axial position of the C(5)α-OH group [12]. The strong negative negative maximum of the CE of (VII) is composed of the negative values of the ECs of the n → π* transitions of the C(20) and C(6) carbonyl groups. The observed broadening of the CD peak is due to contributions of the bathochromically shifted CD maximum of the 5α-OH–6-CO fragment and the hypsochromic shift of the CD maximum of the 17α-OH-20-CO grouping. In the latter case, the hypsochromic shift is caused by the equatorial or pseudoequatorial C(17)-α-OH group, which corresponds to the chair conformation of ring E in (VII) [13].

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were measured on a UR-20 spectrometer; mass spectra on a Varian MAT CH-6 mass spectrometer with the direct introduction of the sample into the ion source at an ionizing voltage of 70 eV; PMR spectra on a Tesla BS 497 instrument (internal standard TMS) in $CDCl_3$; and ^{13}C NMR spectra on a Bruker WP-60 instrument in $CDCl_3$ at 32°C with TMS as internal standard. CD spectra were recorded on a Spektropol-1 dichrograph (200-600 nm) at 20°C in CH_3CN, and UV spectra on a Unicam SP-700 instrument in CH_3CN. Sikica gel 5/40 μ (+13% of gypsum) was used for TLC. Mixtures were separated on columns of SiO_2 40/100 μ in an atmosphere of N_2.

3β-Acetoxy-5α,17α-dihydroxy-16β,23-epoxy-21,24-dinorcholane-6,20-dione (VII). A mixture consisting of 250 mg of (IIa), 250 mg of m-chloroperbenzoic acid (CPBA), and 10 ml of CH_2Cl_2 was kept at 20°C in the dark for 24 h. Then it was treated with solutions of Na_2SO_3 and of $NaHCO_3$ and with water and was extracted with Ch_2Cl_2, and the extract was dried with $MgSO_4$ and evaporated. This gave 90 mg of the α-oxide (V). IR spectrum (ν, cm^{-1}): 1250, 1705, 1735, 3490 (KBr). Mol. wt. 418. Mass spectrum (m/z): 418 (M), 400 (M – 18), 358 (M – 60), (M–60–18), 304, 286, 244, 226, 115 ($C_5H_7O_3$). Compound (V) (100 mg in 5 ml of dioxane) was treated with 0.06 ml of 67% $HClO_4$ and 0.06 ml of water for 1 h.

After the disappearance of the (V) (TLC), the reaction mixtures as neutralized with $KHCO_3$ solution and extracted with ethyl acetate, and the extract was dried with $MgSO_4$ and

evaporated. This gave 100 mg of (VI), mp 182-184°C (from a mixture of hexane and acetone). IR spectrum (ν, cm^{-1}): 1250, 1705, 1740, 3455, 3630 (KBr). Mol. wt. 436. Mass spectrum (m/z): 436 (M), 418 (M − 18), 408, 400 (M − 2 × 18), 376 (M − 60), 358 (M − 60 − 18), 340 (M − 60 − 2 × 18), 330, 318, 304, 291, 115 ($C_5H_7O_3$).

The diol (VI) was dissolved in a 9:1 mixture of dioxane and water (10 ml), and 100 mg of N-bromosuccinimide (NBS) was added. After 24 h, another 50 mg of NBS was added, and after the disappearance of the initial substance (TLC), the reaction mixture was treated with water and extracted with ethyl acetate, and the extract was dried with Na_2SO_4 and evaporated. This gave 90 mg of the 6,20-dione (VII), mp 216-219°C (from hexane–acetone). IR spectrum (ν, cm^{-1}): 1250, 1280, 1705-1720, 3400, 3520. Mol. wt. 434. Mass spectrum (m/z): 434 (M), 416 (M−18), 374 (M − 60), 356 (M − 60 − 18), 338 (M − 60 − 2 × 18), 320 (M − 60 − 3 × 18), 115 ($C_5H_7O_3$).

Reduction of 3-Acetoxy-17-hydroxy-16β,23-epoxy-21,24-dinorchol-5-en-20-one (IIa) and 3-Acetoxy-17-hydroxy-16 β,23-epoxy-21,24-dinorchola-5,22(23)-dien-20-one (I) with Sodium Tetrahydroborate. A solution of 1.100 g of (I) in 50 ml of DMFA was treated with a solution of 310 mg of $NaBH_4$ in 5 ml of water. After 20 h, the reaction mixture was diluted with water, and dried with $MgSO_4$. After evaporation of the solvent, 1.07 g of a mixture of (IIIa) and (IVa) was obtained. After the acetylation of 1 g of this mixture with 2 ml of Ac_2O in 20 ml of Py, the usual working up and separation of the residue on a column of SiO_2 in the heptane–ether (2:1) system yielded:

1) 55 mg of 3β,20β-diacetoxy-17α-hydroxy-16β,23-epoxy-21,24-dinorchola-5,22(23)-diene (IVb), mp 195.5-196.5°C (from ether–hexane). UV spectrum (ν, cm^{-1}): 1250, 1670, 1710-1730, 3480 (in $CHCl_3$), mol. wt. 444. Mass spectrum (m/z): 444 (M), 426 (M − 18), 384 (M − 60), 366 (M − 18 − 60), 351 (M − 18 − 60 − 15), 324 (M − 2 × 60), 309 (M − 2 × 60 − 15). PMR spectrum (δ, ppm (IVa)): 1.04 s (6 H, 18-CH_3, 19-CH_3); 2.0 s (3 H, acetate); 4.0 m (2 H, 16-H, 20-H); 4.69 m (2 H, 3-H, 22-H); 5.39 m (1 H, 6-H); 6.16 m (1 H, 23-H). PMR spectrum (δ, ppm (IVb)): 0.98, 1.04 s (6 H, 18-CH_3, 19-CH_3); 2.03, 2.13 s (acetates); 4.06 s (1 H, OH, disappears on the addition of CD_3OD); 4.18 m (1 H, 16-H); 4.65 m (1 H, 22-H, $J_{20,22}$ = 2.6 Hz, $J_{22,23}$ = 6 Hz); 4.6 m (1 H, 3-H); 5.54 t (1 H, 20-H, $J_{20,22}$ = 2.6 Hz, $J_{20,23}$ = 2.0 Hz); 5.34 m (1 H, 6-H); 6.33 dd (1 H, 23-H, $J_{23,22}$ = 6 Hz, $J_{23,20}$ = 2.0 Hz); and

2) 500 mg of 3β-20β-diacetoxy-20β-hydroxy-16β,23-epoxy-21,24-dinorchol-5-ene (IIIc), mp 217-219°C (from CH_3OH). IR spectra (ν, cm^{-1}): 1250, 1740, 3460, (KBr). Mol. wt. 446. Mass spectrum (m/z): 446 (M), 386 (M−60), 326 (M− 2 × 60), 308 (M − 2 × 60 − 18), 293 (M − 2 × 60 − 18 − 15). PMR spectrum (δ, ppm): 1.03, 0.98 s (6 H, 18-CH_3, 19-CH_3); 1.96, 2.06 s (6 H, acetates); 3.4 m (2 H, 23-OCH_2); 3.6-4.0 m (2 H, 16-H, OH); 5.12 dd (1 H, J_{aa} = 12 Hz, J_{ae} = 7 Hz); 5.32 m (1 H, 6-H). The 20-ketone (IIa) (200 mg in 20 ml of DMFA) was reduced with $NaBH_4$ (60 mg in 2.5 ml of water) at 20°C for 3.5 h (TLC). After the usual working up and acetylation, 200 mg of the diacetate (IIIc), identical with the sample described above, was obtained.

3β,20β-Diacetoxy-5α,17α-dihydroxy-16β,23-epoxy-21,24-dinorchol-6-one (VIII). A mixture consisting of 300 mg of (IIIb) in 15 ml of CH_2Cl_2 and 200 mg of CPBA was kept at 20°C in the dark for 72 h. Then it was treated successively with solutions of Na_2SO_3 and $KHCO_3$ and with water and was extracted with CH_2Cl_2, and the extracts were dried with $MgSO_4$ and evaporated. Without additional purification, the residue (the 5,6-epoxide, 180 mg) was dissolved in 5 ml of 67% $HClO_4$ and 0.1 ml of water for 40 min. The solution was treated with water and with $KHCO_3$ and was extracted with ethyl acetate, and the extract was dried and evaporated. This gave 93 mg of the diol. Mol. wt. 480. Mass spectrum (m/z): 480 (M), 462 (M−18), 444 (M − 2 × 18), 342 (M− 2 × 18 − 60), 324 (M−2 × 18 −2 × 60). The product was oxidized with 140 mg of NBS in dioxane-water (9:1; 10 ml) at 20°C for 24 h. After a working up similar to that described above, 73 mg of (VIII) was obtained with mp 268-269°C (from acetone). IR spectrum (ν, cm^{-1}): 1240, 1270, 1710, 1740, 3420 (KBr). Mol. wt. 478. Mass spectrum (m/z). 478 (M − 18), 434 (M − 42), 418 (M − 60), 400 (M − 60 − 18), 366, 358 (M − 2 × 60), 340 (M − 2 × 60 − 18), 322 (M − 2 × 60 − 2 × 18). PMR spectrum (δ, ppm): 0.81, 1.04, s (6 H, 18-CH_3, 19-CH_3); 2.0, 2.11 s (6 H, acetates); 3.80-3.44 m (4 H, 16-H, OH, OCH_2); 5.05-5.27 m (2 H, 3-H, 20-H).

3β,17α,20β-Trimethoxy-16β,23-epoxy-21,24-dinor-5αH-cholan-6-one (IX). The 3-acetate (IIIa) (1.0 g) was hydrolyzed with 12 ml of a 10% solution of K_2CO_3 in CH_3OH–water (1:1). After the end of the reaction (TLC), the mixture was diluted with water and neutralized with 2% HCl, and the resulting precipitate was filtered off, washed on the filter with water and with absolute ether, and was dried over $MgSO_4$. This gave 830 mg of the triol (IIIb). IR spectrum (ν, cm^{-1}): 1095, 1380, 3470 (in $CHCl_3$). A suspension of 100 mg of sodium hydride

(previously washed free from oil with hexane) in 30 ml of DMSO was heated to 50-60°C in an atmosphere of hexane vapor for 1 h, after which practically no solid matter was left and the mixture had become green. After 1 h the mixture was cooled to 20°C and a solution of 360 mg of the 2,17,20-triol (IIIb) in 15 ml of DMSO was added to it. The resulting gel was kept at 20°C for 1 h, and then 0.5 ml of CH_3I was added (at a temperature not exceeding 30°C) and the reaction mixture was kept at 20°C for another 2.5 h, after which it was poured into water and extracted with EtOAc, and the extract was washed with 2% HCl and with water, dried with $MgSO_4$, and evaporated. The residue (380 mg) was purified on a column of SiO_2 in the heptane—ether (4:1) system. This gave 240 mg of the trimethoxy derivative (IIId), mp 158-160°C (from hexane). IR spectrum (ν, cm^{-1}): 1095, 1380, 1470 (in $CHCl_3$). Mol. wt. 404. Mass spectrum (m/z): 404, 389 (M − 15), 372 (M − 32). PMR spectrum (δ, ppm); 1.02, 1.09 s (6 H, 18-CH_3, 19-CH_3); 3.68-3.96 m (5 H, 3-H, 20-H, 16-H, 23-OCH_2); 3.40, 3.33 s (9 H, 3 × OCH_3) (in $CDCl_3$); 0.92, 1.25 (6 H, 18-CH_3, 19-CH_3); 2.92 (23-OCH_2); 3.05, 3.11, 3.13 s (9 H, 3 × OCH_3); 4.12 m (3-H, 20-H) (in C_6H_6). With stirring, 2.5 ml of a 1 M solution of B_2H_6 in THF was added dropwise to a solution of 190 mg of (IIId) in 8 ml of absolute THF. After 2.5 h, the reaction mixture was decomposed by the addition of 1 ml of CH_3OH, 4 ml of 10% NaOH, and (at 0°C) 1.5 ml of 30% H_2O_2, and it was stirred at 20°C for another 2.5 h and at 40°C for 40 min Then the THF and CH_3OH were evaporated off, and the residue was diluted with water and extracted with EtOAc. The extract was washed with 2% HCl and with water and was dried with $MgSO_4$ and evaporated. The residue (200 mg) was dissolved in 6.5 ml of absolute pyridine and was oxidized with the $CrO_3 \cdot 2Py$ complex (350 mg of CrO_3 and 8.1 ml of Py). The working up of the reaction mixture yielded 180 mg of the ketone (IX) with mp 208-210°C (from acetone—ethane). IR spectrum (ν, cm^{-1}): 1090, 1710 (KBr). Mol. wt. 420. Mass spectrum (m/z): 420 (M − 15), 388 (M − 32), 373 (M − 15 − 32). PMR spectrum (δ, ppm): 0.75, 1.04 s (6 H, 19-CH_3, 18-CH_3); 3.60-3.90 m (5 H, 3-H, 16-H, 20-H, 23-OCH_2); 3.33, 3.39 s (9 H, 3 × OCH_3).

3β,20α-Diacetoxy-17α-hydroxy-16β,23-epoxy-21,24-dinor-5αH-cholan-6-one (X). By hydrogenation in 20 ml of CH_3COOH over 25 mg of PtO_2 by method (I), 550 mg of (I) was converted into 510 mg of (IIa). A solution of 480 mg of (IIa) in CH_3OH—dioxane (1:1) was treated with 6.5 ml of a 10% solution of K_2CO_3 in CH_3OH—water (1:1) for 24 h. Then the reaction mixture was neutralized with 2% HCl, the solvent was evaporated off, and the residue was diluted with water, filtered, and evaporated. This gave 410 mg of the 3,17-diol (IIb). To a solution of 450 mg of (IIb) and 1.55 g of dihydropyran in the minimum amount of absolute dioxane was added 31 mg of pyridinium p-toluenesulfonate (PPTS) [3] in 10 ml of absolute CH_2Cl_2. The reaction mixture was left at 20°C for 50 h and was then evaporated to dryness. The residue was dissolved in EtOAc, and the solution was washed with NaCl solution, dried with $MgSO_4$ solution, and evaporated. This gave 230 mg of THP derivative (IIc) with mp 173-174°C; 199-201°C (from ether). A solution of 320 mg of (IIc) in 10 ml of absolute THF was treated with 7 ml of 1 M solution of B_2H_6 in THF. After 20 h, the reaction mixture was decomposed by the successive addition of 15 ml of CH_3OH, 17 ml of 10% NaOH, and 5 ml of H_2O_2. The mixture was stirred at 20°C for 3 h and at 50-60°C for 40 min, and then the THF was evaporated off. The residue was diluted with water and extracted with EtOAc, and the extracts were washed with 2% HCl and with water, dried with $MgSO_4$, and evaporated. The residue (350 mg) was dissolved in 11 ml of pyridine and oxidized with the $CrO_3 \cdot 2Py$ complex (1.05 g of CrO_3 and 24.5 ml of Py). The working up of the reaction mixture yielded 215 mg of a product which, without purification, was dissolved in 30 ml of EtOH. To this solution was added 12 mg of TPPS and the mixture was boiled for 8.5 h, by which time the initial substance had disappeared (GLC). Then the solvent was evaporated off and the residue (220 mg) was acetylated with 0.5 ml of Ac_2O in 5 ml of Py. After the usual working up and purification on a column of SiO_2 in the ether—heptane (4:1) system, 30 mg of the 5αH-6-ketone (X) was obtained with mp 216-217° (from acetone—hexane). IR spectrum (ν, cm^{-1}): 1240, 1710, 1740, 3520 (KBr). Mol. wt. 462. Mass spectrum (m/z): 462 (M), 444 (M − 16), 402 (M − 60), 384 (M − 60 − 18), 342 (M − 2 × 60). PMR spectrum (δ, ppm): 0.79, 0.90 s (6 H, 18-CH_3, 19-CH_3); 2.08, 2.01 s (6 H, acetates); 3.85 m (3 H, 16-H, 23-OCH_2); 5.30 dd (1 H, 2-H, J_{aa} = 11 Hz, J_{ae} = 6 Hz); 4.68 (1 H, 3-H) (in $CDCl_3$); 0.5, 0.78 s (6 H, 18-CH_3, 19-CH_3); 2.08, 2.01, s, (6 H, acetates); 3.68 m, 3 H, 16-H, 23-OCH_2); 5.40, dd (1 H, 20-H, J_{aa} = 11 Hz, J_{ae} = 6 Hz); 4.72 m (1 H, 3-H) (in C_6D_6).

3β,6α,20α-Triacetoxy-16β,23-epoxy-21,24-dinor-5αH-cholan-17α-ol (XI). A solution of 280 mg of (IIa) in 15 ml of absolute THF was treated with 14 ml of a 1 M solution of B_2H_6 in THF. After 16 h (20°C), the reaction mixture decomposed by the successive addition of 20 ml of CH_3OH, 50 ml of 10% NaOH, and 17 ml of 30% H_2O_2 (at 4-7°C). The mixture was stirred at 20°C for 3.5 h and at 40°C for 50 min and then the THF and CH_3OH were evaporated off, the

the aqueous layer was neutralized with 10% HCl and was extracted with EtOAc, and the organic layer was washed with 2% HCl and with water and was dried with $MgSO_4$ and evaporated. The residue (180 mg) was acetylated with 0.5 ml of Ac_2O in 5 ml of Py. After the usual working up and separation on a column of SiO_2 in the heptane–ether (1:2) system, 75 mg of white crystals of (XI) was obtained with mp 210-212°C (from heptane–ether), R_f 0.58 (ether). IR spectra (ν, cm^{-1}): 1250, 1380, 1740, 3480 (KBr). Mol. wt. 506, mass spectrum (m/z): 506 (M), 488 (M-18), 473, 462, 446 (M-60), 386 (M-2 × 60), 368, 326 (M-3 × 60), 287, 274, 227, 214, 199, 159, 158, 147, 145, 143, 133, 131, 113, 112. PMR spectrum (δ, ppm): 0.89, 0.90 s (6 H, 18-CH_3, 19-CH_3); 2.04, 2.08 s (9 H, acetates); 3.62, 3.92 m (3 H, 16-H, 23-OCH_2); 4.7 m (2 H, 3-H, 6-H); 5.28 dd (1 H, 20-H, J_{aa} = 10 Hz, J_{ae} = 6 Hz).

3β,6α,20β-Triacetoxy-16β,23-epoxy-21,24-dinor-5αH-cholan-17α-ol (XII). A solution of 200 mg of (IIIa) in 10 ml of absolute THF was treated with 14 ml of a 1 M solution of B_2H_6 in THF. After 16 h (20°C), the reaction mixture was decomposed by the successive addition of 20 ml of CH_3OH, 25 ml of 10% NaOH, and 2.5 ml of 30% H_2O_2 (at 4-7°C). The mixture was stirred at 20°C for 3 h and at 40°C for 1.5 h and was then neutralized with 10% HCl and extracted with EtOAc. The aqueous layer after extraction with EtOAc was evaporated to turbidity, saturated with NH_4NO_3, and extracted twice more with EtOAc. The combined organic extracts were dried with $NaSO_4$ and evaporated and the residue (130 mg) was acetylated with 0.3 ml of Ac_2O in 3 ml of Py. After the usual working up, 140 mg of an oil was obtained from which, after purification on a column of SiO_2 in the heptane–ether (1:2) system, 29 mg of a white powder of (XII) was obtained with R_f 0.55 (ether). IR spectra (ν, cm^{-1}): 1250, 1380, 1740, 3480 (KBr). Mol. wt. 506. Mass spectrum (m/z): 506 (M), 488 (M-18), 473, 462, 446 (M-60), 386 (M-2 × 60), 368, 326 (M-3 × 60), 387, 274, 227, 214, 199, 159, 158, 147, 143, 133, 131, 113, 112. PMR spectrum (δ , ppm): 0.90, 1.05 s (6 H, 18-CH_3, 19-CH_3); 2.03, 2.12 s (9 H, acetates); 3.42, 3.7, 4.0 m (4 H, 16-H, 23-OCH_2, OH); 4.7 m (2 H, 3-H, 6-H); 5.14 dd (1 H, 20-H, J_{aa} = 11 Hz, J_{ae} = 7 Hz).

3β,6α,20α-Triacetoxy-16β,23-epoxy-21,24-dinor-5αH-cholane (XIV). A solution of 230 mg of (XIII) in 10 ml of absolute THF was treated with 13 ml of 1 M B_2H_6 in TMF. After 16 h (20°C) the following were added successively with stirring: CH_3OH (until the evolution of H_2 ceased), 20 ml of 10% NaOH, and 4.5 ml of 30% H_2O_2 (at 4-7°C). The mixture was stirred at 20°C for 3 h and at 40°C for 1.5 h and was then neutralized with 10% HCl and extracted with EtOAc, the extract was dried with $MgSO_4$ and evaporated, and the residue (260 mg) was acetylated with 1 ml of Ac_2O in 10 ml of Py.

After the usual working up and separation on a column of SiO_2 in the heptane–ether (1:1) system, 125 mg of (IV) was obtained with mp 205-206° (from hexane). IR spectra (ν, cm^{-1}): 1250, 1380, 1740 (KBr). Mol. wt. 490. Mass spectrum (m/z): 490 (M), 448 (m-42), 430 (M-60), 415 (M-60-15), 388 (M-60-42), 370 (M-2 × 60), 355 ((M-2 × 60-15), 340, 328, 310, 295, 274, 261, 214. PMR spectrum (δ, ppm): 0.90. 1.07 s (6 H, 18-CH_3, 19-CH_3); 2.02, 2.00 s (9 H, acetates); 3.3 m (1 H, 16-H); 3.96 m (2 H, OCH_2); 4.66, 5.30 m (3 H, 3-H, 6-H, 20-H).

CONCLUSION

1. 3,17α,20-Trihydroxy-16β,23-epoxy-21,24-dinor-5αH-cholan-6-one and 3,5α,17α,20-tetrahydroxy-16β,23-epoxy-21,24,dinorcholan-6-one and derivatives of them have been synthesized.

2. It has been shown that the reduction of 3,17α-dihyroxy-16β,23-epoxy-21,24-dinorchol-5-en-20-one with sodium tetrahydroborate and diborane takes place stereospecifically with different spatial directivities.

3. It has been shown by the ^1H and ^{13}C NMR methods that in the products of reduction by diborane ring E exists in the boat form.

LITERATURE CITED

1. A. V. Kamernitskii, N. M. Ol'gina, I. G. Reshetova, and K. Yu. Chernyuk, Izv. Akad. Nauk SSSR, Ser. Khim., 411 (1975).
2. A. V. Kamernitskii, V. A. Krivoruchko, and I. G. Reshitova, Khim. Prir. Soedin., 208 (1980).
3. M. Miyashita, A. Yoshioshi, and P. A. Grieco, J. Org. Chem., 42, 3772 (1977).
4. R. Sivakumar, N. Satyamurthy, K. Ramalingam, D. I. O'Donnell, K. Ramarajan, and K. D. Berlin, J. Org. Chem., 44, 1559 (1979).

5. N. S. Bhacca and D. H. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Holden-Day, San Francisco (1964).
6. Yu. T. Struchkov, O. V. Lindeman, V. E. Shklover, M. Yu. Antipin, A. P. Polishchuk, V. A. Karapetyan, A. M. Turuta, I. G. Reshetov, and A. V. Kamernitskii, The Structural Investigation of Synthetic Steroid Hormones and Their Derivatives. Abstracts of Lectures at the IIIrd All-Union Conference on Organic Crystal Chemistry [in Russian], Gor'kii (1981).
7. M. Barfield and B. Chakrabarti, Chem. Rev., 69, 757 (1969).
8. J. A. Peters, J. M. Van Der Toorn, and H. Van Bekkum, Tetrahedron, 31, 2273 (1975).
9. M. E. Gursky, A. S. Shashkov, and B. M. Mikhailov, J. Organometal. Chem., 199, 171 (1980).
10. H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc., 82, 681 (1960).
11. R. B. Turner, J. Am. Chem. Soc., 75, 3484 (1953).
12. J. R. Bull and P. R. Enslin, Tetrahedron, 26, 1525 (1970).
13. A. V. Kamernitskii, V. A. Pavlov, I. G. Reshetova, and G. Snattske, Izv. Akad. Nauk SSSR, Ser. Khim., 1980, 2391 (1980).

STEREOISOMERISM OF THE MATRINE ALKALOIDS

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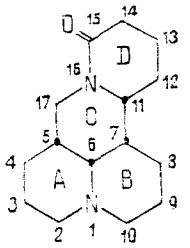
The stereoisomerism of compounds of the matrine series is considered on the basis of the authors' own x-ray structural studies of these alkaloids. A corrected series of eight stereoisomers has been drawn up. It has been shown that the numbers of theoretically possible stereoisomers of matrine is thirty-two.

The molecule of the alkaloid matrine has four asymmetric carbon atoms — C(5), C(6), C(7), and C(11) [1, 2].



This makes the investigations of eight pairs of racemates theoretically possible. The stereoisomerism of these eight alkaloids was first considered in a paper by F. Bohlmann et al. in 1958 [3], and the stereoisomers were subdivided into representatives of the trans and cis series according to the type of linkage of rings A and B.

In 1975, Japanese workers isolated a new stereoisomer of matrine and subsequently established its structure and absolute configuration by x-ray structural analysis [4]. Taking this new compound — (+)-isomatrine — into account, as well, they arranged all the known stereoisomers in the series shown in Fig. 1.

We have previously studied the three-dimensional structures of six stereoisomers (matrine, allomatrine, isosophoridine, sophoridine, tetrahydroneosophoramine, and cis-matrine) by x-ray structural analysis [5-9]. On the basis of the results obtained, a more detailed consideration of the stereoisomerism of the alkaloids of the matrine series is possible.

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