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NEW SYNTHESES OF THE $\Delta_{5,22}$ CIS AND TRANS C_{26} AND C_{27} STEROLS DIMETHYL-24 CHOLA-5, 22 DIEN-3β OL AND CHOLESTA-5,22 DIEN-3β OL

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Previous syntheses of the title sterols have lead to mixtures of their Δ_{22} *cis* and *trans* isomers[1, 2]. We wish to report now[3] new syntheses of the two compounds and the separation of the isomers 7a-8a and 11a-12a.

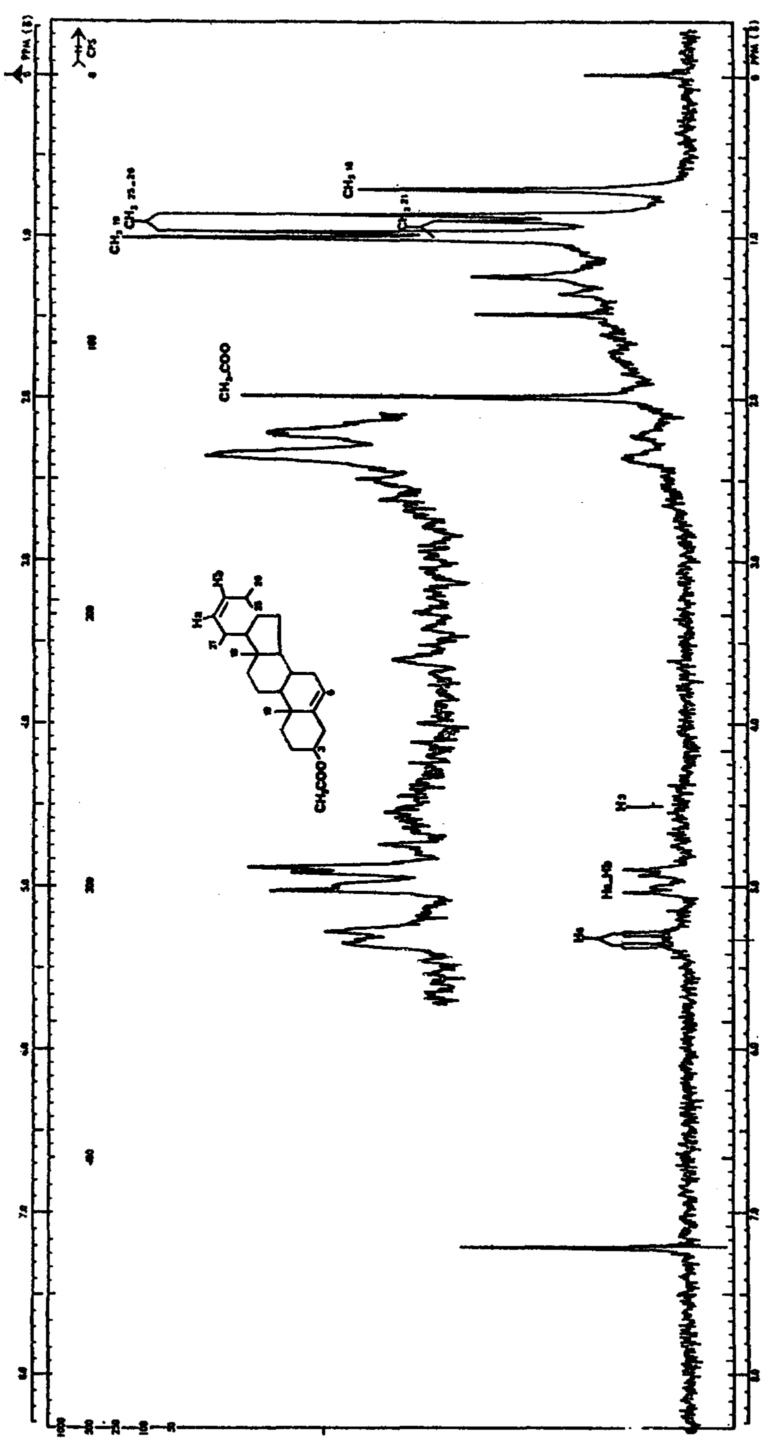
Decarboxylation[4] of 3β-acetoxy cholenic acid 1 by treatment with $Pb(OAc)_4$:$Cu(OAc)_2$ gives the olefin 2 with a 55 % yield (TLC[5] pentane-EtOAc 19:1, Rf 0.78) ; IR, MS and NMR are in agreement with structure 2. After saponification, the tosylate (TsCl/Py) is prepared and rearranged to the 3, 5-cyclosteroid 3a (5 min. reflux Bz./Al_2O_3)[6] ; this product is purified by Al_2O_3 column chromatography (TLC pentane-EtOAc 19:1 Rf 0.33). After acetylation (Ac_2O/Py), 3b shows the expected molecular ion at m/e 370 and fragmentations at 328 M-15-C_2H_3, 313 M-(C_4H_7 + 2H), 255 M-60-C_4H_7, NMR[7] and IR see table. Ozonisation of 3b in CH_2Cl_2/Py 9:1 at -70°C[8] affords the aldehyde 4 (yield 90 %, Rf 0.60 TLC[5] in pentane-EtOAc 9:1) ; immediately used without purification.

A Wittig reaction[9] is performed with 4 and isobutyltriphenylphosphonium bromide (heptane-ether 2:3, BuLi, 12 h. at 20°C and 24 h. at 60°C). After reacetylation of the reaction mixture, the two isomers 5b and 6b are isolated (TLC $Al_2O_3/AgNO_3$, hexane-EtOAc 25:2 Rf 0.90 and 0.80). The saponification gives 5a and 6a (molecular ion at m/e 370, m/e 300 M-(C_5H_9 + H), 271 M-(C_7H_{13} + 2H) which are rearranged to the 3β-acetoxy$\Delta_{5,22}$ *trans* and *cis* sterols 7b and 8b (Al_2O_3/AcOH 5 min. reflux, yield 100 %[6]). The *trans* sterol acetate 7b is characterized by spectrometric methods ; MS m/e 362 M-60, 282 M-60-(C_5H_9 + H), 255 M-60-C_7H_{13} ; NMR, IR/KBr, see table ; (TLC[5] pentane-AcOEt 7:3 Rf 0.85). The *cis* sterol acetate 8b shows a mass spectrum similar to the one of 7b ; NMR and IR/KBr, see table ; (TLC[5] same Rf as for 7b). Saponification of 7b and 8b gives the sterols 7a and 8a : (7a *trans*, mp. 122-124°C, plates, MeOH ; $(\alpha)_D^{20°} = -31 \pm 2°$ $CHCl_3$; 8a *cis*, mp. 163-166°C, needles, MeOH ; $(\alpha)_D^{20°} = -63 \pm 2°$ $CHCl_3$). The yield of 7a + 8a is 12 % from acetoxycholenic acid 1 ; the two isomers are obtained in the ratio 1:2.

A Wittig reaction between 4 and isoamyltriphenylphosphonium iodide (heptane-ether 2:3, PhLi, as above) leads to the *trans* and *cis* C_{27} 3, 5-cyclosteroids 9b and 10b isolated after reacetylation of the reaction mixture ($Al_2O_3/AgNO_3$ 3:1 preparative TLC in hexanebenzene-ether 75:11:1, Rf 9b 0.70 and 10b 0.60). The cis or trans compounds give the molecular ion at m/e 426 ; 366 M-60, 255 M-60-C_8H_5. IR/KBr confirm the trans and cis stereochemistry ; NMR see table. The corresponding 3β-acetoxy$\Delta_{5,22}$ trans and cis sterols 11b and 12b are obtained by rearrangement as above[6] ; (IR, MS). The free sterols 11a and 12a are separated after saponification (11a trans mp. 132-135°C, plates, MeOH ; $(\alpha)_D^{20°}$ = -35 ± 2° $CHCl_3$, 12a cis mp. 135-137°C, needles, MeOH, $(\alpha)_D^{20°}$ = -53 ± 2° $CHCl_3$.

Separations of $\Delta_{5,22}$ cis and trans isomers of sterols is thus possible by $AgNO_3$ chromatography of the corresponding i-steroids. Separations of Δ_{22} cis and trans sterols having a saturated cyclic squeleton has been previously reported[10, 11]. The identification of the isolated isomers is not possible from mass or NMR spectrographical data ; the coupling of protons at C-22 C-23 is quite similar and the coupling constants are small ; in all cases the AB cis system is found at higher fields. With the Δ_5 compounds, only the signals given by protons at C-22 C-23 cis can be distinguished from those of the ethylenic proton at C-6. Finally, the identification of the isomers is only possible from the IR ; as previously observed[10, 11] the cis isomers have shorter Rf values on $Al_2O_3/AgNO_3$ TLC.

	NMR (δ)									IR cm^{-1}
	C_3-H C_4-H_2	18-CH_3	19-CH_3	21-CH_3	25, 26-CH_3 or 26, 27-CH_3	C_{22}-H C_{23}-H		C_6-H		
		s	s	d 6, 5Hz	d 6, 5Hz	δ	J	δ	J	
3b	0.5 0.3	0.75	1.00	1.03		ABC 4.80_{23} 4.95_{22} 4.61_{23}	trans 3Hz cis 2.5Hz	4.43 t	3Hz	1640 910
7b (trans)		0.70	1.02	1.01	0.94	AB 5.25	3.5Hz	5.35 q	5-1Hz	980
8b (cis)		0.70	1.02	0.94	0.90	AB 4.95	2Hz	5.32 q	5-1Hz	770 750
9b (trans)	0.5 0.3	0.75	1.00	1.02	0.88	AB 5.22	3Hz	4.5 t	2Hz	980
10b (cis)	0.5 0.3	0.75	1.00	0.95	0.88	AB 5.17	2Hz	4.5 t	2Hz	760 735



NMR^{7} spectrum of <u>cis</u> dimethyl-24 chola-5,22 dien 3β ol <u>8a</u>

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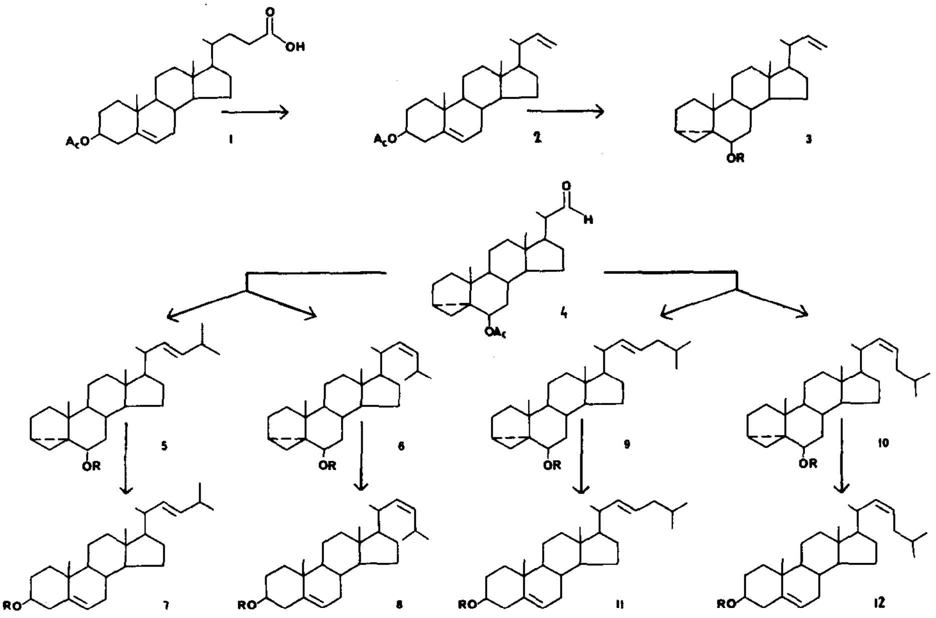

a : R=H , b : R=Ac=CH_3CO

Footnotes and references

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