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THE SYNTHESIS AND ASSIGNMENT OF CONFIGURATION OF SOME 23-SUBSTITUTED CHOLANIC ACID DERIVATIVES

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This communication is prompted following recent publications concerning the circular dichroism of α-hydroxy and α-halogeno acids.[1]

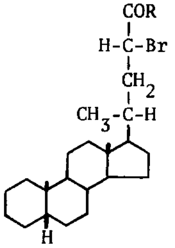
For another research project we desired optically pure epimeric α-bromocholanic acid and derivatives which as yet are unrecorded in the literature. We report the synthesis and determination of configuration of hitherto unknown epimeric 23-bromocholanic acid esters, (R) and (S)-(II), the epimeric N-substituted amides, (R) and (S) of (III) and (IV), and of t-butyl 23-methoxycholanate (VIII-IX).

The bromo-esters (R)-(II) and (S)-(II), were prepared by exposing cholanyl chloride[2] (3 g) in pure thionyl chloride (7 ml) to the action of bromine (0.5 ml) and pyridine (0.25 ml) at 40-60°, and the resulting α-bromo-cholanyl chloride (I) was then quenched in cold dry methanol. Separation of diastereomeric bromo-esters was achieved by thin-layer chromatography on KGF_{254} plates, using petroleum ether (40-60°)-ether (19:1) as eluent.

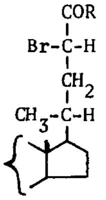
The bromo-amides, (R), (S) of (III) and (IV) were similarly derived from a common precursor (I) by its treatment with the respective amine at 0°, followed by t.l.c. separation (KGF_{254}).

Compounds (VIII) and (IX), which are included here for stereochemical correlations, were obtained from treatment of t-butyl (RS)-23-bromocholanate[3] with sodium methoxide in dry t-butanol, and separated by thin-layer chromatography.

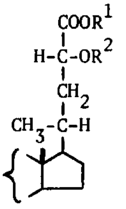
The direct conversion of secondary aliphatic mono-and di-diols to the respective bromo derivatives on reaction with phosphorus pentabromide and pyridine at 0° has been shown to proceed with inversion of configuration.[4] When we applied this reaction to (VII), an epimer of (II) is obtained essentially in pure form. On the above basis we assign the latter the (23S)-configuration and consequently assign the (23R)-configuration to its epimer.



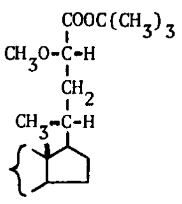
(R)-(II-IV)



(S)-(II-IV)



(R)-(VII-VIII)



(S)-(IX)

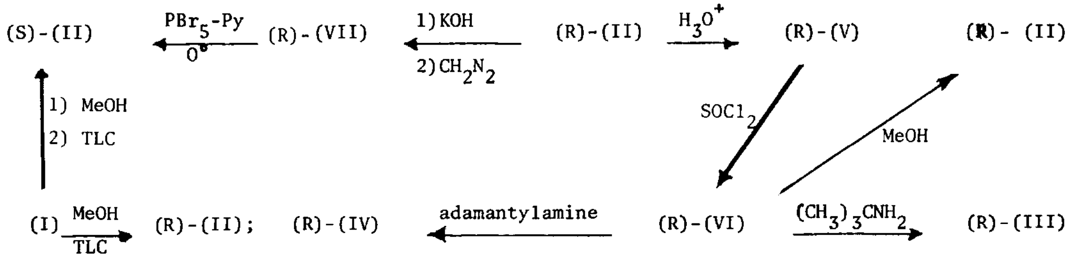
(II), R=OCH_3; (III), R=$NHC(CH_3)_3$;

(IV), R=NH-adamantyl; (V), R=OH; (VI), R=Cl

(VII), $R^1=CH_3$; $R^2=H$

(VIII), $R^1=C(CH_3)_3$; $R^2=CH_3$

The absolute configuration in the bromo-amides (III and IV) is correlated with that of (R)-(II), since (R)-(VI), which results from the sequence (R)-(II) → (R)-(V) → (R)-(VI), yields (R)-(II) on methanolysis, and (R)-(III) and (R)-(IV) upon treatment with the respctive amine. This indicates that throughout all stages in the sequence, the configuration is fully retained.



The c.d. spectra of compounds listed in the Table manifest the expected optically active band near 210 mμ[5], and in addition, an ellipticity band of opposite sign at longer wavelength (240 mμ). The u.v. spectra of these compounds in n-hexane are characterized by a well defined maximum of high intensity below 220 mμ. The bathochromic shift of the 210 mμ band

Table. C-18 Methyl Proton Resonances, UV and CD Data of Epimers of (II) - (IX).

Compound	MP °C	$+[\alpha]_D^{20}$ ($CHCl_3$)	δ 18-CH_3 Hz	Ultraviolet Spectra				CD Spectra*	
				λ_{max}	ε	λ_{max}	ε	λ_{max}	$[\Theta]_{max}$
				(n-C_6H_{12})		(dioxane)		(dioxane)	
(R)-(II)	110-111	60.2°	41.5	208	483	229	1180	207.5	-2780
				226	527			237.5	+5841
(S)-(II)	82-84	14.1	37.5	213	653	-	-	207.5	+2336
								237.5	-6438
(S)-(III)	80-83	57.0	40.5	213	1609	226	1523	210	-2627
				245	315			252.5	+3987
(S)-(III)	118-121	8.3	37.5	215	1672	223	2358	203	+9735
				245	410			250	-4792
(R)-(IV)	117	49.8	40.8	215	1000	227.5	1733	207.5	-1494
				240	365			255	+4081
(S)-(IV)	122	7.0	38.0	217	662	226	3128	202	+9900
				242	290			250	-3974
(R)-(V)	191-193	49.4	42.0	-	-	227	595	210	-1448
								242.5	+3228
(R)-(VII)	128-130	20.1	41.5	210	123	-	-	$[\phi]_{220}$	-19400 (trough)
(R)-(VIII)	110-111	34.4	40.0	205	105	225	232	220	-2673
				223	235				
(S)-(IX)	-	12.6	38.5	204	301	225	199	222.5	+ 997
				225	290			240	- 713

*CD measurements were made on Cary Model 60 Spectropolarimeter with a 6001 CD accessory.

and the hypsochromic shift of the longer wavelength band noted in going from hexane to dioxane are characteristic of n → π* transitions[6,7]. In (S)-lactic acid[1] and its esters and ethoxy-esters[1b], the weak negative c.d. band at 240 mμ was attributed to coupling of an oxygen lone-pair electrons with the carbonyl chromophore. Similarly, in (S)-amino acid esters,[1a] the strong positive dichroic band at 209 mμ was attributed to a form of maximum angle between dipoles, while the observed negative c.d. band near 230 mμ attributed to interaction between the nitrogen and carbonyl moieties.

In bromo-amides (III-IV), the intensity of the dichroic band near 210 mμ is dependent both on configuration at C-23 and on substitution on the nitrogen, whereas that of the longer wavelength appears not to be so. This allows the conclusion that the sign of the Cotton effect in the 210 mμ region has a direct relationship to the chirality of carbon-23 in compounds listed in the Table. The assignment of (R)-configuration to compounds showing negative Cotton effect, and in turn, (S)-configuration to those manifesting positive effect near 210 mμ is in agreement with most recent publications[1].

Of particular interest are the relative C-18 methyl resonances of epimeric hydroxy-, methoxy- and bromo-esters, and of bromo-amides. The C-18 methyl group protons are consistently more shielded in the (S)-series than in the (R)-series. This provides an additional very convenient method to assign chirality at asymmetric carbons in the cholanic acid sidechain.

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