292. Synthesis and Absolute Configuration of New Trichloro Steroids with Cyclopropane-Containing Side Chains

by **Robert W. Lang** and **Carl Djerassi**

Department of Chemistry, Stanford University, Stanford, California 94305

and **Phyllis D. Strong, Dale C. Swenson** and **William L. Duax**

Molecular Biophysics Department, Medical Foundation of Buffalo, Inc., Buffalo, New York 14203

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Summary

The determination of the absolute configuration of the trichloro steroids **2a** and **2c** *(cf. Scheme 1)* by means of two X-ray crystal structure analyses is reported and applies also to the determination of the absolute configurations of several derived steroidal cyclopropanes [1]. The preparation of the chlorinated derivatives **2a–c** is described and the spectroscopic properties of **1** and **2** are summarized.

In connection with our synthesis of sterols with cyclopropane-containing side chains, we were especially interested in the configuration at the three-membered ring [1]. This is due to the fact that we required several stereoisomers and, therefore, used the non-stereospecific carbene-addition route to generate the cyclopropane moiety starting from the corresponding, isomerically pure substituted olefins. In spite of finding reasonable differences in physical and spectroscopic properties of diastereoisomeric steroidal cyclopropanes [1], for all practical purposes the determination of the absolute configuration can be accomplished only by X-ray analysis.

In searching for suitable derivatives for X-ray analysis, we assumed that the primary dichlorocarbene adducts **1a–d** [1] would serve as practical intermediates. It is well known [2] that the steroidal i-methyl-ether moiety can easily be transformed to the corresponding 3β-chloro Δ^5-system by treatment with HCl in acetic acid. Therefore we examined this possibility to introduce a third halogen atom into the sterol compounds *(Scheme)*. The use of highly diluted HCl in dioxane/water 4:1 promised to avoid the occurrence of any side-reactions which could affect the dichlorocyclopropane ring. Indeed, after heating such a solution of the halogenated steroidal i-methyl-ether for 45 min under reflux, a (3:1)-mixture of the 3β-chloro and the 3β-hydroxy steroid – easily separable by column chromatography and/or by reverse-phase high-performance liquid chromatography – could be isolated in almost quantitative overall yield.

In order to show the most striking differences of their spectroscopic properties, we have summarized the ^{1}H-NMR.-methyl-group signals as well as the main mass

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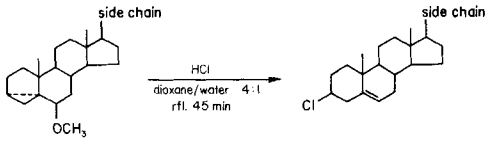
Scheme



1 **2**

a (23*R*,24*S*) **b** (23*S*,24*R*) **c** (24*R*,28*R*) **d** (24*S*,28*S*)

spectral fragments of **1** and **2** – having the three-membered ring in either the 23,24- or the 24,28-position – in *Table 1* and *2*, respectively.

It is obvious from *Table 1*, that the differences in diastereoisomerically substituted steroidal cyclopropanes can be observed in their NMR. spectra (*cf.* **1a** *vs.* **1b** and **1c** *vs.* **1d**), but not in their mass spectra *(Table 2)*. Nevertheless, steroids having the three-membered ring in different positions of the side chain (*cf.* **1a** *vs.* **1c**) may easily be differentiated from each other by both NMR. and mass spectra. Although no striking differences are measurable between the i-methyl-ethers **1** and the 3β-chloro steroids **2** in the ^{1}H-NMR. chemical shifts of the side-chain methyl groups, only the mass spectra of the trichloro steroids **2a** and **2b** show the expected loss of $C_5H_8Cl_2$ (concomitant fission of C(23),C(24)- and C(23),C(28)-bonds with a reasonable intensity at *m/z* 346, whereas the corresponding peak at *m/z* 342 in **1a** and **1b** is missing. However for the 24,28-dichloromethylene analogs (the i-methyl-ethers **1c** and **1d**, as well as the steroid **2c**), the appropriate fragmentation peak, which occurs from loss of $C_3H_4Cl_2$ and leads to *m/z* 398 and 402, respectively, may be observed in both cases with similar intensity *(Table 2)*.

Table 1. *Methyl group region ^{1}H-NMR. (360 MHz, $CDCl_3$) chemical shifts*[a])

Compound	C(18)	C(19)	C(21)	C(26)/C(27)	C(29)
1a (23*R*,24*S*)	0.762	1.027	0.945	1.106/1.056	
			(6.63)	(6.43/6.56)	
2a (23*R*,24*S*)	0.723	1.035	0.942	1.105/1.060	
			(6.62)	(6.42/6.52)	
1b (23*S*,24*R*)	0.740	1.026	0.979	1.105/1.073	
			(6.55)	(6.43/6.55)	
2b (23*S*,24*R*)	0.701	1.031	0.978	1.105/1.078	
			(6.56)	(6.44/6.59)	
1c (24*R*,28*R*)	0.710	1.019	0.913	1.134/1.028	1.154
			(6.47)	(6.88/6.49)	(*s*!)
2c (24*R*,28*R*)	0.670	1.025	0.916	1.131/1.025	1.153
			(6.36)	(6.98/6.93)	(*s*!)
1d (24*S*,28*S*)	0.709	1.020	0.924	1.127/1.033	1.168
			(5.92)	(6.95/6.95)	(*s*!)

[a]) Given as δ values; (*J*) values are in Hz. ^{1}H-NMR. values of the i-methyl-ethers **1a–d** are taken from [1].

Table 2. *Main mass spectral* fragments of **1** and **2**[a]) [*m/z*-values (average intensity, fragments)]

1a (23*R*,24*S*), **1b** (23*S*,24*R*)	**2a** (23*R*,24*S*), **2b** (23*S*,24*R*)	**1c** (24*R*,28*R*), **1d** (24*S*,28*S*)	**2c** (24*R*,28*R*)
480 (59, M^+)	484 (22, M^+)	508 (5, M^+)	512 (3, M^+)
465 (55, $M-CH_3$)	469 (14, $M-CH_3$)	493 (15, $M-CH_3$)	476 (4, $M-HCl$)
448 (92, $M-CH_3OH$)	448 (23, $M-HCl$)	476 (10, $M-CH_3OH$)	402 (46, $M-C_3H_4Cl_2$!)
425 (100, M – A-ring)	433 (8, $M-CH_3-HCl$)	453 (32, M – A-ring)	387 (19, 402 – CH_3)
327 (22)	346 (39, $M-C_5H_8Cl_2$!)	398 (40, $M-C_3H_4Cl_2$!)	332 (7)
285 (14)	331 (11)	383 (62, 398 – CH_3)	318 (47)
255 (64)	319 (41)	351 (22)	289 (100)
253 (80)	317 (34)	343 (53, 398 – A-ring)	
229 (35)	303 (18)	314 (26)	
213 (72)	291 (62)	285 (99)	
	289 (100)	253 (100)	

[a]) Low resolution data obtained at 70 eV. Mass spectral data of the i-methyl-ethers **1a–d** are taken from [1].

The assignments of the absolute configurations at the cyclopropane rings of all compounds described above and of most in [1] were based on the two following X-ray crystal structure analyses of the trichloro steroids **2a** and **2c**, which were recrystallized from ethyl acetate/ethanol to yield long and homogeneous needles.

The absolute configurations of the two structures are illustrated in the *Figure*. The cholesterol side chain conformations are defined by the torsion angles of *Table 3*. The methylene substituent introduces a *cis*-conformation of ω_3, C(22)–C(23)–C(24)–C(25) in derivative **2a**. Such a conformation is not observed in the side chains of 96 cholestanes whose X-ray crystal structures have recently been surveyed [3]. The side chain conformation observed in derivative **2c** is also

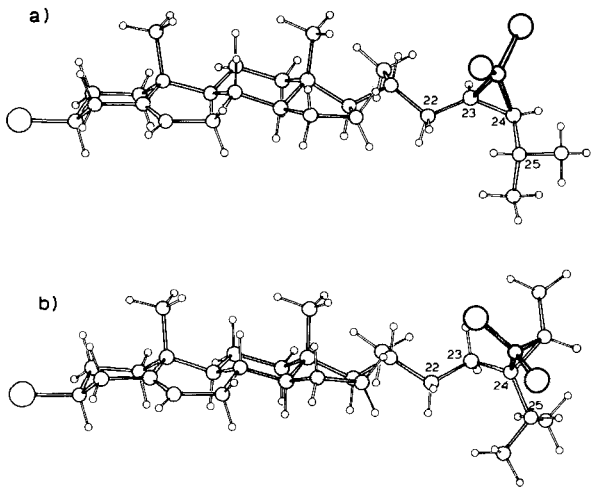


Figure. *The observed absolute configurations and conformations of* (**a**) *(23*R*,24*S*)-3β-chloro-23,24-dichloromethylenecholest-5-ene* (**2a**) *and* (**b**) *(24*R*,28*R*)-3β-chloro-24,28-dichloromethylene-24-ethyl-cholest-5-ene* (**2c**)

Table 3. *Torsion angles defining the side chain conformation*

		2a	2c
ω_1	C(13)–C(17)–C(20)–C(22)	– 177.6°	178.9°
ω_2	C(17)–C(20)–C(22)–C(23)	– 173.3	– 167.9
ω_3	C(20)–C(22)–C(23)–C(24)	157.0	151.5
ω_4	C(22)–C(23)–C(24)–C(25)	– 1.3	70.2
ω_5	C(23)–C(24)–C(25)–C(26)	– 156.3	– 61.0
ω_6	C(23)–C(24)–C(25)–C(27)	81.5	63.2

unusual in that the C(26)- and C(27)-methyl groups are both *gauche* with respect to C(23). Such a conformation is observed only once in the 96 cholestanes studied crystallographically. Corresponding bond lengths and angles in the two structures are within three standard deviations of each other and appear unexceptional when compared with previous X-ray crystal structure determinations.

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Experimental Part

General remarks. Conditions and equipment used for the physical measurements in the synthetic section were those described in [1].

The crystal data for the trichloro steroids **2a** and **2c** are presented in *Table 4.* In each case the cell constants were determined by least-squares analysis of the θ values for 25 reflections centered on a diffractometer. For compound **2a**, integrated intensities for 2376 independent reflexions having $\theta < 60°$ were measured on an *Enraf-Nonius* CAD-4 diffractometer using Cu$K\alpha$ radiation. The structure

Table 4. *Crystal data of compounds* **2a** *and* **2c**

	2a	2c
Molecular formula	$C_{28}H_{43}Cl_3$	$C_{30}H_{47}Cl_3$
Molecular weight	486.21	514.12
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$
Z	4	2
Cell dimensions (Å)		
a	12.580 (3)	18.150 (4)
b	35.347 (9)	21.903 (4)
c	6.203 (1)	12.502 (3)
β	–	105.82 (2)
Vol. [Å^3]	2758.2	1466.4
Density [g/cm^3]	1.17	1.16
Crystal size [mm]	0.04 × 0.28 × 1.3	0.20 × 0.28 × 0.60
λ [Å]	1.54184 (Cu$K\alpha$)	0.7107 (Mo$K\alpha$)

was solved by direct methods [4] and refined by full matrix least-squares. H-Atoms were introduced at geometrically expected positions and not refined. The crystal size and shape produced data suitable for unambigous determination of the configuration at C(23) and C(24). However, the rapid fall-off in intensities from the best crystals that could be obtained precluded H-atom location and the degree of geometric accuracy routinely achieved in X-ray crystal structure determinations. The final conventional R indices were 13.5% for all data and 9.2% for the 1689 reflections having intensities greater than twice their standard deviation.

For compound **2c** integrated intensities for 4622 independent reflections having $\theta < 30°$ were measured on a *Nicolet-Syntex* P3 diffractometer using Mo$K\alpha$ radiation. The intensities were reduced to structure factor amplitudes, and phase angles sufficient for location of the non-H-atoms were derived using the direct-methods program MULTAN [4]. H-Atoms were introduced at geometrically expected positions. In the final cycles of full matrix least-squares refinement, positional parameters for all the atoms, and anisotropic thermal vibration parameters for the non-H-atoms were varied. The H-atoms were assigned isotropic thermal parameters equivalent to the C-atom to which they were attached and their thermal motion was not refined.

The quantities $(1/\sigma_F^2)$ were used to weight the least-squares differences; data having $F < 3.0\ \sigma_F$ were given zero weight and not included in the refinement. The refinement converged as a residual $(R = \Sigma \| F_o| - |F_c\| / \Sigma |F_o|)$ of 0.08 and 0.159 for all data; the weighted residual $[R_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w F_o^2]^{1/2}]$ was calculated to be 0.09 and the standard deviation of an observation of unit weight $[S^2 = \Sigma w \Delta^2/(m\text{-}n)$ where m is the number of observations and n is the number of parameters] was found to be 2.7.

Positional parameters for both structures are given in *Table 5*. Coordinates for H-atom positions, anisotropic thermal parameters, non-H-atoms, and other crystallographic details are available from the *Buffalo* authors upon request.

Acidification of **1** *with aqueous HCl-solution.* The synthesis and the spectroscopic properties of the starting i-methyl-ethers **1a–d** are described in [1]. Acidification of **1** was accomplished generally by dissolving the protected dichloro sterol **1** (0.06 mmol) in a (4:1)-mixture of dioxane/water (18 ml) and adding a small amount of conc. HCl-solution (*ca.* 5 drops). After heating the reaction mixture under reflux for 45 min, the cold solution was evaporated in RV. at reduced pressure. Dilution with water and extraction with CH_2Cl_2 furnished a (1:3)-mixture (HPLC. analysis) of the 3β-hydroxy compound (TLC., more polar) and the desired 3β-chloro compound **2** (TLC., less polar) in almost quantitative overall yield. Product separation was accomplished by either column chromatography and/or by reverse-phase HPLC. and the analytical data for the trichloro steroids **2a–c** are listed herewith.

*(23*R*,24*S*)-3β-Chloro-23,24-dichloromethylenecholest-5-ene* (**2a**). M.p. 136–137° (AcOEt/EtOH); $[\alpha]_{589}^{20} = -21.64°$, $[\alpha]_{546}^{20} = -26.18°$ ($c = 5.5$ mg/ml, $CHCl_3$); Rf 0.83 (CH_2Cl_2). – ^{1}H-NMR. (360 MHz): 5.37 (*m*, 1H, H–C(6)); 3.77 (*m*, 1H, H(α)–C(3)); 1.105 and 1.060 (each *d*, $J = 6.42$ and 6.52 resp., each 3 H, $H_3C(26)$ and $H_3C(27)$); 1.035 (*s*, 3 H, $H_3C(19)$); 0.942 (*d*, $J = 6.62$, 3 H, $H_3C(21)$); 0.723 (*s*, 3 H, $H_3C(18)$). –MS. (HR.)(*m/z*, relative intensity): 484.2452 (24, M^+, calc. for $C_{28}H_{43}Cl_3$ 484.2430), 469.2132 (11, $C_{27}H_{40}Cl_3$, $M - CH_3$), 448.2688 (34, $C_{28}H_{42}Cl_2$, $M - HCl$), 433.2409 (10, $C_{27}H_{39}Cl_2$, $M - CH_3 - HCl$), 346.2428 (25, $C_{23}H_{35}Cl$, $M - C_5H_8Cl_2$!), 331.2173 (10, $C_{22}H_{32}Cl$), 319.2206 (38, $C_{21}H_{32}Cl$), 317.2079 (32, $C_{21}H_{30}Cl$), 303.1947 (13, $C_{20}H_{28}Cl$), 291.1772 (66, $C_{19}H_{28}Cl$), 289.1709 (100, $C_{19}H_{26}Cl$).

*(23*S*,24*R*)-3β-Chloro-23,24-dichloromethylenecholest-5-ene* (**2b**). M.p. 134–135° (AcOEt/EtOH); $[\alpha]_{589}^{20} = -19.09°$, $[\alpha]_{546}^{20} = -23.09°$ ($c = 5.5$ mg/ml, $CHCl_3$); Rf 0.83 (CH_2Cl_2). – ^{1}H-NMR. (360 MHz): 5.37 (*m*, 1H, H–C(6)); 3.77 (*m*, 1H, H(α)–C(3)); 1.105 and 1.078 (each *d*, $J = 6.44$ and 6.59 resp., each 3 H, $H_3C(26)$ and $H_3C(27)$); 1.031 (*s*, 3 H, $H_3C(19)$); 0.978 (*d*, $J = 6.56$, 3 H, $H_3C(21)$); 0.701 (*s*, 3 H, $H_3C(18)$). –MS. (HR.)(*m/z*, relative intensity): 484.2403 (20, M^+, calc. for $C_{28}H_{43}Cl_3$ 484.2430), 469.2102 (17, $C_{27}H_{40}Cl_3$, $M - CH_3$), 448.2649 (11, $C_{28}H_{42}Cl_2$, $M - HCl$), 433.2409 (6, $C_{27}H_{39}Cl_2$, $M - CH_3 - HCl$), 346.2426 (53, $C_{23}H_{35}Cl$, $M - C_5H_8 - Cl_2$!), 331.2196 (12, $C_{22}H_{32}Cl$), 319.2166 (44, $C_{21}H_{32}Cl$), 317.2053 (37, $C_{21}H_{30}Cl$), 303.1880 (23, $C_{20}H_{28}Cl$), 291.1801 (57, $C_{19}H_{28}Cl$), 289.1738 (100, $C_{19}H_{26}Cl$).

*(24*R*,28*R*)-3β-Chloro-24,28-dichloromethylene-24-ethylcholest-5-ene* (**2c**). M.p. 146–148° (AcOEt/EtOH); $[\alpha]_{589}^{20} = -35.14°$, $[\alpha]_{546}^{20} = -40.54°$ ($c = 3.7$ mg/ml, $CHCl_3$); T_R (HPLC., ODS-2) 87 min. –

Table 5. *Non-H-atomic coordinates* ($\times 10^4$) *and isotropic thermal parameters* ($\times 10$) *for* (a) *(23R,24S)-3β-chloro-23,24-dichloromethylenecholest-5-ene* (**2a**) *and* (b) *(24R,28R)-3β-chloro-24,28-dichloromethylene-24-ethylcholest-5-ene* (**2c**)

Atom	X/A (σ)	Y/B (σ)	Z/C (σ)	BISO (σ)	Atom	X/A (σ)	Y/B (σ)	Z/C (σ)	BISO (σ)
(a)									
C(1)	5656 (6)	3783 (2)	3047 (12)	62 (2)	C(17)	4888 (5)	5594 (2)	5554 (12)	48 (2)
C(2)	5998 (6)	3373 (2)	2996 (14)	69 (2)	C(18)	3794 (5)	5121 (2)	7665 (13)	55 (2)
C(3)	7089 (6)	3321 (2)	4011 (16)	72 (3)	C(19)	4741 (5)	3784 (2)	6677 (14)	57 (2)
C(4)	7080 (6)	3464 (2)	6340 (16)	70 (3)	C(20)	3961 (5)	5888 (2)	5312 (14)	61 (2)
C(5)	6695 (5)	3864 (2)	6465 (12)	50 (2)	C(21)	3167 (6)	5771 (2)	3513 (17)	87 (3)
C(6)	7240 (5)	4117 (2)	7611 (14)	60 (2)	C(22)	4393 (5)	6281 (2)	4874 (13)	55 (2)
C(7)	6948 (5)	4516 (2)	7943 (12)	52 (2)	C(23)	3558 (5)	6592 (2)	4875 (12)	57 (2)
C(8)	5832 (4)	4617 (2)	7182 (10)	46 (2)	C(24)	3781 (6)	7002 (2)	5273 (14)	63 (2)
C(9)	5539 (4)	4391 (2)	5091 (10)	43 (2)	C(25)	4888 (6)	7164 (2)	5784 (17)	70 (3)
C(10)	5652 (5)	3961 (2)	5368 (11)	47 (2)	C(26)	4795 (7)	7533 (2)	6973 (17)	81 (3)
C(11)	4453 (5)	4520 (2)	4269 (13)	55 (2)	C(27)	5477 (7)	7210 (2)	3580 (22)	100 (4)
C(12)	4373 (5)	4947 (2)	3855 (12)	54 (2)	C(28)	3196 (6)	6772 (2)	6961 (14)	67 (2)
C(13)	4641 (4)	5178 (2)	5912 (12)	45 (2)	CL(3B)	7501 (2)	2838 (1)	3849 (6)	106 (1)
C(14)	5745 (4)	5041 (2)	6665 (10)	42 (2)	CL(28A)	3743 (3)	6648 (1)	9362 (4)	109 (1)
C(15)	6090 (5)	5332 (2)	8312 (11)	52 (2)	CL(28B)	1798 (2)	6849 (1)	7142 (7)	123 (1)
C(16)	5627 (5)	5704 (2)	7495 (13)	56 (2)					
(b)									
C(1)	487 (1)	791 (1)	183 (1)	49 (2)	C(18)	203 (1)	932 (1)	−185 (1)	50 (2)
C(2)	531 (1)	768 (1)	317 (1)	51 (2)	C(19)	356 (1)	836 (1)	207 (1)	50 (2)
C(3)	560 (1)	948 (1)	366 (1)	52 (2)	C(20)	196 (1)	1001 (1)	−450 (1)	41 (1)
C(4)	495 (1)	1080 (1)	362 (1)	51 (2)	C(21)	221 (1)	806 (1)	−475 (1)	75 (2)
C(5)	445 (1)	1101 (1)	232 (1)	41 (2)	C(22)	182 (1)	1119 (1)	−564 (1)	43 (1)
C(6)	425 (1)	1266 (1)	188 (1)	48 (2)	C(23)	115 (1)	1055 (1)	−667 (1)	49 (2)
C(7)	375 (1)	1303 (1)	64 (1)	46 (2)	C(24)	76 (1)	1204 (1)	−753 (1)	42 (1)
C(8)	338 (1)	1134 (1)	−2 (1)	36 (1)	C(25)	117 (1)	1296 (2)	−839 (1)	74 (3)
C(9)	393 (1)	974 (1)	24 (1)	34 (1)	C(26)	189 (1)	1391 (2)	−783 (1)	98 (4)
C(10)	419 (1)	926 (1)	161 (1)	34 (1)	C(27)	130 (1)	1151 (3)	−926 (1)	129 (6)
C(11)	365 (1)	807 (1)	−58 (1)	43 (1)	C(28)	22 (1)	1330 (1)	−706 (1)	51 (2)
C(12)	335 (1)	854 (1)	−193 (1)	42 (1)	C(29)	−11 (1)	1193 (1)	−807 (1)	54 (2)
C(13)	274 (1)	1002	−216 (1)	33 (1)	C(30)	−58 (1)	1033 (1)	−784 (1)	73 (3)
C(14)	310 (1)	1170 (1)	−138 (1)	34 (1)	CL(3B)	617 (1)	929 (1)	522 (1)	73 (1)
C(15)	254 (1)	1325 (1)	−181 (1)	51 (2)	CL(28A)	10 (1)	1290 (1)	−563 (1)	82 (1)
C(16)	225 (1)	1290 (1)	−319 (1)	51 (2)	CL(28B)	15 (1)	1566 (1)	−736 (1)	88 (1)
C(17)	252 (1)	1095 (1)	−343 (1)	35 (1)					

^{1}H-NMR. (360 MHz): 5.37 (*m*, 1H, H–C(6)); 3.77 (*m*, 1H, H–C(3)); 1.153 (*s*!, 3H, H_3C(29)); 1.131 and 1.025 (each *d*, J=6.98 and 6.93 resp., each 3H, H_3C(26) and H_3C(27)); 1.025 (*s*, 3H, H_3C(19)); 0.916 (*d*, J=6.36, 3H, H_3C(21)); 0.670 (*s*, 3H, H_3C(18)). – MS. (HR.) (*m/z*, relative intensity): 512.2765 (3, M^+, calc. for $C_{30}H_{47}Cl_3$ 512.2743), 476.2989 (4, $C_{30}H_{46}Cl_2$, M – HCl), 402.3072 (46, $C_{27}H_{43}Cl$, $M-C_3H_4Cl_2$!), 387.2840 (19, $C_{26}H_{40}Cl$, $402-CH_3$), 332.2284 (7, $C_{22}H_{33}Cl$), 318.2092 (47, $C_{21}H_{31}Cl$), 289.1726 (100, $C_{19}H_{26}Cl$).

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