STUDIES ON THE CONVENIENT PREPARATION OF PURE Δ_2-CHOLESTENE

By I. TÖMÖSKÖZI and F. URESCH

Institute of Organic Chemistry, The University, Szeged

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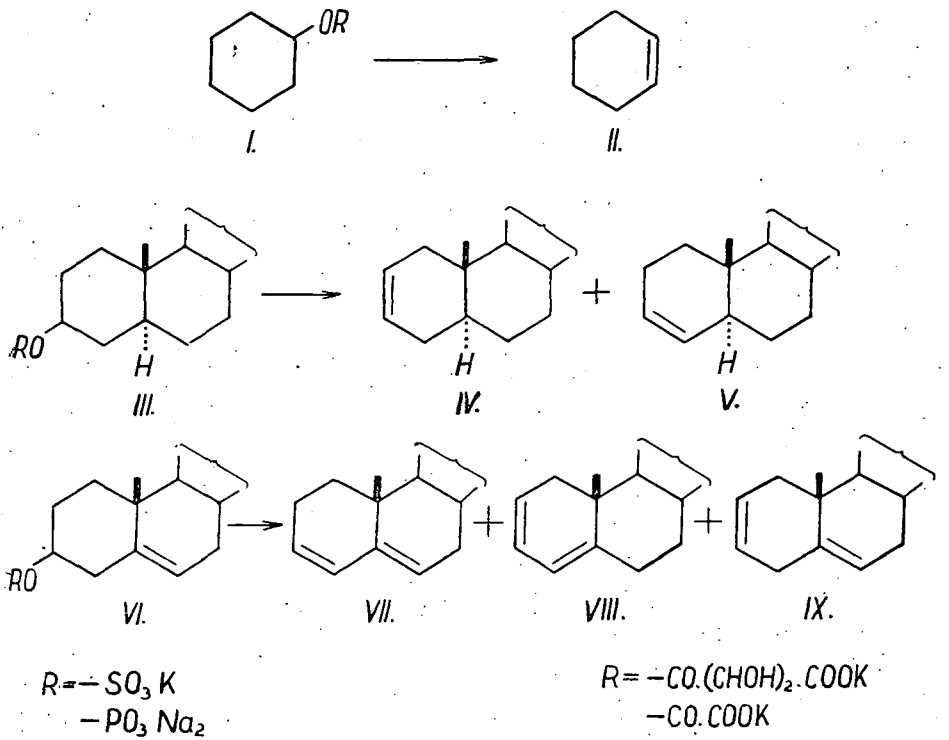
Several methods for the preparation of Δ_2-cholestene (IV) and — parallel to it — of $\Delta_{3,5}$-cholestadiene (VII) described in literature were subjected to a critical study, with special respects to the quick production of the end product and to the reproducibility of the process. In order to improve the SOBEL and ROSEN method [11], a simple method was evolved for the convenient preparation of Δ_2-cholestene (IV) of adequate purity.

In the course of researches carried out in this Institute, the necessity of preparing large quantities of Δ_2-cholestene of adequate purity (IV) arose. As the homogeneity of cholestene as well as the quickness and cheapness of preparation were factors of equal importance in our research plan, it seemed practical to subject methods described so far in literature to a critical survey and, respectively, to compare the physical constants of cholestenes prepared by simple thermolytic methods with those of Δ_2-cholestene of "standard" purity in order to decide whether cholestenes obtained by this way are suitable for our purposes. At the survey of literature it appeared advisable to consider also the possibilities of preparing $\Delta_{3,5}$-cholestadiene from cholesterol, since methods of this type are described in literature parallel to those referring to cholestene [9], [11], [14], [17], [36], [50].

Methods of preparing Δ_2-cholestene and constants of products are summarized in Table I. It can be seen that observations are different as regards the melting point and rotatory power of Δ_2-cholestene.

The fluctuation of physical constants indicates the presence of a mixture of isomers (Δ_2-cholestene and Δ_3-cholestene) [7], [9], [17], [50]. This is confirmed by the observation that cholestene prepared by pyrolysis or thermolysis shows, in general, lower values of melting point and rotatory power [6], [11], [14], [17], [50], even when refining operations more careful than in the case of cholestene prepared by ionic elimination are applied. This may be obviously interpreted by the fact that in reactions proceeding at higher temperatures, molecules are capable of converting into isomers less stable at room temperature, while under the milder conditions of ionic elimination statistically less molecules may arrive to states adequately rich in energy. Thermic methods proved to be doubtlessly simpler processes requiring less labour and readily lending themselves to the preparation of larger batches as



well. Our experiments were conducted with the aim to combine the advantages which appear promising and to evolve a simple method for producing large quantities of pure Δ_2-cholestene (IV). For this purpose, several methods listed in Table I. [1]—[4], [8], [11], [15], [17] were reproduced. It was attempted further to remove Δ_3-cholestene (V) from Δ_2-cholestene (IV) prepared by the thermic method, by the refining process through the dibromide [7] to an extent that the value of the physical constants of the pure product free of contaminations should attain the data of melting point and rotatory power of Δ_2-cholestene (IV) prepared by ionic elimination [2].

Dehydrohalogenation [1]—[4] by quinoline as a method yielding products of the highest purity attained so far, was chosen for the preparation of "authentic" Δ_2-cholestene (IV). On reproducing 1. the FIESER and DOMINGUEZ method [8], 2. the SOBEL and ROSEN method [11], 3. the SCHOPPEE method [15] and 4. the NACE method [17] for producing cholestene, the obtained crude Δ_2-cholestene was each time converted into the *dibromide* [7] which was repeatedly recrystallised from acetone. Then a treatment with zinc dust in a glacial acetic acid medium was applied to recover the olefin [7] which latter was repeatedly recrystallised from acetone. Δ_2-cholestene purified by this method showed on mixing with the "standard" Δ_2-cholestene no depression of melting point. The purified cholesten had m. p. higher than 72°C and rotatory power exceeding +67°. Attempts to raise m. p. and $[\alpha]_D$

values by chromatography of crude Δ_2-cholestene prepared from potassium cholesterol sulphate, using a neutral alumina column (activity II.) and repeated recrystallisation failed. The purest product showed m. p. 70°C and $[\alpha]_D$ +64,5°, *i. e.* values much below those of Δ_2-cholestene purified through the dibromide. Since the thermolysis of potassium cholestanyl sulphate, when combined with purification through the dibromide [7], afforded Δ_2-cholestene (IV) of satisfactory purity, it seemed worth to deal with further simplifications of this process. Chlorosulphonic acid was applied in place of pyridinium sulphur trioxide inconvenient in operations. By this technique, two steps of the original reaction were combined without affecting the yield and the values of the physical constants of the crude Δ_2-cholestene obtained. As a further modification, it was attempted to produce olefins by heating substances with inorganic salts. In this phase, our tests were extended to the preparation of cyclohexene from cyclohexanol and, respectively, of cholestadiene from cholesterol as well. The heat treatment of

1. cyclohexanol, cholestanol, cholesterol with $KHSO_4$,
2. 3α-chlorcholestane, 3-chlorcholesterol with Na_3PO_4, potassium oxalate and potassium tartrate,
3. 3β-chlorcholestane with sodium phosphate, potassium oxalate or potassium tartrate yielded

1. cyclohexene (II), Δ_2-cholestene (IV), $\Delta_{3,5}$-cholestadiene (VII),
2. Δ_2-cholestene (IV) and $\Delta_{3,5}$-cholestadiene (VII), respectively,
3. a sticky mass not studied further.

As olefin preparation with $KHSO_4$ appeared most suitable from the point of view of labour requirement, attempts were made to refine crude Δ_2-cholestene through the dibromide [7]. Olefin recovered from the dibromide showed on admixture with "standard" Δ_2-cholestene no depression of m. p.

In the case of $\Delta_{3,5}$-cholestadiene (VII) deviations of characteristic constants (see Table II) are apparently higher than with Δ_2-cholestene. In order to facilitate orientation it must be considered that the formation of the second double bond multiplies the number of possible isomers, in comparison to Δ_2-cholestene [$\Delta_{2,5}$-cholestadiene (VIII), $\Delta_{2,4}$-cholestadiene (IX), $\Delta_{3,5}$-cholestadiene (VII)] and the appearance of these isomers is responsible for the variations in the values of melting point and, to a greater extent, of $[\alpha]_D$ as well.

Considering the known rule [33] that a double bond between atoms C_4 and C_5 results in dextrorotation whereas a double bond between atoms C_5 and C_6 leads to levorotation, it may be easily understood, that the presence of even minimum amounts of $\Delta_{2,4}$-cholestadiene (IX) of an approximately identical but opposite rotatory power can appreciably affect the $[\alpha]_D$ values of the isomer mixture. The presence of $\Delta_{2,5}$-cholestadiene (VIII) in the mixture of isomers may be explained by the fact [42] that, in contrast to attempts of isomerisation and against expectations, it did not convert into conjugated diene and its partial isomerisation was effected only under rather vigorous conditions (heating in sealed tube at 320—340°C for 6 hours).

For the preparation of "authentic" $\Delta_{3,5}$-cholestadiene (VII) the SOBEL and ROSEN method appeared to be the most suitable one [11]. Comparison of cholestadiene obtained by heating cholesteryl chloride with trisodium

phosphate, sodium oxalate and potassium tartrate, respectively, with the "authentic" $\Delta_{3,5}$-cholestadiene (VII) was considered superfluous. Namely, the mentioned reactions of much lower yields and more inconvenient operation are in every respect more disadvantageous than the methods of preparing $\Delta_{3,5}$-cholestadiene (VII) with chlorosulphonic acid or with potassium hydrosulphate. Besides, the reactions take place at higher temperatures where *e.g.* the decomposition of oxalate is rather appreciable.

Potassium cholesteryl sulphate was prepared in an excellent yield by reacting cholesterol with chlorosulphonic acid [11]. $\Delta_{3,5}$-cholestadiene (VII) produced by thermolysis with capryl alcohol proved to be in every respect equivalent to "authentic" diene. No depression of melting point was observed on the admixture of $\Delta_{3,5}$-cholestadiene (VII) obtained by heating cholesterol with potassium hydrosulphate, to $\Delta_{3,5}$-cholestadiene (VII) prepared by the SOBEL and ROSEN method [11]. (This is in accordance with the observation of the mentioned authors, in connection with the melting point of $\Delta_{3,5}$-cholestadiene (VII) prepared by heating potassium cholesteryl sulphate in a sealed tube.) On heating with hydrochloric acid, the original substance was recovered. When treating with metallic sodium in an amylalcoholic medium, no uptake of hydrogen was observed [33] and the original substance was isolated.

Experimental

3β-cholestanol (III; R = —H). Cholesterol of commercial purity was hydrogenated by the NACE method [50] in a 1 : 2 mixture of glacial acetic acid and cyclohexane at room temperature under atmospheric pressure, in the presence of ADAMS platinum catalyst. Yield: 95 %, m. p. 138—139° C. $[\alpha]_D^{21} = +22{,}3°$ ($c = 1{,}97$; $CHCl_3$). Faint LIEBERMANN-BURCHARD colour test.

3α-chloro-cholestane. Prepared by the RUZICKA method [48]. On repeated recrystallisation from acetone, prismatic crystals, m. p. 103—104° C. $[\alpha]_D^{20} = +30{,}6°$ ($c = 2{,}30$; $CHCl_3$).

3β-chloro-cholestane [35]. The solution of 7,75 g of cholestanol in 20 ml of waterfree ether was treated, under cooling, with small portions of 3 g thionyl chloride in 10 ml of ether; the mixture was allowed to stand for 24 hours at room temperature, the solvent removed and the residue recrystallised from acetone. Yield: 7,4 g prismatic crystals (91 %), m. p. 114° C. $[\alpha]_D^{20} = +26{,}5°$ ($c = 2{,}28$; $CHCl_3$).

Cholesteryl chloride (β) [35]. Prepared similarly to the previous compound, by treating cholesterol in an ethereal medium by thionyl chloride. Yield: 80 %, m. p. 97° C. $[\alpha]_D^{20} = -26°$ ($c = 2{,}37$; $CHCl_3$).

β-cholestanyl tosylate (III; R = —p—$SO_2 \cdot C_6H_4 \cdot CH_3$). Prepared by the STOLL method [10]. Yield: 86 %, m. p. 134—135° C (decomposition). $[\alpha]_D^{21} = +6{,}5°$ ($c = 2{,}41$; $CHCl_3$).

α-cholestanyl tosylate. Prepared by the NACE method [17]. Yield: 50 %, m. p. 104—135° C. $[\alpha]_D^{21} = +12°$ ($c = 2{,}57$; $CHCl_3$).

Potassium cholestanyl sulphate (III; R = —SO_3K). Pyridinium sulphur trioxide was prepared by the BAUMGARTEN method [49], on treating waterfree

pyridine with chlorosulphonic acid. However, the process could not be reproduced to a satisfactory extent in any attempts. Replacing chlorosulphonic acid by sulphur trioxide, the operation was more inconvenient but the yield and the quality of product appreciably improved.

Potassium cholestanyl sulphate was obtained in almost quantitative yields by the SOBEL and SPOERRI method [11a, 11b]. M. p. 228—234°C (decomposition), against 236°C in literature [11], [11a], [11b].

In order to avoid the inconvenient preparation of pyridinium sulphur trioxide, the production of $Py^{(+)}—SO_3^{(-)}$ was combined with preparing cholestanyl sulphate in the same step in that 10 g of cholestanol were dissolved in a three-neck flask in a mixture of 15 ml of waterfree pyridine and 50 ml of waterfree carbon tetrachloride (in the absence of pyridine tar was formed). The mixture was cooled by a salt and ice mixture below 0°C. Under vigorous stirring, 4 g of chlorosulphonic acid was dropwise added to the mixture in the three-neck flask equipped with reflux condenser closed by a calcium chloride tube, dropping funnel and stirrer. After the addition of chlorosulphonic acid, ice cooling was replaced by water bath and the temperature gradually raised, the mixture being kept for 30 minutes at 100°C. On cooling, the solution of 5 g potassium hydroxide in 30 ml of water was added, the formed white precipitate filtered by suction and washed with warm methanol to afford 11,5 g (88%) of product with m. p. 223—224°C (decomposition), against 236°C in literature [11], [11a], [11b]. On recrystallisation from 70% methanol, m. p. 223—224°C (decomposition).

Potassium cholesteryl sulphate (VI; R = —SO_3K). Prepared similarly to the previous compound, by the SOBEL and SPOERRI method [11b], and by the modified process. Yield: 78—86%, m. p. 214° and 215°C respectively (decomposition).

Δ_2-cholestene (IV). The dehydrohalogenation of 3α-chlorocholestane and 3β-chlorocholestane, respectively, with quinolene was carried out by the FÜRST and PLATTNER method [1]. On repeated recrystallisation from acetone, the produced Δ_2-cholestene showed a m. p. 74—75°C. $[\alpha]_D = +67{,}2°$ ($CHCl_3$). Calcd. C 87,49; H 12,51%. Found C 87,65; H 12,60%.

Using the FIESER and DOMINGUEZ method [8], Δ_2-cholestene was prepared from cholestanol in an overall yield of 15%. On repeated recrystallisation from acetone, m. p. 69—70°C. $[\alpha]_D = +64{,}3°$ ($CHCl_3$).

No depression of m. p. was observed on admixture of "authentic" Δ_2-cholestene prepared by the FÜRST and PLATTNER method [1].

Methanolysis of α- and β-cholestanyl tosylate according to NACE [17] afforded Δ_2-cholestene in yields of 70% and 5%, respectively. M. p. 71—72°C in both cases, whereas $[\alpha]_D$ was +67° in the case of Δ_2-cholestene prepared from α-tosylate, and +66° ($CHCl_3$) in the case of that from β-tosylate, respectively. On admixture of "authentic" cholestene, neither of the products showed depression of m. p.

The thermolysis of potassium cholestanyl sulphate in capryl alcohol containing sodium caproxide [11] gave Δ_2-cholestene in yields of 75—80%. On recrystallisation from acetone repeated three times, the product showed

m. p. 69,0—69,5° C, $[\alpha]_D^{20} = +64,7°$ ($c = 2,05$; $CHCl_3$). A slight depression of m. p. (up to 0,5° C) appeared on admixture of "authentic" Δ_2-cholestene.

Preparations of cholestene obtained by the above described methods were converted to dibromide by the BARTON and ROSENFELDER method [7] and recrystallised from ethylacetate-methanol and further from acetone, repeated three times (on further repetitions the value of m. p. and $[\alpha]_D$ did not change any more). Subsequently, the glacial acetic acid solution of the dibromide was treated with zinc dust [7] at the temperature of the water bath and cholestene recovered by this way recrystallised from acetone.

Preparations of 2,3-dibromo-cholestane obtained by different methods and Δ_2-cholestene afforded by the treatment with zinc dust and glacial acetic acid showed the following physical constants:

Method	1,2-dibromo-cholestane m. p. °C	$[\alpha]_D$	Δ_2-cholestene m. p. °C	$[\alpha]_D$
FÜRST and PLATTNER [1]	125	+76,5°	75	+67,4°
FIESER and DOMINGUEZ [8]	125	+75,9°	73	+67°
SOBEL and ROSEN [11]	124	+75,9°	72,5	+67,1°
SOBEL and ROSEN (modified)	124	+75,8°	73	+67°
SCHOPPEE [15]	125	+75,0°	74	+67,4°
NACE [17] (from α-tosylate)	123	+74°	72	+65°
NACE [17] (from β-tosylate)	124	+74°	71-72	+65,4°

Pyrolysis of cholestanol with potassium hydrosulphate. Cholestanol (1,94 g) was rubbed in a porcelain mortar with 2 g of potassium hydrosulphate, then heated in a sealed tube for 4 hours at 190—195° C. A brownish oily substance separated and, on cooling, water condensed on the walls of the tube. The oily mass was separated from inorganic substance, by 50 ml of chloroform clarified by carbon, filtered and the solvent removed *in vacuo*. The solution of the residue in petroleum ether was poured onto a column of neutral alumina (activity II) eluted with pentane and recrystallised from acetone. Yield: 0,75 g (40,5 %) of Δ_2-cholestene, m. p. 73,5—77,0° C. $[\alpha]_D^{20} = +67 \pm 1°$ ($c = 2,77$; $CHCl_3$). Calcd. C 87,49; H 12,51%. Found C 87,52; H 12,47 %.

Thermolysis of potassium cholesteryl sulphate. Thermolysis by the SOBEL and ROSEN method [11] at 185° C in capryl alcohol with sodium caproxide afforded $\Delta_{3,5}$-cholestadiene in 80 % yield, m. p. 79,5—80,0° C. $[\alpha]_D = -120,3°$ ($CHCl_3$) against m. p. 79,5—80,0° C and $[\alpha]_D = -123,2°$ ($CHCl_3$) in literature [11].

Pyrolysis of cholesterol with potassium hydrosulphate. On heating 2 g of cholesterol with 2 g of potassium hydrosulphate for 4 hours at 230—240° C in a sealed tube, 1,34 g (64 %) of product was obtained, m. p. 78—79° C. $[\alpha]_D = -83,6°$ ($c = 1,97$; $CHCl_3$). By heating the product with hydrochloric

acid, the original substance was recovered. On treating the solution of the product in amyl alcohol, no uptake of hydrogen was observed [33]. No depression of m. p. was observed when mixed with "authentic" $\Delta_{3,5}$-cholestadiene.

Cyclohexene (II) *from cyclohexanol.* On heating 10 g of cyclohexanol with 10 g of potassium hydrosulphate in a distilling apparatus in an oil bath of 130—150° C, cyclohexene and some water distilled and the reaction was terminated in 40—50 minutes. The aqueous cyclohexene was dried over sodium sulphate and rectified in a column filled up with Raschig rings. Yield: 8 g (approximately 80 %), b. p. 82,5° C. Consumption of Br: 99,2 %.

Δ_2-cholestene (IV) *from 3α-chloro-cholestane.* The mixture of 2 g portions of 3α-chloro-cholestane with 3 g portions of a) trisodium phosphate, b) potassium oxalate and c) potassium tartrate was rubbed as described previously and subsequently heated in a sealed tube for 2 hours at 120° C, then for further 4 hours at 200° C. The product was processed as follows. The sticky mass was dissolved in 20 ml of chloroform, clarified with carbon, filtered, the solvent removed, the residual brownish oil dissolved in a 4:1 mixture of ethanol: acetone, clarified with carbon, filtered, the filtrate concentrated and allowed to crystallize in an ice box. Yields of Δ_2-cholestene were a) 0,78 g (42 %), m. p. 65—68° C, b) 0,22 g (12 %), m. p. 64—68° C, c) 0,28 g (15 %), m. p. 64—67° C. A similar treatment of 3β-chloro-cholestane did not give Δ_2-cholestene and on raising the temperature to 300—350° C, and heating the sealed tube for 8 hours, a sticky mass formed which we were unable to identify. As by the method previously used, cholestene could not be isolated from this mass, its further examination was not attempted.

$\Delta_{3,5}$-cholestadiene (VII) *from 3-chloro-cholesterol.* A similar pyrolysis of 2 g portions of 3-chloro-cholesterol with 3 g portions of a) trisodium phosphate, b) potassium oxalate and c) potassium tartrate afforded a) 0,191 g (10,5 %) of $\Delta_{3,5}$-cholestadiene, m. p. 75—78° C, b) an amorphous brown dust the processing of which seemed to be unpromising, and c) 0,12 g (6—7 %) of $\Delta_{3,5}$-cholestadiene, m. p. 75—79° C.

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Table I.

M. p. °C	$[\alpha]_D$	Method	M. p. °C of dibromide	$[\alpha]_D$ of dibromide	Literature
66—68	+58,5	Reductive desulphuration of Δ_1-cholesten-3-one ethylenthioketal .	—	—	[12]
67—68	+60,3	Heating epicholestanyl tosylate in piperidine	—	—	[13]
67—68	+62	Pyrolysis of cholestanyl benzoate at 400° C	—	—	[6]
68—69	+64	CHUGAEV decomposition of β-cholestanyl-S-methyl xanthates	—	+42	[14]
68—69	+ 64,4	Thermolysis of potassium cholestanyl sulphate in capryl alcohol containing caproxide	—	—	[11]
69	+64	Methanolysis of epicholestanyl tosylate	—	—	[10]
75	+67,4	3-Bromo-cholestane + quinolene . .	—	—	[1]
75	+67,4	3-Chloro-cholestane + quinolene . . .	125	+75,27	[2]
69	+64,07	3-Chloro-cholestane + quinolene . .	—	—	[3], [4]
69—70	+63	2-Bromo-cholestane-3-ol + zinc dust, glacial acetic acid	125	+75	[8]
69—70	+64	3α-chloro-cholestane acetolyzed . . .	—	—	[15]
		3β-chloro-cholestane acetolyzed . . .	—	—	[15]
70,5—72	+64	3β-cholestanyl tosylate, subjected for 3 days to methanolysis	—	+46	[17]
—	+59	3β-cholestanyl tosylate, subjected for 6 hours to methanolysis	—	+45	[17]
73—74	+67	Reduction of Δ_2-cholestene—6-ene .	—	—	[16]
74,5—75	+69	Pyrolysis of cholestanyl benzoate at 400° C	124 · 124,5	+76	[7]
75	+63,9	Cholestane-3-ol, boiled with acid clay	122	+81,1	[5]
74,5—75	+69	3α-cholestanyl from dimethylamine by HOFFMANN degradation	—	—	[9]
64—68	+64	Pyrolysis of cholestanol by sodium orthoborate			[18]

Table II

No.	Method	M. p. °C	$[\alpha]_D$	Literature
1.	Cholesterol + copper sulphate	80	−104	[19] [20]
2.	Cholesterol + zinc dust (distilled)	68,75	+1,45 - −53	[21]
3.	Cholesterol + kieselguhr	79	−47	[22]
4.	Cholesteryl chloride + sodium ethylate	79—80	−65,9	[19]
5.	Cholesteryl chloride + calcium oxide	79	−61,55	[23]
6.	Cholesteryl chloride + quinolene	77	−86,09	[24]
7.	Cholesteryl chloride + zinc oxide	79—80	−116,2	[24]
8.	Cholesteryl chloride + potassium cholesterolate	79—80	—	[24]
9.	Cholesteryl bromide + NaI in acetone	77—78	−65,4	[25]
10.	Cholesteryl bromide + NaI + piperidine acetate, in acetone	78—79	−103	[25]
11.	Cholesteryl phenyl urethane (distd.)	75	—	[32]
12.	Methyl cholesteryl xanthate (distd.)	79—80	—	[26] [28]
13.	Cholesterol + phosphoric acid	79—80,5	—	[19]
14.	Monocholesteryl phosphate (heated)	76	−68,99	[29]
15.	Dicholesteryl phosphate (heated)	78,2	−77,53	[29]
16.	Allo- or epiallocholesterol + HCl	80	−112	[30]
17.	Epicholesterol + HCl	76—77	−78,3	[31]
18.	Reduction of 7-ketocholesterylene semicarbazone	78—79	−63,75	[32]
19.	K-cholesteryl sulphate treated for 1 hour with caproxide-sodium in caprylalcohol at 177° C	80	−123,2	[11]
20.	HOFMANN degradation of cholest - 5-ene—3β-trimethylammonium iodide	77—78	—	[9]
21.	Pyrolysis of cholesteryl—S-methyl xanthate at 20 mm and 220° C for 3 hours	80	−122	[35]
22.	4,5-Dibromo-cholestane	75,9—80	−103,24	[37]
23.	Cholesteryl chloride + quinolene	79,5—80	−100,33	[38]
24.	Pyrolysis of benzyl cholesteryl carbamate at 150° C for 2 hours	78,5—80	−112	[39]
25.	Reduction of 6-chloro−3-benzyl oxy-Δ_4-cholestane with aluminium amalgam	80—81	−129,6	[40]
26.	Cholesteryl—p-toluene sulphonate + KCN	76—77	−96,5	[41]
27.	Thermic decomposition of alkyl and aryl cholesteryl xanthates	78—80	−90 - −110	[36]
28.	Pyrolysis of cholesteryl—2-naphtyl carbonate	78—79	−120,7	[42]
29.	Treatment of 3α.5-dioxy-cholestane carbonate with concentrated HCl	79—80	−111	[43]
30.	3β-Cl-cholest-5-ene + triethanolamine	77—78	−116	[44]
31.	Δ_4-cholestene-3-one-3 benzyl thioenolether + Raney nickel	78—79	−101	[45]
32.	Epi-cholesteryl tosylate in waterfree methanol + potassium acetate	79—80	−115,5	[46]
33.	3β-Dimethylamino-cholest-5-ene, HOFMANN degradation	82,5 - 83	−130, ±3	[47]
34.	Pyrolysis of methylcholestanyl sulphate	70—74	−81	[34]

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