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REACTION OF IODOBENZENE DICHLORIDE WITH C_5–C_6 UNSATURATED STEROIDS

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Abstract—Light and heat induced reactions of iodobenzene dichloride with 3β-substituted cholest-5-enes has been studied. The ratio of the isomeric 5,6-dichlorides formed was found to be nearly independent of the 3β-substituent. Radical mechanisms are proposed for these reactions. Chlorination of 3-iodocholest-5-enes may be complicated by side reactions in which iodine is liberated.

Halogenation of the ethylenic C_5–C_6 bond in the steroidal skeleton under ionic conditions with molecular chlorine or bromine leads to the formation of 5α,6β-*trans*-diaxial dihalides in agreement with the generally accepted mechanism.[1] The course of chlorination with iodobenzene dichloride (IBD) is more complex. This reaction, first observed by Berg and Wallis[2] until recently was investigated only in the case of cholesteryl benzoate. Its mechanism and the quantitative composition of products have not been elucidated.

Barton and Miller[3] reported that on refluxing a chloroform solution of cholesteryl benzoate **4** and IBD significant amounts of *cis*-5α,6α-dichloride **4b** are formed in addition to *trans*-5α,6β-dichloride **4a**. These authors suggested that *cis*-dichloride **4b** is formed by simultaneous addition of two Cl atoms involving a cyclic intermediate. However, the X-ray determination[4] of bond length and angles in IBD showed clearly that such a mechanism is incorrect. Jacquesy and Levisalles[5] confirmed the structure of the "abnormal" *cis*-dichloride.

In order to elucidate the stereochemical and mechanistic aspects of this reaction we carried out chlorination of several 5-cholestene derivatives with IBD under various conditions. Steroidal olefines substituted at the C_3 carbon atom with groups having different inductive effects (5-cholestene **1**, cholesterol **2**, 3β-methoxy-5-cholestene **3**, cholesteryl benzoate **4**, 3β-chloro-5-cholestene **5** and 3β-iodo-5-cholestene **6**) were chosen for this investigation.

In the first series of our experiments (Procedure A) a carbon tetrachloride solution of steroidal olefine and IBD was irradiated by means of a 200 W incandescent lamp at 0°C in argon atmosphere. Within 10–20 min the substrates disappeared and the formation of two products was observed by TLC. The products were separated by preparative TLC; the yields and ratios of *trans* to *cis* dichlorides are presented in Table 1. The same solution remained unchanged after standing in the dark or in diffuse day light for several hours. The rate of photoinducted reaction could be reduced drastically by passing O_2 through the solution; after 48 hr of irradiation in a stream of O_2, the major part of the starting olefine was unchanged.

In the second series of experiments (Procedure B) a chloroform solution of unsaturated steroid and IBD was refluxed for 30–60 min. Also in this case two products were obtained; the results are summarised in Table 1. Under these conditions 3β-iodo-5-cholestene **6** behaved differently from other substrates. In this case the addition to double bond was accompanied by replacement of iodine with chlorine (see below). However in boiling carbon tetrachloride the normal addition of chlorine to double bond took place.

We have also found that when pyridine is added to the reaction mixture it catalyses the addition of chlorine at room temperature and in this case the products are exclusively the *trans* diaxial dichlorides.[6] In the presence of IBD and pyridine cholesterol gave a complex mixture of chlorinated and oxidized products. Oxidation of alcohols by IBD and pyridine and by chlorine and pyridine has been reported.[6,7]

The known dichlorides were identified by comparison of their physical constants with those described in the literature; the structures of new compounds (**1b**, **3a**, **3b**, **5b**, **6a** and **6b**) were elucidated on the basis of analytical and spectral data and especially their PMR spectra (Tables 2 and 3 and Experimental).

The substrates were obtained by known methods; unexpectedly[8] cholesteryl tosylate and sodium iodide in boiling acetone yielded both epimeric 3-iodides **6** and **7** (in the ratio of 1:1), which were separated by high performance liquid chromatography.

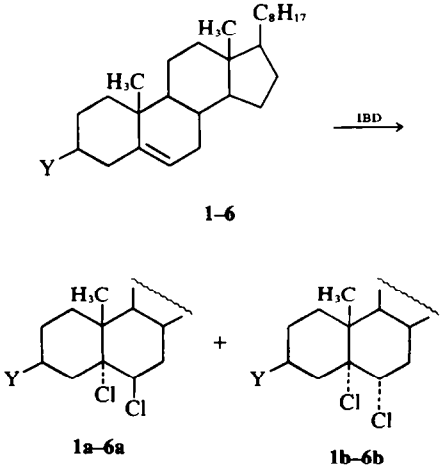


Fig. 1. The meaning of Y and the numbers of compounds are given in Table 1.

Table 1. Yields of products obtained by the two chlorination procedures

Starting compound No.	Y	Procedure A Yield (%) of a	b	Ratio a:b	Procedure B Yield (%) of a	b	Ratio a:b
1	H	50	43	1·16	41	45	0·91
2	OH	45	52	0·87	38	31	1·22
3	OCH_3	35	39	0·90	38	38	1·00
4	OBz	49	50	0·98	53	36	1·47
5	Cl	46	55	0·84	52	39	1·33
6	I	60	35	1·71	61[a]	26[a]	2·33[a]

[a]Reaction was carried out in carbon tetrachloride (Procedure B').

DISCUSSION

Reaction of IBD with steroidal 5-enes at room temperature is initiated by light and is quenched by oxygen, hence it is a typical free radical process. Since the ratio of *trans* to *cis* products for different substrates is approximately the same it is independent of the inductive effect of substituents in position 3.

When the substrates were treated with IBD at reflux temperature in chloroform a similar composition of products was observed, although the reaction was less clean (the solution became yellow). Our results suggested that also under these conditions the free radical mechanism is involved. This conclusion was drawn from the fact that the ratio of isomers for all compounds investigated was practically the same as that observed in the case of the light induced reaction and was essentially independent of the character of substituent at C_3. If the reaction in boiling chloroform had the ionic character or if the ionic reaction was simultaneously taking place one could expect a different ratio of *trans* to *cis* isomers for differently substituted at C_3 substrates since, under these conditions the intermediate chloronium ions would have different stabilities. The effect of an electron donating tendency of substituents at C_3 on ionic reactions of olefinic C_5–C_6 bond has been described.[9,10]

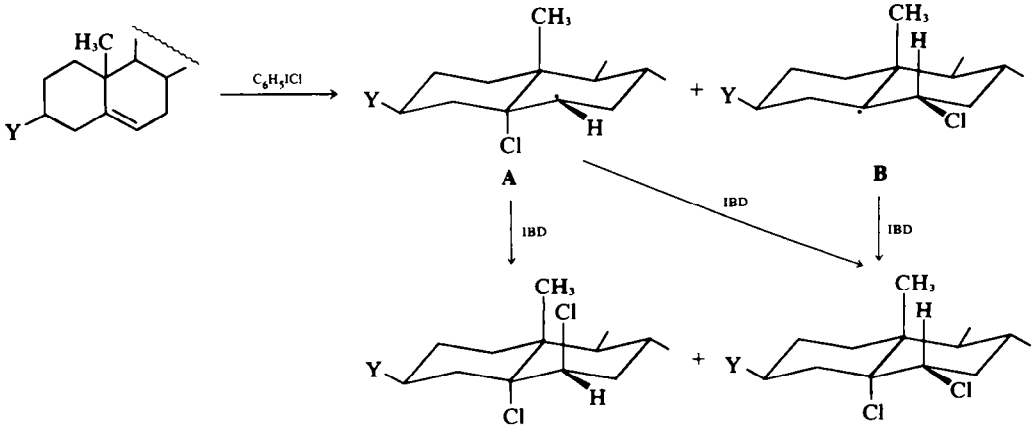
Tanner and Gidley[11] and Masson and Thuillier[12] recently obtained similar results in the case of IBD chlorination of irradiated acyclic and cyclic olefines. They also found that the chain reaction is not promoted by chlorine radicals and suggested that the $C_6H_5ICl^{\cdot}$ radical is responsible for the chain transfer reaction. Radical chlorination of sterically unhindered cycloalkenes with IBD also gives *trans* diaxial dichlorides. The steric course of the reaction can be explained assuming that the bulky $C_6H_5ICl^{\cdot}$ is a chain transfer agent in the chlorination of the isolated C_5–C_6 double bond in steroids. The first stage of this reaction (Scheme 1) consists of the attack of this radical on the less hindered α-side of the molecule resulting in the addition of chlorine to C_5 or C_6 carbon atom and the formation of intermediate radicals A or B respectively.

The intermediate radical A containing the 5α-chloro substituent can add the next Cl atom from IBD either on the α or on the β side since the steric hinderance above and below the plane of ring B in the C_6 region is approximately the same; the formation of the *trans* product (5α,6β) seems to be preferred. The situation is different in the case of the intermediate B having the radical centre at C_5. If the geometry of the radical centre[13] is planar similar to that of olefines and the conformation of ring B is chair-like the steric hinderance on the two sides of the molecule is different since the angular Me group C_{19} shields the β side. Consequently the next attack of IBD takes place on the less hindered α-side and leads to the formation of the 5α,6α-dichloride.

As mentioned, the reaction of 3β-iodo-5-cholestene **6** with IBD, unlike the reactions of other substrates, was accompanied by a rapid evolution of iodine. The steroidal product (obtained after the removal of iodine by means of thiosulfate solution) decomposed during chromatography on silica gel and on standing in the form of an oil or in the form of solutions in chloroform or in ether.† The only compound isolated in the pure form was cholesteryl chloride **5**.

Since IBD was used in excess, chloroolefine **5** must have been formed from the primary product during the isolation procedure. It is probable that unstable components of the reaction mixture are iodo derivatives of type **8** which are formed as a result of addition of iodine chloride[14] (ICl) to the double bond of cholesteryl chloride or iodide. Iodine chloride is probably formed during the exchange of an I atom at C_3 for a Cl atom. In order to check this hypothesis we prepared 3β,5-dichloro-6β-iodo-5α-cholestane **8** by treating cholesteryl chloride **5** with iodine chloride. Compound **8** (m.p. 123–125°) was found to be relatively stable in the crystalline form and also in solutions in carbon tetrachloride and in hexane but on

†The mixture was relatively stable in carbon tetrachloride solution.



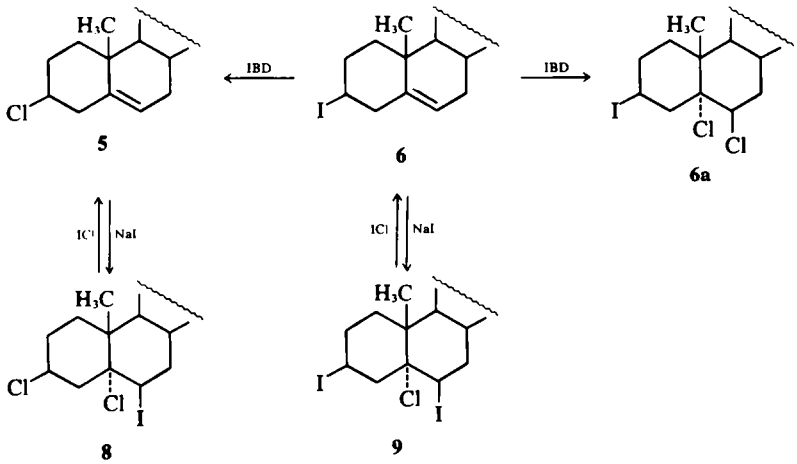
Scheme 1.

dissolving in chloroform or ether it decomposed with liberation of iodine. It similarly decomposed after adsorption on silica gel. The treatment of **8** with sodium iodide in acetone led to the regeneration of cholesteryl chloride. These properties of iodochloride **8** indicate that it was present in the reaction mixture resulting from the treatment of cholesteryl iodide with IBD in boiling chloroform. It is of interest that 3β-iodo-5,6β-dichloro-5α-cholestane **6a** treated with IBD in boiling chloroform practically remains unchanged, since it shows that the C_5–C_6 double bond considerably increases the rate of exchange of I for Cl at the C_3 carbon atom. However, when the reaction of cholesteryl iodide with IBD in chloroform was carried out in the NMR cell so that the NMR spectrum of the mixture could be observed the signals corresponding to cyclopropane protons were absent.

Table 2. PMR characteristics of 5,6β - dichloro - 5α - cholestanes

Compound	Y	Solvent	H_{18}	H_{19}	$H_4{}^{ad}$	$H_{6\alpha}{}^{bd}$	$H_{3\alpha}{}^{cd}$
1a	H	$CDCl_3$	0·74	1·38		4·41	
3a	OCH_3	$CDCl_3$	0·66	1·35		4·30	3·76
4a	OBz	$CDCl_3$	0·74	1·48	2·78	4·45	5·7
5a	Cl	CCl_4	0·73	1·39	2·24	4·26	4·3
6a	I	CCl_4	0·72	1·41	3·07	4·20	4·6

[a] A pair of doublets (part A of ABX system: J_1 about 7·5 Hz, J_2 about 11 Hz).
[b] Narrow multiplet ($W_{1/2}$ about 7 Hz).
[c] Broad multiplet.
[d] The values correspond to the middle points of the systems.



Scheme 2.

The mixture resulting from the treatment of cholesteryl iodide **6** with IBD in boiling chloroform was treated with a solution of sodium iodide in acetone and was chromatographed on silica gel. The fastest fraction was cholesteryl iodide **6**. It was followed by the main fraction consisting of two inseparable compounds which were identified on the basis of NMR spectra as cholesteryl chloride **5** and 3β-iodo-5,6β-dichloro-5α-cholestane **6a**. This confirms the conclusion that iodides **8** and **9** are formed during the reaction of cholesteryl iodide with IBD according to Scheme 2.

When the axial iodide **7** was treated with IBD the liberation of iodine took place at 0° even when carbon tetrachloride was used as solvent. The product of this reaction was an unstable mixture from which we could not isolate any compounds.

Table 3. PMR characteristics of 5,6α - dichloro - 5α - cholestanes

Compound	Y	Solvent	H_{18}	H_{19}	$H_4{}^{ad}$	$H_{6\beta}{}^{bd}$	$H_{3\alpha}{}^{cd}$
1b	H	$CDCl_3$	0·73	1·15		4·27	
2b[e]	OH	$CDCl_3$			2·55	4·21	4·21
3b	OCH_3	CCl_4	0·65	1·11	2·68	4·09	3·6
4b	OBz	$CDCl_3$	0·70	1·25	2·88	4·31	5·7
5b	Cl	$CDCl_3$	0·65	1·16	2·83	4·18	4·4
6b	I	CCl_4	0·65	1·18	2·89	4·08	5·3

[a] A pair of doublets (part A of ABX system: J_1 about 13 Hz, J_2 about 5 Hz).
[b] 1:2:1 triplet (part X of ABX system: $J_1 + J_2$ about 15 Hz).
[c] Broad multiplet.
[d] The values correspond to the middle points of the systems.
[e] Taken from Ref. 5.

EXPERIMENTAL

All the m.ps were determined by means of Kofler hot stage microscope and are uncorrected. All the optical rotations were measured in a Perkin-Elmer 141 polarimeter in chloroform soln in a 1-dm tube at concentrations about 1% at room temp (17–22°). PMR spectra were recorded in a Jeol 100 MHz instrument in the solvents stated containing TMS as internal reference; chemical shifts are expressed in δ-values (ppm). All the spectral and analytical measurements were carried out in the Physicochemical Department of this Institute. Mixtures were separated by silica gel preparative TLC unless otherwise stated. Organic extracts were dried with Na_2SO_4 and solvents were evaporated *in vacuo*. Alcohol-free chloroform was prepared by shaking the commercial product several times with conc. H_2SO_4, neutralisation with K_2CO_3 and distillation over P_2O_5. Argon was passed through BMD catalyst and then through KOH pellets. IBD was recrystallized from chloroform before use.

Procedure A. Crystalline IBD was added to an argon-purged soln of unsaturated steroid in CCl_4. The mixture was immersed in ice-water and was irradiated by means of a 200 W incandescent lamp from a short distance. During the irradiation the mixture was stirred by means of a magnetic stirrer. When IBD crystals disappeared (10–20 min) and the TLC test showed that all the starting material was consumed the clear and colorless mixture was shaken with an $Na_2S_2O_3$ aq and after drying with Na_2SO_4 it was evaporated *in vacuo*. Chromatographic separation of the

residue afforded pure isomers. Removal of iodobenzene prior to chromatography by repeated evaporation with water was in most cases unnecessary.

Procedure B. Crystalline IBD was added to a refluxing soln of unsaturated steroid in alcohol-free chloroform. The mixture was refluxed until the time when TLC showed the absence of the starting material (30–60 min). Then the clear yellow soln was treated as in Procedure A.

Chlorination of cholest-5-ene (**1**, Y = H)

Procedure	Substrate mg (mmole)	Solvent (ml)	IBD mg (mmole)	Yield of 1a mg	Yield of 1b mg
A	100 (0·27)	CCl_4 (5)	88 (0·32)	59·1	51·4
B	100 (0·27)	$CHCl_3$ (5)	83 (0·30)	49·0	54·0

1a, m.p. 121–123° (Me_2CO) (lit.,[3] m.p. 121–122°).

1b, m.p. 113–114° (Me_2CO), $[\alpha]_D$ −14·4° (lit.[6]). Found: C, 73·31; H, 10·86; Cl, 15·33. $C_{27}H_{46}Cl_2$ requires: C, 73·44; H, 10·50; Cl, 16·06.

Chlorination of cholesterol (**2**, Y = OH)

Procedure	Substrate mg (mmole)	Solvent (ml)	IBD mg (mmole)	Yield of 2a mg	Yield of 2b mg
A	100 (0·26)	CCl_4 (5)	79 (0·29)	53	62
B	104 (0·27)	$CHCl_3$ (5)	88 (0·32)	48	39

2a, m.p. 140–142° (EtOH) (lit.,[3] m.p. 143–144°).

2b, m.p. 174–176° (Et_2O-hexane) (lit.,[5] m.p. 174–175°).

Chlorination of 3β-methoxycholest-5-ene (**3**, Y = OCH_3)

Procedure	Substrate mg (mmole)	Solvent (ml)	IBD mg (mmole)	Yield of 3a mg	Yield of 3b mg
A	100 (0·25)	CCl_4 (5)	71 (0·26)	41	46
B	102 (0·25)	$CHCl_3$ (5)	75 (0·27)	46	46

3a, m.p. 82–84° (Me_2CO), $[\alpha]_D$ −41·8°. Found: C, 72·19; H, 10·68; Cl, 14·76. $C_{28}H_{48}Cl_2O$ requires: C, 71·31; H, 10·26; Cl, 15·04.

3b, m.p. 125–126° (Me_2CO), $[\alpha]_D$ −17·4°. Found: C, 71·54; H, 10·12; Cl, 15·08.

Chlorination of cholesteryl benzoate (**4**, Y = OBz)

Procedure	Substrate mg (mmole)	Solvent (ml)	IBD mg (mmole)	Yield[a] of 4a mg	Yield[a] of 4b mg
A	111 (0·23)	CCl_4 (5)	92 (0·33)	62	64
B	112 (0·23)	$CHCl_3$ (5)	96 (0·35)	68	46

[a]These mixtures were separated by silica gel column chromatography using CCl_4 as eluent.

4a, plates, m.p. 117–120° (Me_2CO) (lit.,[2] m.p. 117–120°); needles, m.p. 131–134° (Et_2O–EtOH) (lit.,[3] m.p. 130–131°).

4b, m.p. 250–251° (EtOAc) (lit.,[3] m.p. 248–249°).

Chlorination of cholesteryl chloride (**5**, Y = Cl)

Procedure	Substrate mg (mmole)	Solvent (ml)	IBD mg (mmole)	Yield of 5a mg	Yield of 5b mg
A	100 (0·25)	CCl_4 (5)	77 (0·28)	49	55
B	102 (0·25)	$CHCl_3$ (5)	84 (0·31)	61	46

5a, rectangular plates, m.p. 108–109° (Me_2CO) (lit.,[15] m.p. 106°); needles, m.p. 113–114·5° (Me_2CO).

5b, m.p. 82–89 (Et_2O–EtOH), $[\alpha]_D$ +4°. Found: C, 68·37; H, 9·51; Cl, 22·56. $C_{27}H_{45}Cl_3$ requires: C, 68·13; H, 9·53; Cl, 22·34.

Chlorination of cholesteryl iodide (**6**, Y = I)

Procedure	Substrate mg (mmole)	Solvent (ml)	IBD mg (mmole)	Yield of 6a mg	Yield of 6b mg
A	126 (0·25)	CCl_4 (5)	91 (0·33)	87	50
B′	100 (0·17)	CCl_4 (5)	57 (0·21)	69	30

6a, m.p. 110–112° (Me_2CO), $[\alpha]_D$ −32·5°. Found: C, 57·18; H, 7·99; I, 22·26. $C_{27}H_{45}Cl_2I$ requires: C, 57·14; H, 8·00; I, 22·36.

6b, m.p. 118–120° (Me_2CO), $[\alpha]_D$ +23·2°. Found: C, 57·46; H, 8·15; I, 22·44.

Chlorination of cholesteryl iodide (**6**) *in boiling chloroform*

Crystalline IBD (102 mg; 0·37 mmole) was added to a soln of cholesteryl iodide (176 mg; 0·35 mmole) in $CHCl_3$ (5 ml) and the mixture was heated in an oil bath. Iodine was liberated long before the b.p. was reached. The dark violet soln was refluxed for 15 min, then it was decolorized with $Na_2S_2O_3$ aq and was evaporated *in vacuo*. The oily residue was dissolved in acetone and was mixed with a soln of NaI in acetone. A brown coloration appeared immediately. The mixture was stirred for several min, then it was partly evaporated and after diluting with water it was extracted with ether. The brown ether extract was decolorized with $Na_2S_2O_3$ aq and after washing with water it was evaporated. The product was chromatographed on a silica gel using hexane as the developing solvent. The first fraction (15 mg) was **6**, m.p. 104–6°. The second fraction (103 mg) was an inseparable mixture of two components. PMR spectrum of this mixture was identical with superposed spectra of **5** and **6a**. The further fractions consisted of at least six compounds (total weight 17 mg), and a colored very polar material (14 mg).

Preparation of cholesteryl iodide (**6**)

This material was prepared by refluxing cholesteryl *p*-toluenesulfonate with NaI in acetone soln. The resulting mixture of three products contained a large amount of the starting material. It was dissolved in hexane and was passed through silica to remove cholesteryl tosylate. Then it was separated on a column packed with Kieselgel 60 (Merck) using hexane as the eluent. The first small fraction was not analyzed. The second fraction (1·41 g) was the required **6**,[16] m.p. 107–8·5° (Et_2O–EtOH) and the third fraction (1·58 g) was **7**, needles from Et_2O–EtOH, m.p. 132–133°, $[\alpha]_D$ −19·5° (lit.,[17] m.p. 130–130·5°).

Preparation of 3β,5-dichloro-6β-iodo-5α-cholestane (**8**)

Iodine (270 mg, 1·06 mmole) was dissolved in CCl_4 (10 ml) containing 1 mmole of Cl. The resulting dark soln was added gradually to a soln of cholesteryl chloride (850 mg, 2·1 mmole) in CCl_4 (5 ml). After standing for 15 min at room temp. the violet mixture was decolorized with Na_2SO_3 aq and after drying with Na_2SO_4 it was evaporated *in vacuo* at room temp. The oily product was diluted with warm hexane (iodine colour appeared). This soln gave on cooling 546 mg of the crude product which after several crystallisations from hexane gave gray-white crystals, m.p. 123–125° (dec), $[\alpha]_D$ −71·5°, PMR (CCl_4) δ 0·73 (18-CH_3),

1·42 (19-CH_3), 2·40, 2·48 (1H each, d, J = 8 Hz, 4-CH_2), 2·75 (1H, m, b, C-7), 4·6 (1H, m, b, C-3), 4·86 (1H, m, C-6). The assignment of the δ 2·75 signal was verified by double resonance experiment: irradiation at δ 4·86 caused simplification of the multiplet at δ 2·75. (Found: C, 57·44; H, 8·09; I, 22·35. $C_{27}H_{45}Cl_2I$ requires: C, 57·14; H, 8·00; I, 22·36%). This product was stored in a refrigerator for several days without discernible decomposition, but its solns in ether or chloroform decomposed with liberation of iodine in a few minutes at room temp. Solns in CCl_4 or in hexane were more stable.

Reaction of 3β - 5 - *dichloro* - 6β - *iodo* - 5α - *cholestane* (**8**) *with sodium iodide in acetone*

Compound **8** (100 mg) suspended in 3 ml acetone was treated with an excess of NaI in acetone. A brown colour appeared immediately. The mixture was stirred for about 15 min, then the major part of acetone was evaporated *in vacuo*, the residue was diluted with water and was extracted with ether. The brown extract was decolorized with $Na_2S_2O_3$ and after drying with Na_2SO_4 it was evaporated. The product was crystallized three times from acetone. The resulting crystals (43 mg, m.p. 96–7°) were identical with an authentic sample of cholesteryl chloride.

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