(b.p. 30–60°) produced thick, colorless needles melting at 71.0–71.5°, alone or when mixed with this pyrone obtained from the cyclopropane II.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.19. Found: C, 64.6; H, 7.51.

The ester was subjected to hydrolysis according to the procedure of Bickel[9] but the pyrone acid (V, R′ = H) could not be obtained as a solid.

3-Carbomethoxy-4-isopropyl-6-methyl-α-pyrone (V, R′ = CH_3).—Substitution of methyl malonate for ethyl malonate in the above preparation led to the methyl ester V, R = CH_3 (34%), but this could not be obtained as a solid. It boiled at 140–146° (0.5 mm.); the analytical sample, still not pure, boiled at 127° (0.07 mm.).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.71. Found: C, 63.8; H, 7.39.

4-Isopropyl-6-methyl-2-pyridone (VIII, R′ = H).—The methyl ester of the α-pyrone acid (1.4 g.) was added to a saturated solution of ammonia gas in dry methanol (25 cc.) at 0°. The flask was stoppered and set aside for 18 hours. The solvent and ammonia were removed in a current of air and the residual oil was extracted with petroleum ether (75 cc., b.p. 68–70°) and the extract, when cooled, deposited an oil. The solution was decanted from the oil and concentrated in a current of dry air. The solid (m.p. 106–109°) was removed and sublimed at 90° (0.3 mm.), when it melted at 112.5–113.5°.

Anal. Calcd. for $C_9H_{13}ON$: C, 71.5; H, 8.66; N, 9.27. Found: C, 72.0; H, 8.81; N, 9.40.

Hydrolysis and decarboxylation thus occurred when methanolic ammonia reacted with the methyl ester. This also occurred when the ethyl ester (1 g.) was subjected to the same reaction; the product (0.31 g., 45%), after crystallization from petroleum ether (b.p. 30–60°), melted at 108–110° alone or when mixed with that obtained from the methyl ester of the pyrone acid.

The ultraviolet absorption spectrum of VIII (R′ = H) (c 9.9 × 10^{-5} mole/l.) in ethanol was determined.[14]

(14) The complete curve may be found in the Ph.D. thesis of Ralph E. Kelly, ref. 2.

MINNEAPOLIS 14, MINNESOTA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Cathylation (Carbethoxylation) of Steroid Alcohols

BY LOUIS F. FIESER, JOSEF E. HERZ, MURLE W. KLOHS, MIGUEL A. ROMERO AND TORLIEF UTNE[1]

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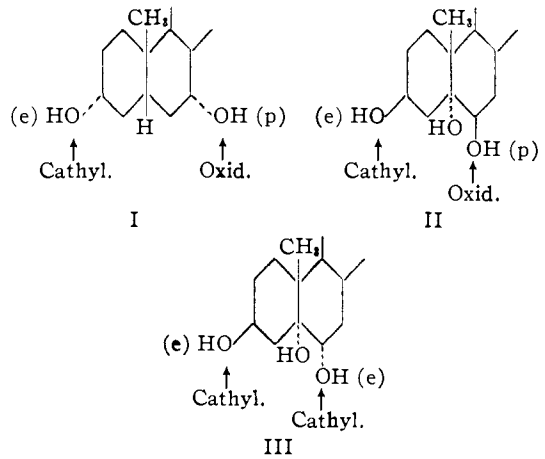
The high degree of selectivity previously observed in the reaction of methyl cholate with a large excess of ethyl chlorocarbonate to give the 3-cathyl (carbethoxyl) derivative in high yield has been interpreted by Barton in terms of the concept of polar and equatorial bonds. Study of cholestane-3β,5α,6β-triol, cholestane-3β,5α,6α-triol, cholestane-3β,7α-diol, cholestane-3β,7β-diol and androstane-3β,17β-diol has now shown that equatorial hydroxyl groups at C_6, C_7, C_{12} and C_{17} are invariably cathylated while polar hydroxyl groups are not. Less selectivity was observed in oxidations with N-bromosuccinimide. That 3α- and 3β-hydroxy derivatives of both cholestane and coprostane all afforded cathylates, if in varying yield, probably means that ring A is less rigid than the rest of the molecule. Allylic alcoholic functions, whether equatorial or polar, invariably are subject to cathylation; hence activation by a double bond overcomes hindrance effects.

In 1924 Borsche[2] reported that methyl cholate reacts with ethyl chloroformate in pyridine solution to yield the 3-carbethoxyl derivative. In recent publications we have confirmed Borsche's observation,[3] shown that methyl 3-carbethoxycholate is the exclusive reaction product even when a large excess of ethyl chloroformate is employed and can be obtained in 93% yield,[4] and reported certain other observations[4,5] indicating special advantages of the process of carbethoxylation for effecting selective acylation and for producing derivatives often characterized by excellent crystallizability and stability. It is now suggested that the useful reaction be designated cathylation and that the products be described as cathyl derivatives, analogous to tosyl, mesyl and trityl derivatives.

That methyl cholate is selectively acylated at C_3 but is oxidized with almost comparable selectivity at C_7[3] presented a perplexing problem until Barton[6] advanced a plausible interpretation based upon the general theory[7] of polar (p) and equatorial (e) bonds. In a steroid of the coprostane series, such as methyl cholate(I, assuming the chair-chair-chair conformation[6]) the 3α-hydroxyl group is equatorial and hence more vulnerable than the polar oriented



7α- and 12α-hydroxyl groups. Since in an oxidation the rate-determining step is attack of the carbon–hydrogen bond,[8] the equatorial hydrogen atom at C_7 is more vulnerable to attack than the polar hydrogen atom at C_3; that C_{12} is less vulnerable than C_7 is probably attributable to the shielding effect of the two angular methyl groups.

In the case of cholestane-3β,5α,6β-triol (II) the theory predicts selective oxidation at C_6 and selec-

(1) We gratefully acknowledge fellowship support from the Abbott Laboratories (J. E. H.), Riker Laboratories, Inc. (M. W. K.), and the Dreyfus Foundation (M. A. R.).

(2) W. Borsche, *Ber.*, **57**, 1620 (1924).

(3) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3935 (1949).

(4) L. F. Fieser and S. Rajagopalan, *ibid.*, **72**, 5530 (1950).

(5) L. F. Fieser and S. Rajagopalan, *ibid.*, **73**, 118 (1951).

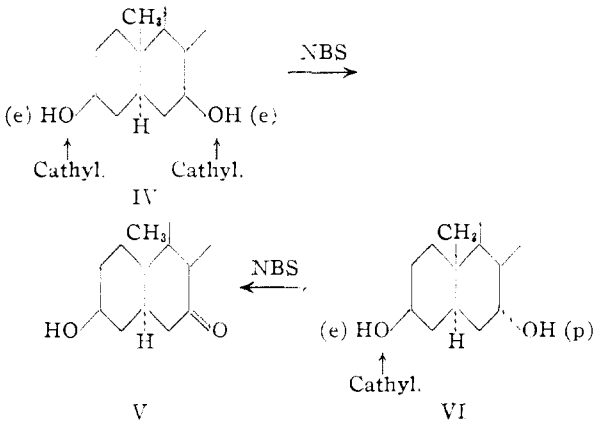
(6) D. H. R. Barton, *Experientia*, **6**, 316 (1950); see also D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

(7) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 149 (1947); C. W. Beckett, K. S. Pitzer and R. Pitzer, THIS JOURNAL, **69**, 2488 (1947).

(8) F. H. Westheimer and N. Nicolaides, *ibid.*, **71**, 25 (1949).

tive acylation at C_3. Fieser and Rajagopalan[9] indeed showed that the *trans*-triol is attacked exclusively at C_6 on oxidation by N-bromosuccinimide and affords cholestane-3β,5α-diol-6-one in yields of 93–96%. We have now verified the second prediction by the observation that the 3-cathylate is the sole product of reaction of II with excess reagent at room temperature (yield 83%). The structure was established by conversion of the monocathylate by oxidation with N-bromosuccinimide and saponification to cholestane-3β,5α-diol-6-one. In line with expectations, cholestane-3β,5α,6α-triol (III), in which both secondary alcoholic functions are in the equatorial orientation, gave a dicathylate.

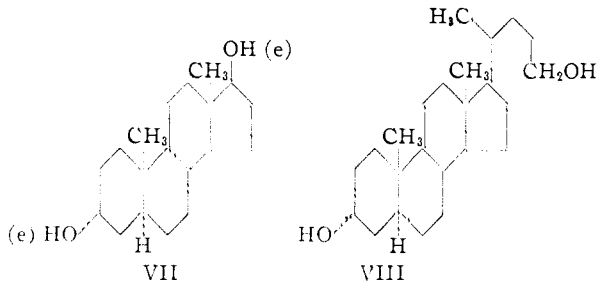
In the cholestane series a 3β-hydroxyl group is equatorial and a hydroxyl group at C_7 is equatorial in the β-orientation (IV) and polar in the α-orientation (VI). In keeping with expectations, we found



that under the same conditions cholestane-3β,7β-diol[10] (IV) yields a dicathylate whereas cholestane-3β,7α-diol[9] yields only a monocathylate. However, both 3,7-diols are oxidized by N-bromosuccinimide to 7-ketocholestanol (V), and a polarimetric study revealed no substantial difference in the reaction rates. Thus in this instance selectivity is not as pronounced in oxidation as in cathylation. The anomalous resistance of methyl $\Delta^{9(11)}$-lithocholenate to oxidation by N-bromosuccinimide in aqueous acetone or aqueous *t*-butanol has been reported.[5]

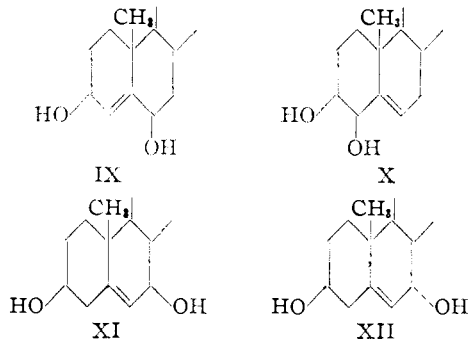
The cathylates of cholesterol,[11] dehydroepiandrosterone, cholestanol and Δ^7-cholestenol were all obtained in high yield. If Δ^5-stenols resemble cholestane derivatives in conformation,[12] these reactions all involve attack of an equatorial hydroxyl group. Epicholestanol reacted less smoothly, and a reaction product was isolated only by chromatography and in low yield. That a cathylate was produced at all is in contrast to the all-or-none reactions of the 6- and 7-hydroxy compounds discussed above and is contrary to theoretical expectations. Similarly, whereas epicoprostanol would be expected to undergo acylation more readily than coprostanol, both epimers yielded cathylates, isolated in pilot experiments by chromatography in 51 and 34% yield. The results suggest that there is little energy barrier to a reversion in ring A to a conformation other than that representing maximum stability.

In androstane-3β,17β-diol (VII) both hydroxyl groups are equatorial. Although the hydroxyl



function in ring D is subject to some hindrance, the diol was found to yield a dicathylate. Lithocholanyl alcohol (VIII), prepared by lithium aluminum hydride reduction of lithocholic acid, was studied with the idea of comparing the ease of cathylation of primary and secondary alcoholic functions. The diol formed a dicathylate readily, but attempted monocathylation was unsuccessful.

The behavior of the cholestenediols IX–XII was investigated to see if an allylic hydroxyl group



in any of the positions and orientations represented would resist cathylation, since such a result might provide evidence of the conformation of the unsaturated steroids. However, all four isomers gave dicathylates; evidently activation in the allylic systems overcomes steric hindrance effects.

Some of the experiments reported were done with the view to possible improvement in the process for the conversion of cholic acid into a cortisone intermediate *via* a methyl ester dicathylate.[13] Acetylation of methyl cholate-3-cathylate gave the 3-cathylate-7-acetate in over-all yield substantially the same as in the conversion of methyl cholate into the 3,7-diacetate.

Optical rotations of typical cathylates are summarized in Table I. In eight instances the specific rotation in dioxane is slightly more dextrorotatory than the value in chloroform and in one instance the solvent effect operates in the opposite direction: the average difference is +4.5°. In compounds of three structural or configurational types, the M_D

(9) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3938 (1949).

(10) Absolute proof of the configurations at C_7 is presented by H. Heymann and L. F. Fieser, *Helv. Chim. Acta*, **35**, 631 (1952).

(11) The preparation of cholesteryl cathylate is described by J. Robberect, *Bull. soc. chim. Belg.*, **47**, 497 (1938); see also O. Däumer, Dissertation, Halle, 1912.

(12) Evidence in support of this proposition is available from experiments on complex formation to be reported by one of us (L. F. F.).

(13) L. F. Fieser, S. Rajagopalan, E. Wilson and M. Tishler, THIS JOURNAL, **73**, 4133 (1951).

increments for cathylation are of the same sign as the increments for acetylation and the effects are of the same order of magnitude.

TABLE I

OPTICAL ROTATIONS OF 3-CATHYLATES

Parent alcohol	Cathylate M_D Chf	M_D Differences (Chf) ΔCath	ΔAc	Solvent effect α_DDi − α_DChf
Cholesterol	−165	− 14	− 35 ± 16[a]	+ 6°
7-Ketocholesterol[b]	−414	+ 2		+14.5
Dehydroepiandrosterone	0	− 3	− 20	+ 3
Cholestanol	+ 60	− 33	− 34 ± 11[a]	+ 1
Cholestane-3β,7α-diol	+ 10	− 22		
Δ⁷-Cholestenol	+ 6	− 9	− 5[c]	+ 8.6
Methyl chlolate	+198	+101	+125[d]	+ 3
Epicoprostanol	+195	+ 72		+ 6.6
Cholestane-3β,5α,-6β-triol	− 69			+ 3
Methyl 3α-hydroxy-12-ketocholanate				− 5

[a] D. H. R. Barton, *J. Chem. Soc.*, 813 (1945). [b] α_D −104° Chf; S. Bergstrom and O. Wintersteiner, *J. Biol. Chem.*, 141, 597 (1941). [c] L. F. Fieser, THIS JOURNAL, **73**, 5007 (1951). [d] Methyl cholate-3-acetate, $\alpha^{15}D$ + 48.0° Chf; Pl. A. Plattner and H. Heuser, *Helv. Chim. Acta*, **27**, 755 (1944).

The relative molecular rotations of various series of sterol esters and ethers presents an interesting problem challenging theoretical interpretation. In the series of cholesteryl esters, $C_{27}H_{45}OCOR$, values calculated from available data[14] for the increment M_D (R = alkyl) − M_D (R = H) are as follows: CH_3 = +13, CH_3CH_2 = +35, $(CH_3)_2CH$ = +43, $CH_3CH_2CH_2$ = +50, C_4H_9 to $C_{17}H_{35}$ = +56 (average for nine homologs). The order approximates the order of inductive effects inferred from the relative rates of bromination of olefins.

Experimental

Methyl Cholate-3-cathylate (L.F.F.).—Methyl cholate was prepared by warming 100.0 g. of cholic acid (m.p. 197–198°) with 300 cc. of methanol and 20 cc. of freshly distilled boron fluoride etherate on the steam-bath at the boiling point for 40 minutes (the solid dissolved in 3–5 minutes). After cooling to 27°, crystallization was initiated by either seeding or scratching and was allowed to continue at 3° overnight. The first crop of ester was dried at room temperature (102 g., sintered at 110°) and then at 80°: 95.84 g., m.p. 154.5–156°, $\alpha^{23}D$ +22.9 ± 0.5° Chf; a second crop, dried at 80°: 4.70 g., m.p. 147° (total yield, 96%). A satisfactory procedure of cathylation alternative to that described[2] is as follows. A solution of 2.0 g. of methyl cholate, m.p. 154–156°, in 10 cc. of dioxane and 1.6 cc. of pyridine was treated with 2 cc. of ethyl chlorocarbonate, added dropwise with cooling under the tap. Initially each drop precipitated an oil that subsequently dissolved, but after the half-way point the oil persisted; mild gassing occurred at the very end of the addition. After standing for ½ hour the mixture was treated with 25 cc. of water and 1 cc. of 36% hydrochloric acid, warmed for ½ hr. on the steam-bath, and cooled. The initially oily product crystallized on brief scratching and gave a white microcrystalline powder of satisfactory 3-cathylate; yield 2.28 g. (97.5%), m.p. 143°, remelting at 174–175°. The ester is so soluble in methanol that crystallization is attended with losses (recovery, in two crops, 64%, m.p. 177.5–178.5° with no previous softening). Crystallization from benzene–petroleum ether (30–60°) seemed more satisfactory and gave round tufts of needles, m.p. 177–178°, $\alpha^{22.5}D$ +40 ± 0.2° Chf, +43 ± 0.1° Di.

(14) Elsevier's "Encyclopaedia of Organic Chemistry," Vol. 14, Elsevier Publishing Co., New York-Amsterdam, 1940, pp. 51-55.

Methyl Cholate-3-cathylate-7-acetate (L.F.F.).—A solution of 1.0 g. of methyl cholate-3-cathylate in 5 cc. of dioxane, 2 cc. of pyridine, and 3 cc. of acetic anhydride was let stand at 28–30° for 40 hr. and then diluted with 6 cc. of water; the acetate separated in prisms, m.p. 160–162°, 0.51 g. Crystallization from methanol to constant m.p. gave small prisms, m.p. 165–166°.

Anal. Calcd. for $C_{30}H_{48}O_8$ (536.68): C, 67.14; H, 9.02. Found: C, 67.03; H, 9.03.

Methyl Cholate-3-cathylate-7,12-diformate (L.F.F.).—A solution of 1.0 g. of methyl cholate-3-cathylate in 5 cc. of 85% formic acid was let stand at 25° for 50 hr. and diluted with water. The precipitated material was crushed to a powder and collected: 1.13 g., m.p. 181–184°. Crystallization from methanol (moderately soluble) gave 0.87 g., m.p. 187–188°, and a second crop of 0.18 g., m.p. 183–184°. Recrystallization of the first crop gave large, rectangular prismatic plates, m.p. 187–188°.

Anal. Calcd. for $C_{30}H_{46}O_9$ (550.67): C, 65.43; H, 8.42. Found: C, 65.50; H, 8.54.

Methyl 3α-Cathyloxy-7α-acetoxy-12-ketocholanate (L.F.F.).—A solution of 5 g. methyl cholate-3-cathylate-7-acetate in 25 cc. of acetic acid was cooled to room temperature (28°) and treated with 1.55 g. (1.5 × theory) of sodium dichromate dihydrate. The mixture was swirled and the temperature controlled to 24–28° by cooling. In ½ hr. 40 cc. of water was added and the precipitated solid was collected, washed and dried: 4.84 g., m.p. 153–154.5°. The substance is more soluble in methanol than the precursor alcohol, very soluble in ethyl acetate, moderately soluble in 60–90° ligroin. Crystallization from methanol gave 3.83 g., m.p. 155–156°; the molten liquor material, precipitated with water, dried, and crystallized from ligroin, gave 0.80 g., m.p. 153–154° (total yield, 92.5%). A sample crystallized twice from methanol (large prismatic needles) and then once from ligroin (fine needles) melted at 155–156°, $\alpha^{27}D$ +69.0 ± 0.5° Chf, +64.0 ± 0.5° Di.

Anal. Calcd. for $C_{30}H_{46}O_8$ (534.67): C, 67.39; H, 8.67. Found: C, 67.33; H, 8.79.

Cholestane-3β,5α,6β-triol-3-cathylate. (a) In Dioxane (L.F.F.).—A solution of 1 g. of cholestane-3β,5α,6β-triol in 10 cc. of dioxane and 1.6 cc. of pyridine was cooled to 25° and treated dropwise and with cooling with 2 cc. of ethyl chlorocarbonate. Toward the end of the addition an oil separated and then soon solidified. After 1 hr. 25 cc. of water and 1 cc. of 36% hydrochloric acid were added and the mixture heated for ½ hr. on the steam-bath and cooled, when the oil solidified. The product was a granular white solid; 1.19 g., m.p. 180–182°. Crystallization from methanol (75 cc.) gave a first crop of 0.62 g. of prisms, m.p. 184.5–185°, and a second crop, 0.38 g., m.p. 183–184° (total yield 83%). Two recrystallizations of 1st-crop material gave prisms, m.p. 184–185°, $\alpha^{22.5}D$ −16 ± 1° Chf, −13 ± 1° Di.

(b) **In Pyridine (J.E.H.).**—One gram of triol in 20 cc. of pyridine was treated with 3 cc. of ethyl chlorocarbonate and after 2 hr. the solution was diluted and the product crystallized twice from aqueous acetone to give 0.85 g., m.p. 184–185°, $\alpha^{22}D$ −14 ± 2° Chf.

Anal. Calcd. for $C_{30}H_{52}O_5$ (492.72): C, 73.28; H, 10.80. Found: C, 73.12; H, 10.64.

3α-Cathyloxy-5α-hydroxycholestane-6-one (J.E.H.).—A solution of 1.8 g. of the triol 3-cathylate and 0.725 g. of N-bromosuccinimide in 30 cc. of dioxane and 3 cc. of water was let stand at 25° for 2 hr. and diluted with water. The crude precipitate (1.7 g., m.p. 211–213°), crystallized twice from aqueous acetone, yielded 1.0 g. of ketone, m.p. 217–218°, $\alpha^{22}D$ −45 ± 2° Di.

Anal. Calcd. for $C_{30}H_{50}O_5$ (490.70): C, 73.43; H, 10.27. Found: C, 73.66; H, 10.25.

The residual material from the mother liquor was saponified; the product, crystallized from aqueous acetone, afforded crystals, m.p. 232–234°, that showed no depression with cholestane-3β,5α-diol-6-one.

Cholestane-3β,5α,6α-triol-3,6-dicathylate (J.E.H.).—Reaction of 0.5 g. of cholestane-3β,5α,6α-triol, m.p. 236–238°, α_D +21 ± 2° Di, with 2 cc. of ethyl chlorocarbonate in 20 cc. of pyridine (18 hr., 25°) and crystallization of the product from aqueous acetone, aqueous ethanol and aqueous methanol yielded 0.35 g. of product, m.p. 158–160°. The main fraction eluted from alumina by benzene on crystalli-

zation from aqueous ethanol melted at 165–167°, $\alpha^{25}D$ +12.3 ± 2° Di, yield 0.25 g. (52%).

Anal. Calcd. for $C_{33}H_{56}O_7$ (564.78): C, 70.33; H, 9.99. Found: C, 70.08; H, 9.97.

Preparation of 7α- and 7β-Hydroxycholestanol (T.U.).—Reduction of 18.5 g. of 7-ketocholestanyl acetate with lithium aluminum hydride (20% excess) in ether was conducted as described,[15] but it was found that separation of the epimers does not require chromatography but can be accomplished by crystallization, as follows. A solution of the total reaction mixture from 200 cc. of benzene on cooling deposited 5 g. of crude 7β-epimer, m.p. 155–159°; concentration of the mother liquor afforded three further crops totaling 2.7 g. Recrystallization of the total crude 7β-epimer from ethanol water (low-melting form, m.p. 156–159°) and then from benzene (high-melting form) gave a total of 5.9 g. (35%) of **cholestane-3β,7β-diol**, m.p. 169–170°, $\alpha^{24}D$ +53.3° Chf. On saturation of the residual benzene mother liquor with 30–60° ligroin, 3 g. of crude 7α-epimer was obtained, m.p. 138–145°, $\alpha^{24}D$ +7° Chf. Further crops totalling 2.5 g. were obtained on concentrating the mother liquor, and finally by addition of methanol, acetone and a little water. Recrystallization of the crude product from benzene–ligroin and finally from aqueous ethanol gave 3.9 g. (23%) of cholestane-3β,7α-diol, m.p. 153–154°, $\alpha^{24}D$ +8.5° Chf.

Cholestane-3β,7α-diol 3-Cathylate (T.U.).—A solution of 0.5 g. of 7α-hydroxycholestanol in 20 cc. of pyridine was treated with 2 cc. of ethyl chlorocarbonate, let stand for 14 hr., and diluted with water. The oily precipitate was crystallized from ethanol–water several times and gave 0.29 g. of crystals, m.p. 135°, $\alpha^{22}D$ +2.1 ± 0.3° Chf.

Anal. Calcd. for $C_{30}H_{52}O_4$ (476.72): C, 75.58; H, 11.00. Found: C, 75.43; H, 11.00.

Cholestane-3β,7β-diol 3,7-Dicathylate (T.U.).—Cathylation of the 7β-epimer in the same way gave an oily product that on several crystallizations from ethanol–water afforded a constant melting product in 45% yield; m.p. 122°, $\alpha^{22}D$ +38.3 ± 0.3° Chf.

Anal. Calcd. for $C_{33}H_{56}O_6$ (548.78): C, 72.22; H, 10.29. Found: C, 72.25; H, 10.29.

Oxidation of 7α- and 7β-Hydroxycholestanol with N-Bromosuccinimide (T.U.).—A solution of 0.40 g. of 7α-hydroxycholesterol in 30 cc. of dioxane and 2 cc. of water was treated at 28° with 0.41 g. of N-bromosuccinimide and the mixture was shaken until the solid had dissolved. The solution became brownish; after 1 hr. dilution with about 10 cc. of water caused separation of a crystalline product. Recrystallization from ethanol–water gave 0.26 g. (65%) of **7-ketocholestanol**, m.p. 160°, $\alpha^{21}D$ −33.8° Chf (analysis a, below), identical in infrared spectrum with an authentic sample.

Oxidation of 0.40 g. of 7β-hydroxycholestanol in the same manner gave 0.25 g. (62%) of 7-ketocholestanol, m.p. 161°, $\alpha^{22}D$ −32.0° Chf, no depression in mixed m.p. (analysis b).

Anal. Calcd. for $C_{27}H_{46}O_2$ (402.64): C, 80.54; H, 11.52. Found: (a) C, 80.48; H, 11.59; (b) C, 80.55; H, 11.51.

Since 7α- and 7β-hydroxycholesterol are dextrorotatory whereas 7-ketocholestanol, the oxidation product derived from both epimers, is levorotatory, the oxidations can be followed polarimetrically. The results of several comparative experiments indicated that both epimers are oxidized at substantially the same rate and that the best yields result from use of at least 2 equivalents of N-bromosuccinimide per mole of sterol. The oxidations were accelerated by addition of hydrogen bromide and retarded by addition of sodium bicarbonate.

Methyl Δ¹¹-Lithocholenate-3-cathylate.[16]—Cathylation in pyridine and crystallization from methanol gave colorless plates, m.p. 135–136°, $\alpha^{25}D$ +43 ± 2° Di.

Anal. Calcd. for $C_{28}H_{44}O_5$ (460.63): C, 73.00; H, 9.63. Found: C, 73.11; H, 9.64.

Cholesteryl Cathylate. (a) In Dioxane (L.F.F.).—To a solution of 10 g. of commercial cholesterol in 50 cc. of dioxane and 16 cc. of pyridine 20 cc. of ethyl chlorocarbonate was added dropwise with cooling under the tap. An oil separated and there was some foaming at the end of the addition. After ½ hr. the mixture was treated with 125 c. of water and 10 cc. of 36% hydrochloric acid and let stand overnight. The mixture was then extracted with ether and the washed and dried extract evaporated to about 100 cc., treated with 100 cc. of methanol, boiled down to about 150 cc. and let stand. A first crop of prisms separated, 10.66 g., m.p. 83–84°; a second crop melted at 81–83°, 0.56 g. (total yield 95%). For recrystallization, the total product was dissolved in 50 cc. of absolute ether and the solution diluted with 100 cc. of hot methanol; the cathylate separated in large prisms. After a further crystallization, the substance had the constants: m.p. 83–84° (striking bluish color—apparent fluorescence—as the melt cools), $\alpha^{22.5}D$ −36.0 ± 1° Chf, −30.0 ± 1° Di.

(b) In Pyridine (J.E.H.).—Four cc. of ethyl chlorocarbonate was added in the above manner to a solution of 2 g. of cholesterol in 30 cc. of pyridine; the solution became deep red then yellow, and white crystals separated. After 6 hr. at 25° water was added and the solid that precipitated was crystallized from aqueous methanol to give 1.6 g. (64%) of needles, m.p. 82–84°.

Anal. Calcd. for $C_{30}H_{50}O_3$ (458.70): C, 78.55; H, 10.99. Found: C, 78.78; H, 10.90.

7-Ketocholesteryl Cathylate (L.F.F.).—A solution of 3 g. of cholesteryl cathylate in 40 cc. of acetic acid was stirred at 50° and treated with 2.5 g. of chromic anhydride, added in ½ hr. The mixture was stirred at 50–55° for one hour longer, let stand at 25° for 2 hr., and the product was then extracted with ether and crystallized from methanol. The resulting white solid (0.5 g., m.p. 117°), recrystallized twice, gave needles, m.p. 117–117.5°; $\alpha^{23.5}D$ −87.5 ± 0.4° Chf, −73.0 ± 0.2° Di.

Anal. Calcd. for $C_{30}H_{48}O_4$ (472.68): C, 76.22; H, 10.24. Found: C, 76.32; H, 10.18.

Dehydroepiandrosterone Cathylate (M.W.K.).—Cathylation of 100 mg. of dehydroepiandrosterone (m.p. 148–149°, $\alpha^{23}D$ +1.0 ± 0.4° Chf; 3-acetate, m.p. 169–171°, $\alpha^{23}D$ −6.8 ± 0.5° Chf) in dioxane as described for cholesterol afforded in 94% yield crude cathylate, m.p. 163–170°. After several crystallizations from methanol the substance was obtained as needles, m.p. 184–186°, $\alpha^{26}D$ 0 ± 1° Chf, +3 ± 1° Di.

Anal. Calcd. for $C_{22}H_{32}O_4$ (360.48): C, 73.30; H, 8.95. Found: C, 73.30; H, 8.84.

Cholestanyl Cathylate (L.F.F.).—Excess ethyl chlorocarbonate (1 cc.) was added dropwise with cooling to a solution of 1 g. of cholestanol in 5 cc. of dioxane and 0.8 cc. of pyridine. The mixture turned pinkish, and the oil that initially separated solidified in about ½ hour. The mixture was diluted with water, acidified, warmed for ½ hr. on the steam-bath, and cooled, when the oily product at once solidified. The resulting solid (1.16 g., m.p. about 95°) on crystallization from 100 cc. of methanol afforded 0.88 g. of cathylate, m.p. 105–106°, $\alpha^{25}D$ +13 ± 1° Chf, +14 ± 1° Di.

Anal. Calcd. for $C_{30}H_{52}O_3$ (460.72): C, 78.20; H, 11.38. Found: C, 78.43; H, 11.59.

Δ⁷-Cholestenyl Cathylate (J.E.H.).—Cathylation of 2 g. of stenol ($\alpha^{25}D$ +3.9° Chf) in pyridine and crystallization twice from aqueous acetone gave 1.2 g. of product, m.p. 92–93°, $\alpha^{23}D$ +1.4 ± 0.3° Chf, $\alpha^{22}D$ +10 ± 2° Di, a second crop of 0.4 g., m.p. 90–93°.

Anal. Calcd. for $C_{30}H_{50}O_3$ (458.70): C, 78.55; H, 10.99. Found: C, 78.79; H, 10.93.

Epicholestanyl Cathylate.[17]—A solution of 500 mg. of epicholestanol,[18] m.p. 186–187°, αD +28.4° Chf, in 15 cc. of pyridine was swirled under the tap while 1.5 cc. of ethyl chlorocarbonate was added slowly. After 22 hr. at 25°, water was added and the precipitated solid was washed, dried, and chromatographed on 30 g. of alumina. Petroleum ether–benzene (1:1) eluted 86 mg. of epicholestanyl cathylate, m.p. 96.5–101°, and benzene then eluted the remaining material as unchanged epicholestanol, m.p. 186–187° after crystallization from ethanol. The cathylate gave colorless blades from ethanol, m.p. 102–103°.

Anal. Calcd. for $C_{30}H_{52}O_3$ (460.72): C, 78.20; H, 11.38. Found: C, 77.78; H, 11.36.

(15) L. F. Fieser, M. Fieser and R. N. Chakravarti, THIS JOURNAL, **71**, 2226 (1949).

(16) Experiment by Dr. Srinivasa Rajagopalan.

(17) Experiment by Dr. William P. Schneider.

(18) Prepared by William E. Rosen.

Coprostanyl Cathylate (J.E.H.).—Treatment of 0.5 g. of coprostanol,[18] m.p. 108.5–110°, α_D +27° Chf, in 12 cc. of pyridine with 1 cc. of ethyl chlorocarbonate (25°, overnight) and fractionation of the resulting mixture by chromatography afforded 0.20 g. (34%) of cathylate, m.p. 107–109°, $\alpha^{25}D$ +23.6 ± 2° Di (depresses starting material).

Anal. Calcd. for $C_{30}H_{52}O_3$ (460.72): C, 78.20; H, 11.38. Found: C, 78.43; H, 11.32.

Epicoprostanyl Cathylate (J.E.H.).—Cathylation of 0.5 g. of epicoprostanol,[18] m.p. 109.5–110°, $\alpha^{25}D$ +32° Chf, by the procedure described for coprostanol gave, after chromatography, 0.30 g. (51%) of cathylate, m.p. 101–103° (depression with epicoprostanol), $\alpha^{23}D$ +42.4 ± 0.5° Chf, +49 + 2° Di.

Anal. Calcd. for $C_{30}H_{52}O_3$ (460.72): C, 78.20; H, 11.38. Found: C, 78.63; H, 11.30.

Androstane-3β,17β-diol Dicathylate (M.A.R.).—Cathylation of 380 mg. of androstane-3β,17β-diol (m.p. 158–160°) gave a crude product, m.p. 100–110°; on chromatography 10:1 petroleum ether–benzene eluted 250 mg. (44%) of white plates, m.p. 130–132°. Recrystallization from methanol did not change the m.p.; $\alpha^{22}D$ ± 0 Chf; infrared spectrum, no absorption in the region 2.7–3.0 μ.

Anal. Calcd. for $C_{25}H_{40}O_6$ (436.57): C, 68.77; H, 9.24. Found: C, 68.94; H, 9.46.

Lithocholanyl Alcohol (M.W.K.).—Lithocholic acid (m.p. 183–185°) was reduced by placing 2 g. of acid in the thimble of a soxhlet extractor and 2 g. of lithium aluminum hydride and 350 cc. of ether in a boiling flask fitted with a sealed stirrer. After a reaction period of 6 hr., the acid was all dissolved. After destruction of excess reagent by addition of small pieces of ice, the mixture was acidified with dilute sulfuric acid and the product collected by ether extraction. The crude diol, 1.9 g., m.p. 170–172°, gave crystals from dilute methanol, m.p. 176–178°, $\alpha^{27}D$ +35 ± 2° CH_3OH.

Anal. Calcd. for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.80; H, 11.55.

The dicathylate resulted from reaction of the diol (1 g.) in dioxane (10 cc.)–pyridine (2 cc.) with ethyl chlorocarbonate (2 cc.) as described above. The product, obtained as a semi-solid after considerable scratching (1.38 g.), formed shiny crystals from methanol, m.p. 74–75°. After several recrystallizations the sample melted at 75–76°, $\alpha^{25}D$ +41 ± 2° Di.

Anal. Calcd. for $C_{30}H_{50}O_6$ (506.70): C, 71.11; H, 9.95. Found: C, 71.16; H, 10.07.

The infrared spectrum showed no hydroxyl band and the substance was recovered unchanged after treatment with chromic acid in acetic acid at 25° for 18 hr.

Attempts to prepare a monocathyl derivative did not lead to conclusive results.

Δ⁵-Cholestene-3β,4β-diol Dicathylate (M.A.R.).—A solution prepared from 0.5 g. of Δ⁵-cholestene-3β,4β-diol (m.p. 176–177°, $\alpha^{27}D$ −62 ± 0.3° Chf), 15 cc. of pyridine and 2 cc. of ethyl chlorocarbonate was let stand 10 hr. at 25° and poured into water. The reaction product was eluted from alumina by petroleum ether and then crystallized from methanol; it formed leaflets, m.p. 147–149°; yield 0.5 g. (74%); $\alpha^{22}D$ −79.8 ± 0.5° Chf, λ infrared 5.78, 7.80 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.48; H, 9.95. Found: C, 72.81; H, 10.22.

Δ⁴-Cholestene-3β,6β-diol Dicathylate (M.A.R.).—Reaction of 0.1 g. of Δ⁴-cholestene-3β,6β-diol (m.p. 256–257°, $\alpha^{22}D$ +7.6 ± 0.4° Py) in 15 cc. of pyridine with 0.4 cc. of ethyl chlorocarbonate for 10 hr. and dilution with water gave a solid product that on crystallization from methanol afforded 0.11 g. (80%) of white leaflets, m.p. 168–170°, $\alpha^{22}D$ −19.6 ± 0.6° Chf, λ infrared 5.80, 7.90 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.48; H, 9.95. Found: C, 72.68; H, 9.78.

Δ⁵-Cholestene-3β,7β-diol Dicathylate (M.A.R.).—A solution of 0.4 g. of 7β-hydroxycholesterol (m.p. 174–176°, $\alpha^{26}D$ 0 ± 0.7° Chf) in 10 cc. of pyridine was treated with 0.8 cc. of ethyl chlorocarbonate (cooling) and let stand 6 hr. at 25°. The material that precipitated on dilution crystallized from methanol in needles, m.p. 82–84°; yield 0.3 g. (55%). Two further crystallizations from aqueous acetone gave needles, m.p. 93–95°, λ infrared 5.80, 7.90 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.48; H, 9.95. Found: C, 72.78; H, 10.11.

Cathylation of 7α-hydroxycholesterol (m.p. 186–187°, $\alpha^{22}D$ −89 ± 0.6° Chf) gave a product that could not be obtained crystalline even after chromatography. A homogeneous fraction eluted from alumina by 10:1 petroleum ether–benzene had the constants $\alpha^{22}D$ −79.8 ± 0.4° Chf, λ infrared 5.80, 7.90 μ. The absence of absorption in the hydroxyl band region indicates that the substance is the dicathylate.

Cathylation of coprostane-3β,6α-diol[19] (m.p. 195–196°, α_D +23 ± 0.4° Chf) also gave a non-crystalline product that appears to be a dicathylate: eluted by 10:1 petroleum ether–benzene, $\alpha^{20}D$ +4.5 ± 0.5° Chf, λ infrared 5.80, 7.90 μ (no absorption around 2.8 μ).

(19) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1880 (1944).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

β-Dialkylaminoethyl Esters with Adrenergic Blocking Activity

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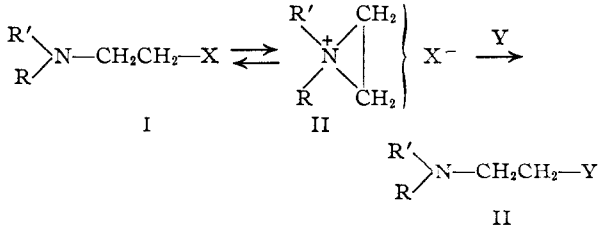
A number of derivatives of β-dialkylaminoethanols have been prepared and compared chemically and pharmacologically with the corresponding β-dialkylamino ethyl chlorides. It was found that sulfonic acid esters of the ethanols possess adrenergic blocking ability. It has been shown that suitable constituted carboxylic esters can react with displacement of the acyloxy grouping, but none of these showed appreciable adrenergic blocking ability. A color reaction of potential usefulness in the estimation *in vivo* of adrenergic blocking agents was studied briefly.

The ability of certain N,N-disubstituted β-haloethylamines (I) (for example, N,N-dibenzyl-β-chloroethylamine) to block excitatory responses to epinephrine and to sympathetic nerve stimulation may be related to their conversion *in vivo* into ethylenimonium intermediates (II) followed by the reaction of these with tissue elements.[1]

(1) (a) M. Nickerson and W. S. Gump, *J. Pharm. Exp. Ther.*, **97**, 25 (1949); (b) M. Nickerson, *Pharm. Rev.*, **1**, 27 (1949); (c) J. F. Kerwin, G. C. Hall, M. Nickerson, W. S. Gump, R. A. McLean, E. J. Fellows and G. E. Ullyot, *Science*, **113**, 315 (1951). See also, B. B. Brodie, L. Aranow, E. Titus and J. Axelrod, *Federation Proc.*, **10**, 283 (1951).

Studies on the relationship between structure and physiological activity in compounds of this type[1a,1c] have indicated the importance of structural factors



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