[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

# On the Epimeric 7-Hydroxycholesterols

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It has been shown recently that 7($\alpha$)- and 7($\beta$)-hydroxycholesterol as well as the corresponding ketone, 7-ketocholesterol, are formed from cholesterol by autoxidation in aqueous colloidal solution.[1,2] In connection with studies on the mechanism of this reaction it seemed of interest to determine whether the reduction of the ketone acetate with aluminum isopropylate, which is the customary method for preparing 7($\alpha$)-hydroxycholesterol,[3] also yields the 7($\beta$)-epimer, as it does in the case of 7-ketoepicholesterol.[4] 7($\beta$)-Hydroxycholesterol has been so far accessible only by permanganate oxidation of cholesteryl acid phthalate,[5] a method which in our hands has given a yield of only 10% or less.

At first we searched for the 7($\beta$)-diol in the resinous mother liquor material remaining after separation of the crystalline portion of the hydrolyzed reduction product which according to Windaus, *et al.*,[3] should be essentially 7($\alpha$)-hydroxycholesterol. We were unable to isolate the desired compound from such fractions, which instead yielded two other substances to be described later. We therefore turned our attention to the crystalline fraction which is obtained by precipitating the ethereal solution of the crude hydrolyzed reduction product with petroleum ether. These crystalline products, with melting points at 165–174°, were consistently found to be levorotatory ($[\alpha]_D$ −11 to −16°), which was surprising in view of the fact that the dibenzoate and the 7-monobenzoate[6] of the 7($\alpha$)-diol have specific rotations of +104 and +94°, respectively. "7-Hydroxycholesterol," presumed to be the $\alpha$-epimer, has so far been described only in a patent by Windaus and Schenk.[7] According to these authors it melts at about 178°, but the specific rotation was not given. We found that fractions rich in 7($\beta$)-hydroxycholesterol could indeed be obtained from the crude crystalline preparations by using a comparatively large amount of hot methanol for recrystallization. Further purification yielded substantial quantities of the levorotatory 7($\beta$)-diol. The identity of the compound was confirmed by the preparation of the dibenzoate.

Recrystallization of the crude diol mixture from ether or acetone yielded a mass of fine long needles, m. p. 174–176°, answering the description of Windaus and Schenk[7] for 7($\alpha$)-hydroxycholesterol, but retaining the levorotation of the starting preparation. Further recrystallization from small volumes of methanol did not change these properties. On benzoylation of this material 7($\alpha$)-hydroxycholesterol dibenzoate was obtained as the sole product in 67% yield, proving that the mixture consisted preponderantly of the 7($\alpha$)-epimer. There remained to be re-investigated the claim of Windaus and Schenk that hydrolysis of the dibenzoate yields again the substance melting at 178°. Our hydrolysis product was a gelatinous mass with a specific rotation of +4.6°, which proved to be much more difficult to crystallize than the epimeric mixture. It eventually yielded a small amount of needles melting at 178.5° and possessing a specific rotation of +7.2°. Benzoylation of the amorphous product resulted in the formation of the dibenzoate in almost theoretical yield. Acetylation in pyridine yielded quantitatively the higher melting (m. p. 107°) of the two forms of the diacetate mentioned in the patent of Windaus and Schenk. We conclude that 7($\alpha$)-hydroxycholesterol is a slightly dextrorotatory substance which is much more soluble in organic solvents than the 7($\beta$)-epimer and cannot be as readily obtained in crystalline form. The presence of small amounts of the 7($\beta$)-epimer evidently improves its capacity to crystallize, probably due to the formation of mixed crystals. From the specific rotations it appears that the crude crystalline diol mixtures contain up to 20% of the 7($\beta$)-epimer. In regard to the over-all yield of the latter compound from cholesterol the route *via* 7-ketocholesterol is inferior to the oxidative method of Barr, *et al.*; it is of practical value only if the $\alpha$-epimer is also desired.

The differences between the specific rotations of 7($\alpha$)- and 7($\beta$)-hydroxycholesterol ($\Delta$ = 98°), and especially of the corresponding dibenzoates

(1) Wintersteiner and Bergström, *J. Biol. Chem.*, **137**, 785 (1941).
(2) Bergström and Wintersteiner, *ibid.*, **141**, 597 (1941).
(3) Windaus, Lettre and Schenk, *Ann.*, **520**, 98 (1935).
(4) Windaus and Naggatz, *ibid.*, **542**, 204 (1939).
(5) Barr, Heilbron, Parry and Spring, *J. Chem. Soc.*, 1437 (1936).
(6) Wintersteiner and Ruigh, THIS JOURNAL, **64**, 1177 (1942).
(7) Windaus and Schenk, U. S. Patent 2,098,985 (1937).

($\Delta$ = 201°) and diacetates ($\Delta$ = 227°) are unusually large for epimers and indicate a marked deflection of valency angles of carbon atom 7 in one or both epimeric forms. It seemed of interest to determine whether this factor influences the speed of ester hydrolysis at $C_7$, relative to that at $C_3$, in the two epimeric dibenzoates. 7($\alpha$)-Benzoxycholesteryl benzoate on hydrolysis with cold methanolic sodium ethylate solution yields almost quantitatively the 7-monoester.[6]

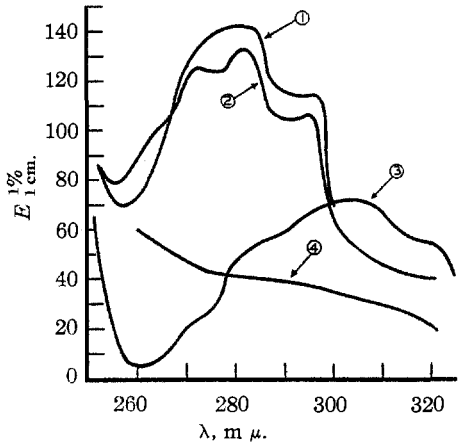


Fig. 1.—Absorption curves in ether solution of crude products formed from: ①, 7($\alpha$)-benzoxycholesterol, boiling dimethylaniline[6]; ②, 7($\alpha$)-benzoxycholesterol, pyrolysis[6]; ③, 7($\beta$)-benzoxycholesterol, pyrolysis; ④, 7($\beta$)-benzoxycholesterol, boiling dimethylaniline.

When the 7-epimeric dibenzoate was subjected to the same treatment, the result was similar in that a monobenzoate was the sole hydrolysis product. The method used for ascertaining the position of the benzoxy group in the 7($\alpha$)-monobenzoate, namely, conversion into 7-dehydrocholesterol, gave inconclusive results, but proof that the new monoester was likewise a 7-benzoate was adduced by reductive removal of the benzoxy group. Extending the observation of Barr, *et al.*,[5] that 7($\beta$)-hydroxycholesterol on catalytic reduction yields cholestanol, we found that the dibenzoates of both 7($\alpha$)- and 7($\beta$)-hydroxycholesterol are reduced under similar conditions to $\beta$-cholestanyl benzoate. When applied to the new monobenzoate the reaction yielded $\beta$-cholestanol, while from a mixed ester, the acid succinate-benzoate, $\beta$-cholestanyl acid succinate was obtained.

It is thus clear that stereochemical factors do not play a role in the relative inertness of the ester linkage at $C_7$ toward alkaline hydrolyzing agents. However, the ease with which benzoic acid can be cleaved from the two epimeric 7-monobenzoates, either by pyrolysis or by treatment with high-boiling amines, to form 7-dehydrocholesterol is definitely influenced by the configuration at $C_7$. This is illustrated in Fig. 1, which shows the absorption spectra of the crude products obtained by these reactions. The 7($\alpha$)-monobenzoate in both reactions yielded products containing 50% or more dehydrosterol, as measured by the extinction at 283 m$\mu$.[6] In contrast, the 7($\beta$)-monobenzoate on pyrolysis gave rise preferentially to a compound with a maximum at 305 m$\mu$, which is probably identical with the cholestatriene obtained under similar conditions by Windaus and Naggatz[4] from 7($\alpha$)-benzoxyepicholesteryl benzoate and by Eckhardt[8] from 7($\alpha$)-hydroxycholesteryl benzoate. The reaction product obtained from the 7($\beta$)-monobenzoate by boiling with dimethylaniline gave an uncharacteristic curve without any clearly differentiated maxima. Further fractionation with digitonin showed that a small amount of 7-dehydrocholesterol was present. We also found that by lowering the pressure during the pyrolysis from 1 to about 0.01 mm., some dehydrosterol was formed in addition to the entity absorbing at 305 m$\mu$. Quite analogous results were obtained in both reactions with the two 7-epimeric dibenzoates. These findings justify the conclusion that 7($\beta$)-hydroxycholesterol is greatly inferior to the 7($\alpha$)-epimer as a starting product for the preparation of 7-dehydrocholesterol.

Spectrographic examination of the non-crystallizable portion of the reduction product revealed the presence of two light-absorbing entities, with maxima around 240 and 280 m$\mu$, respectively. The absorption at 240 m$\mu$ is not merely due to unchanged 7-ketocholesterol, since after treatment of the mixture with Girard's reagent it was found to be associated for the most part with the non-ketonic fraction. From one batch of reduced material a crystalline compound of the composition $(C_{27}H_{44})_2O$ was isolated, the spectrum of which exhibited a high, sharply defined maximum at 243 m$\mu$. This substance was dextrorotatory ($[\alpha]_D$ +92°), and gave an intense Lifschütz color reaction. These properties are compatible with the structure either of a di-$\Delta^{4,6}$-cholestadienyl-3-ether or a di-$\Delta^{3,5}$-cholestadienyl-7-ether. A decision between these alternative structures cannot be made on the basis of the rotation rule which

(8) Eckhardt, *Ber.*, **71**, 461 (1938).

in general permits to distinguish between $\Delta^4$- and $\Delta^5$-compounds containing only one ethylenic bond.[9] $\Delta^{4,6}$-Cholestadiene[10] obeys this rule by being dextrorotatory, but $\Delta^{4,6}$-cholestadienol-3($\beta$) and its esters are levorotatory.[11] On the other hand, in the yet undescribed $\Delta^{3,5}$-cholestadienol-7, and especially in its esters and ethers, the sign of rotation might well depend, as in the 7-hydroxycholesterols, on the configuration of $C_7$.

The dicholestadienyl ether is undoubtedly only an incidental by-product formed in small amounts, the isolation of which was facilitated by its comparative stability. We have spectroscopic and other evidence that the parent alcohol is likewise present among the reduction products, but repeated attempts to effect its isolation were unsuccessful.

The compound absorbing in the region around 280 m$\mu$ was not, as might have been supposed, $\Delta^{3,5}$-cholestadienone-7, but was identified as the epimeric $\Delta^{4,6}$-cholestadienone-3. The formation of the 3-ketone from 7-ketocholesteryl acetate by the action of aluminum isopropylate is obviously preceded by ester hydrolysis, which is known to occur under these conditions.[7] The mechanism of the subsequent oxidation at $C_3$ probably follows the same pattern as the dismutation of dehydroisoandrosterone to testosterone described by Oppenauer,[12] with the 7-keto group in the present case functioning as the hydrogen acceptor. Migration of the double bond from the 5–6 to the 4–5 position, followed by dehydration of the 7-hydroxy group, could then occur under the tendency to establish a triply conjugated system. Alternatively, the precursor may be 7($\beta$)-hydroxycholesterol, which is capable of rearranging into $\Delta^6$-cholestenediol-3($\beta$),5[2]; the latter compound is known to yield $\Delta^{4,6}$-cholestadienone-3 on oxidation with acetone and aluminum phenolate.[13]

## Experimental

**7($\beta$)-Hydroxycholesterol.**—Twenty-five grams of 7-ketocholesteryl acetate was reduced with isopropyl alcohol (500 cc.) and aluminum isopropylate (43 g.) in the usual manner.[8] The mixture was poured into 3 liters of 2% aqueous potassium hydroxide solution, allowed to stand for two hours at room temperature, and extracted with ether. The washed and dried ether solution was evaporated to 75 cc. On addition of 300 cc. of pentane, a precipitate of fluffy needles formed on standing (7.8 g., $[\alpha]_D$ −15.5°, 1.80% in chloroform). Recrystallization from methanol (70 cc.) yielded 1.27 g. of material with an $[\alpha]_D$ −70.6°, 1.0% in chloroform. After three more crystallizations from methanol, 577 mg. of 7($\beta$)-hydroxycholesterol, m. p. 184–185°, $[\alpha]_D$ −84° (0.99% in chloroform) was obtained. The melting point of a mixture with a preparation obtained by the procedure of Barr, *et al.*,[5] showed no depression.

The results obtained on another batch of reduced 7-ketocholesteryl acetate were similar. The crude crystalline diol mixtures (m. p. 173–174°, $[\alpha]_D$ −14.3°, 1.33% in chloroform) did not materially change its properties on recrystallization from acetone, or from a small volume of methanol. Recrystallization from a larger amount of the latter solvent yielded 7($\beta$)-hydroxycholesterol, m. p. 177–178.5°, $[\alpha]^{23}_D$ −87.6° (0.96% in chloroform).[14] The preparation lost 3.4% of solvent on drying *in vacuo* at 100° for one hour.

*Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.52; H, 11.52. Found: C, 80.74; H, 11.73.

One hundred milligrams was benzoylated with pyridine and benzoyl chloride. The resulting product melted at 151–152.5°. The melting point of a mixture with authentic 7($\beta$)-benzoxycholesteryl benzoate, m. p. 151–152.5°[15] showed no depression ($[\alpha]^{23}_D$ −107.5° (0.66% in chloroform)).

*Anal.* Calcd. for $C_{41}H_{54}O_4$: C, 80.60; H, 8.92. Found: C, 80.94; H, 9.01.

**7($\alpha$)-Hydroxycholesterol.**—Five grams of 7($\alpha$)-benzoxycholesteryl benzoate was refluxed in 100 cc. of 5% methanolic potassium hydroxide solution for six hours. The hydrolysis product, recovered by ether extraction, was a white amorphous mass melting at 167–170°, $[\alpha]_D$ +4.6° (0.85% in chloroform). Five hundred milligrams was treated with various solvents, and finally a small amount of needles, m. p. 177–178.5°, was obtained from ether. On recrystallization from the same solvent, the melting point became less sharp (55 mg., m. p. 169–177°, $[\alpha]_D$ +7.2° (1.0% in chloroform)). 250 mg. of the amorphous preparation yielded on re-benzoylation 327 mg. of crude dibenzoate, m. p. 169.5–170.5° (85%). On acetylation in pyridine, a *diacetate* melting at 105–106° was obtained in theoretical yield; on recrystallization from ether–methanol the compound separated as blunt prisms, m. p. 106–107°, $[\alpha]^{27}_D$ +51.8° (1.1% in chloroform).

(9) Stavely and Bergmann, *J. Org. Chem.*, **1**, 575 (1937).

(10) Eck, Van Peursem and Hollingsworth, THIS JOURNAL, **61**, 171 (1939).

(11) Petrow, *J. Chem. Soc.*, 66 (1940); Spring and Swain, *ibid.*, 320 (1941).

(12) Oppenauer, *Acta Brevia Neerland. Physiol. Pharmacal, Microbiol.*, **7**, 176 (1937); *Rec. trav. chim.*, **56**, 137 (1937).

(13) Bergström and Wintersteiner, *J. Biol. Chem.*, **143**, 503 (1942).

(14) 7($\beta$)-Hydroxycholesterol, m. p. 186° contains 1 mole of methanol of crystallization; the methanol-free form melts at 154–157° and forms mixed crystals of intermediate melting points and methanol content with the high-melting modification (*cf.* Wintersteiner and Ritzmann, *J. Biol. Chem.*, **136**, 697 (1940)). The specific rotation is, therefore, a better criterion of purity than the melting point, which may show erratic changes on recrystallization if the more stable low-melting modification is once present. The highest specific rotation observed for the methanol-containing form was −91.2° (*loc. cit.*). Barr, *et al.*, gave −86.4°, which is closer to the values found in the present work.

(15) The melting point of this preparation had been previously reported as 155–157° (Wintersteiner and Ritzmann, ref. 14). The higher value is incorrect and was traced to a standardized thermometer which had become defective.

*Anal.* Calcd. for $C_{31}H_{50}O_4$: C, 76.48; H, 10.36. Found: C, 76.29; H, 10.27.

**7(β)-Benzoxycholesterol.**—To one gram of 7(β)-benzoxycholesteryl benzoate in 20 cc. of benzene was added a solution of sodium methylate (0.66 g.) in absolute methanol (33 cc.). The mixture was allowed to stand at 25° for seventeen hours. The hydrolysis product was recovered by ether extraction. The oily ether residue was dissolved in a few cc. of warm ether. On standing in the refrigerator, the solution deposited crystals, the amount of which increased on addition of 30 cc. of pentane. Another crop was obtained from the mother liquor material by repetition of this process. Altogether 744 mg. (90%) of 7(β)-benzoxycholesterol was recovered in form of fine needles, which melted at 145–146°, $[\alpha]^{26}D$ −201° (1.04% in chloroform). It is not precipitated by digitonin in 90% ethanol, a behavior also shown by the 7(α)-monobenzoate.

*Anal.* Calcd. for $C_{34}H_{50}O_3$: C, 80.58; H, 9.95. Found: C, 80.15; H, 9.95.

The absorption spectrum in alcohol confirmed the presence of only one benzoxy group: $\epsilon_{231\ m\mu}$ = 12,500, $\epsilon_{272\ m\mu}$ = 705. 7(β)-Hydroxycholesterol dibenzoate, $\epsilon_{231\ m\mu}$ = 28,000, $\epsilon_{272\ m\mu}$ = 1480.

Benzoylation in pyridine yielded the diester, 7(β)-benzoxycholesteryl benzoate, m. p. 150–151.5°.

The monoester (101 mg.) dissolved in acid-free ethanol (15 cc.) was shaken with palladium black (51 mg.) in a hydrogen atmosphere. The hydrogen uptake was extremely slow, and shaking had to be continued for several days for completion of the reaction. After filtering and evaporation of the solvent the reaction product was taken up in ether, and the latter extracted with sodium carbonate solution, from which was recovered 17.6 mg. of benzoic acid, m. p. 121°. The material recovered from the ether phase was purified by means of digitonin. Decomposition of the digitonide (253 mg.) yielded a crystalline product which after two recrystallizations from ethanol melted at 139.5–140° and did not depress the melting point of authentic β-cholestanol, m. p. 140.5°. The acetate prepared from this material melted at 108.5–109.5°, as did a mixture with authentic β-cholestanyl acetate of the same melting point.

**7(β)-Benzoxycholesteryl 3,5-Dinitrobenzoate.**—The mixed ester was prepared in the usual manner. It crystallized from benzene–alcohol as needles, m. p. 178.5–179.5°; $[\alpha]^{23}D$ −88.2° (1.0% in chloroform).

*Anal.* Calcd. for $C_{41}H_{52}O_8N_2$: C, 70.26; H, 7.48; N, 4.00. Found: C, 70.59; H, 7.84; N, 4.24.

**7(β)-Benzoxycholesteryl Acid Succinate.**—A solution of 70 mg. of the monoester and 300 mg. of succinic anhydride in 3 cc. of pyridine was refluxed for two hours. The acid ester was recovered in the usual way by extraction from ether with potassium carbonate solution, acidification and transfer into ether (73.4 mg.). Recrystallization of the ether residue from methanol yielded small needles melting at 150–151°.

*Anal.* Calcd. for $C_{38}H_{54}O_6$: C, 75.20; H, 8.97. Found: C, 75.20; H, 8.98.

Ninety-one mg. of 7(β)-benzoxycholesteryl acid succinate was hydrogenated for seventeen hours in a mixture of ethanol (5 cc.) and glacial acetic (3 cc.) with palladium black (45 mg.). The crystalline portion of the reaction product (32 mg.) was recrystallized once from methanol and formed plates melting at 165–167°, $[\alpha]^{26}D$ +13.0° (0.61% in chloroform). An authentic sample of β-cholestanyl acid succinate of the same melting point had an $[\alpha]^{26}D$ of +13.2°. The melting point of the mixture showed no depression.

**Dicholestadienyl Ether.**—The mother liquor of the crystalline diol mixture from the reduction of 40 g. of 7-ketocholesterol was concentrated to a sirup, which was acetylated in pyridine and chromatographed in pentane solution according to the scheme described in a previous paper.[2] About 5 g. of material passed into the first washings with pentane. When dissolved in a small volume of warm benzene–ethanol 1:2 it deposited a crystalline product (600 mg., m. p. 150–160°). Several crystallizations from ethyl acetate yielded rosets of small needles melting at 158–160°, $[\alpha]D$ +90.6° (0.90% in chloroform). The compound is readily soluble in ether, benzene and hexane, sparingly soluble in ethyl acetate, and practically insoluble in methanol and ethanol. It remained unchanged on boiling in 5% methanolic potassium hydroxide solution, and was not adsorbed from hexane solution by aluminum oxide. Its chromogenic potency in the Lifschütz reaction is about equal to that of 7(β)-hydroxycholesterol.

*Anal.* Calcd. for $C_{54}H_{88}O$: C, 86.10; H, 11.78; mol. wt., 752.7. Found: C, 86.29, 86.25; H, 11.58, 11.84; mol. wt. (Rast), 663.

The absorption spectrum of the compound shows a high and very narrow band (indicative of the presence of two identical chromophoric groups) at 243 mμ, ε = 54,000 (in ether). The curve shows an inflection at about 249 mμ (ε = 48,000). These properties are in accord with the spectrographic data for $\Delta^{4,6}$-cholestadienyl-3-acetate, $\epsilon_{239\ m\mu}$ = 26,000[11] and of $\Delta^{4,6,22}$-ergostatrienyl acetate, $\epsilon_{240\ m\mu}$ = 27,000.[16]

On hydrogenation in ethyl acetate solution with platinum oxide as catalyst, 2 moles of hydrogen was consumed per sterol residue. No crystalline products could be obtained from the reaction product. It failed to be adsorbed on aluminum oxide, and was purified by precipitation from ether solution with acetone (m. p. 148–162°, $[\alpha]D$ +44°, Lifschütz reaction negative). The analysis indicated the composition $C_{27}H_{46-48}O_{1/2}$. Obviously, a mixture of isomeric reduced ethers had been formed.

**$\Delta^{4,6}$-Cholestadienone-3.**—In the hope to effect a separation of the dicholestadienyl ether by its insolubility in methanol, 12.7 g. of pentane-soluble mother liquor material from another reduction batch was dissolved in 50 g. of hot methanol. The oil which separated on cooling (2.9 g.) was dissolved in hexane and chromatographed on aluminum oxide in the usual manner. The fractions eluted with benzene–hexane 1:4, together 460 mg., were crystalline, and on recrystallization from 90% alcohol yielded heavy plates melting at 80–81°, which gave no depression of the melting point on admixture of $\Delta^{4,6}$-cholestadienone-3, m. p. 80–81°, prepared by the method of Dane, Wang and Schulte.[17]

*Anal.* Calcd. for $C_{27}H_{42}O$: C, 84.65; H, 11.07. Found: C, 84.45; H, 11.18.

(16) Güntzel, *Ber.*, **72**, 1317 (1939).

(17) Dane, Wang and Schulte, *Z. physiol. Chem.*, **245**, 80 (1937).

The semicarbazone melted at 228–229°; the mixture with an authentic sample showed no depression.

The ultraviolet absorption properties of the ketone ($\epsilon_{285\ m\mu}$ = 26,000, in ethanol) and of the semicarbazone ($\epsilon_{305\ m\mu}$ = 46,000, in dioxane) closely agreed with those of the authentic preparations.[13]

We are indebted to Dr. N. H. Coy of the Vitamin Laboratory of E. R. Squibb and Sons for the spectrographic measurements, and to Miss Mildred Moore for able technical assistance.

The microanalyses were carried out by J. F. Alicino, Fordham University.

## Summary

The crystalline, levorotatory product obtained by reduction of 7-ketocholesteryl acetate with aluminum isopropylate is a mixture of 7(α)- and 7(β)-hydroxycholesterol containing up to 20% of the latter epimer. Free 7(α)-hydroxycholesterol, in contradistinction to its esters, is only slightly dextrorotatory. It cannot be as readily obtained in crystalline form as the β-epimer or the epimeric mixture.

7(β)-Benzoxycholesteryl benzoate on hydrolysis with sodium methylate in the cold yields quantitatively 7(β)-benzoxycholesterol. The position of the benzoxy group was proved by its reductive removal, since the monoester, unlike its epimer, 7(α)-benzoxycholesterol, is not amenable to conversion into 7-dehydrocholesterol.

Two by-products of the reduction of 7-ketocholesteryl acetate, a dicholestadienyl ether and $\Delta^{4,6}$-cholestadienone-3, have been isolated. Possible mechanisms for the formation of the latter compound are discussed.

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[CONTRIBUTION FROM RÖHM AND HAAS COMPANY, INC., AND RESINOUS PRODUCTS & CHEMICAL CO.]

# The Chemistry of Acrylonitrile. I. Cyanoethylation of Active Methylene Groups

BY HERMAN ALEXANDER BRUSON

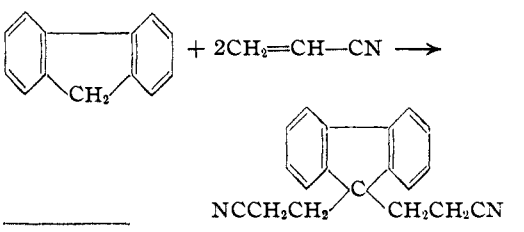
The reactions of acrylonitrile with amines,[1] phenols,[2] hydrogen sulfide,[3] butadiene[4] and halogens[5] have been described almost exclusively in the patent literature. Concerning the chemical behavior of acrylonitrile with other types of compounds, very little is known.

Because of its extremely reactive double bond, acrylonitrile condenses readily with a variety of organic compounds having labile hydrogen atoms or active methylene groups. These reactions occur in the presence of small quantities of alkaline condensing agents and are of the Michael type. The unique property of acrylonitrile in this respect is that it seeks out every available reactive hydrogen atom and by direct addition introduces the $-CH_2-CH_2-CN$ group in place thereof.

A powerful alkaline catalyst which is effective for promoting the cyanoethylation of many types of organic compounds is trimethylbenzylammonium hydroxide which is employed in the form of an aqueous 40% solution known as "Triton B" (Trade Mark). In some cases sodium or potassium methylate, 30% methanolic potassium hydroxide, or even aqueous 40% sodium hydroxide are effective, but the solubility of "Triton B" and its high degree of alkalinity renders it particularly effective where the other alkalies either fail to initiate the reaction at all or to give good yields.

In this paper, the condensation of acrylonitrile with compounds having the reactive methylene or methenyl grouping $C{=}C{-}\underset{|}{C}H{-}C{=}C$ in a carbocycle is described.[6] Such a grouping is present in fluorene, indene, cyclopentadiene, anthrone, the fulvenes and many of their substituted derivatives.

In the presence of a catalytic amount of "Triton B," acrylonitrile readily condenses with fluorene to yield *bis*-9,9-(β-cyanoethyl)-fluorene (I).




(I)

(1) British Patent 404,744 (1934), 457,621 (1936), I. G. Farbenindustrie; Hoffmann and Jacobi, U. S. Patents 1,992,615 (1935), 2,017,537 (1935).

(2) German Patent 670,357 (1939); Langley and Adams, THIS JOURNAL, **44**, 2326 (1922).

(3) German Patent 669,961 (1939); U. S. Patent 2,163,176.

(4) Wolfe, U. S. Patent 2,217,632 (1940).

(5) Long, U. S. Patent 2,231,363 (1941); Lichty, U. S. Patent 2,231,838 (1941); D'Ianni, U. S. Patent 2,231,360 (1941).

(6) See also Bruson, U. S. Patent 2,280,058 (1942).