[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Structure and Absorption Spectra. II. 3-Acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic Acid

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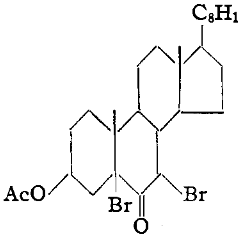
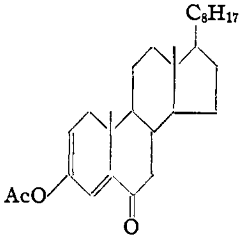
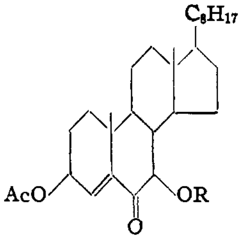
By the action of boiling pyridine on 5- or 5′,7-dibromo-3-acetoxy-6-ketocholestane (I), Heilbron, *et al.*,[1] obtained 3-acetoxy-6-keto-$\Delta^{2,4}$-cholestadiene (II) and a *product*, $C_{29}H_{46}O_4$, which appeared to be formed from the dibromoketone by the abstraction of one atom of bromine as hydrobromic acid, with the formation of a double bond, and the replacement of the other by hydroxyl. The presence of one double bond and one active hydrogen atom was confirmed by quantitative microhydrogenation and a Zerewitinoff determination. The substance was accordingly formulated as 3-acetoxy-6-keto-7-hydroxy-Δ^4-cholestene (III, R = H). The preparation of a benzoate, presumably III (R = $—COC_6H_5$), by the action of benzoyl chloride in pyridine, was adduced in further support of this view. A similar *product*, $C_{31}H_{50}O_4$, obtained from the 5′,7-dibromoketone by the action of sodium acetate in ethanol, was presumed to be the corresponding 7-ethoxy compound (III, R = C_2H_5). The determination by the English investigators of the absorption spectra of these substances, carried out in order to confirm the presence in them of an α,β-unsaturated carbonyl system, revealed $\lambda_{max.} \leqslant 230$ mμ (log $\epsilon \sim 4$).



I



II



III

In a previous paper,[2] it has been pointed out that this position of the absorption maximum is incompatible with formula III. Since the latter contains a disubstituted α,β-unsaturated carbonyl system, the wave length of maximum absorption for the intense band should be in the region 239 ± 5 mμ. Moreover if the substances are in fact α,β-unsaturated ketones, there should be in addition to the intense band in the short wave length region a band of small intensity (log $\epsilon \leqslant 2$) in the vicinity of 300 mμ.

Since the previous spectral determination did not include measurements below log ϵ = 3.2, we have endeavored to clarify this point by a redetermination of the absorption spectrum[3] (Fig. 1).

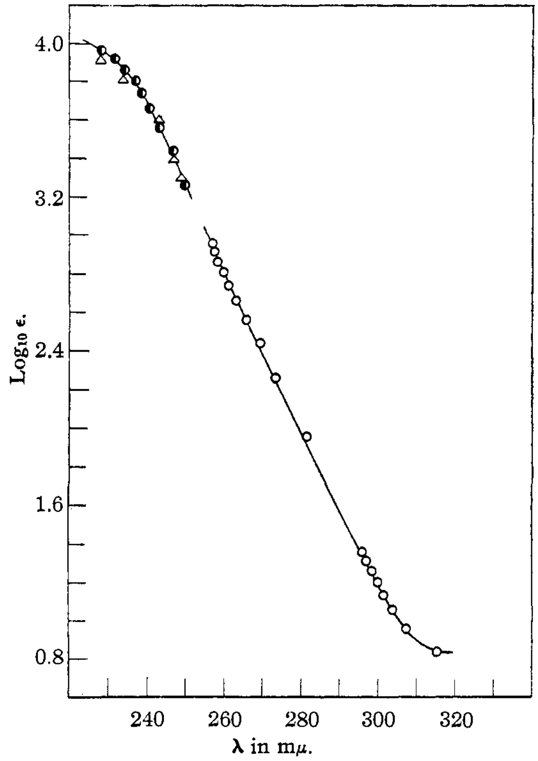


Fig. 1.—Absorption spectrum of 3-acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic acid: ○, points taken in dioxane; ◐, points taken in dioxane (10%) + ethanol (90%); △, points taken from Heilbron's curve (ethanol).

Our measurements agree very well with the previous results as far as the latter extend, but be-

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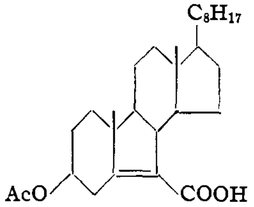
[1] Heilbron, Jackson, Jones and Spring, *J. Chem. Soc.*, 102 (1938).

[2] Woodward, THIS JOURNAL, **63**, 1123 (1941).

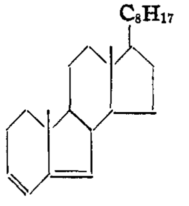
[3] We are indebted to Mr. J. J. Leavitt of this Laboratory for the carrying out of these measurements.

yond this, the extension of the curve reveals that there is no low intensity band in the longer wave length region. This is conclusive evidence that the compounds in question are not α,β-unsaturated ketones.

We now turn to the proposed[2] alternate formulation of the substances as 3-acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic acid (IV) and the corresponding ethyl ester. This view may be accommodated with the empirical formula $C_{29}H_{46}O_4$,



IV

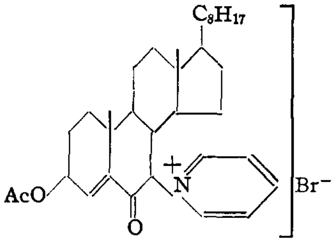


V

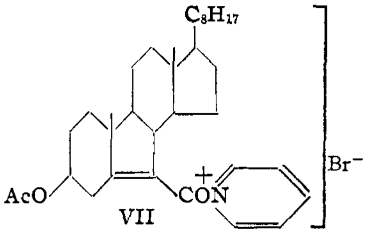
as well as with the observed presence of one double bond and one active hydrogen atom. The "benzoate" obtained by Heilbron may be formulated as a mixed anhydride of benzoic acid and the (6)-*nor*-cholestene acid. Further, the absorption spectrum is similar to that observed for other substances having an α,β-unsaturated carboxylic acid system.[4]

On the chemical side, the evidence which follows provides unequivocal proof of the new structure. The substance, $C_{29}H_{46}O_4$, is an acid which forms difficultly soluble alkali metal salts on trituration with alkali carbonates. On boiling with ethanol containing a small amount of sulfuric acid it is converted, with removal of the acetyl group, into a hydroxy-ester, which on the one hand is converted by acetylation into the compound $C_{31}H_{50}O_4$, and on the other is hydrolyzed by boiling with alkali to the corresponding hydroxy-acid. On distillation *in vacuo*, the acid is converted with loss of carbon dioxide and acetic acid into the known hydrocarbon, $\Delta^{3,5}$-(6)-*nor*-cholestadiene[5] (V).

The removal of bromine from 3-acetoxy-5-(*or* 5')-7-dibromo-6-ketocholestane therefore proceeds partially with rearrangement of the carbon skeleton of the molecule. The new mode of reaction clarifies another point which was hitherto obscure. Since the reaction was carried out in boiling *anhydrous* pyridine the mode of replacement of bromine by hydroxyl was not at all clear. It seemed unlikely that the presumable intermediate (VI) would undergo subsequent reaction with water to form the hydroxy ketone (III, R = H). It is now evident that the intermediate should be



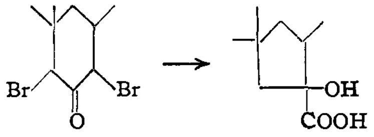
VI



VII

formulated as VII, and judging by the very labile character of the known acyl pyridinium halides, it is not surprising that this intermediate is rapidly hydrolyzed by water to the acid (IV).

It is noteworthy that Wallach[6] has observed similar rearrangements in the treatment of many simpler α,α'-dibromocyclohexanones with aqueous bases, *e. g.*



In view of the apparent generality of such rearrangements, it seems probable that the low yields of unsaturated ketones obtained in other debromination reactions[7] may in part be ascribed to side reactions of the type outlined above.

Experimental

3-Acetoxy-5',7-dibromo-6-ketocholestane.—Some difficulty was experienced in preparing the dibromoketone in the manner described by Heilbron,[1] *et al.* The following method consistently gave good yields of product.

3-Acetoxy-6-ketocholestane (6 g.) was dissolved in 18 cc. of glacial acetic acid. Two to three drops of concentrated hydrobromic acid (40%) was added, without shaking. A few drops of a solution of 1.38 cc. of bromine in 65 cc. of glacial acetic acid was then added and the reaction mixture was shaken until the bromine color was discharged. A further quantity of bromine solution was then added in like manner. With each further addition, a larger quantity could be added without stopping the reaction, which

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[4] *Cf.* Dimroth, *Angew. Chem.*, **52**, 552 (1939).

[5] Windaus and Resau, *Ber.*, **48**, 851 (1915); Lettré, *Z. physiol. Chem.*, **218** 67 (1933).

[6] Wallach, *Ann.*, **414**, 292 (1918).

[7] *Cf.* Inhoffen and Huang-Minlon, *Ber.*, **71**, 1720 (1938); **72**, 1686 (1939).

appears to be inhibited by excess bromine. When about half the bromine had been added, a copious precipitate of the monobromoketone separated. The remainder of the bromine solution was then added rapidly. After standing for *ca.* forty-five minutes, the precipitate redissolved. After eighteen hours the larger part of the acetic acid was removed *in vacuo* and the crystalline dibromide which separated was collected. The filtrate was further concentrated *in vacuo* and a second crop removed. After one further repetition of this process, the combined three crops were recrystallized from aqueous acetone. The desired product (4.5 g.) separated in shining leaflets, m. p. 123–128°. This material is not entirely free of the isomeric 5,7-dibromoketone, but can be used directly in the subsequent reactions, since either dibromoketone gives the same products.

3-Acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic Acid.—The dibromide (3 g.) obtained as described above was dissolved in 75 cc. of pure pyridine and heated under reflux for six and one-half hours. The solution was then diluted with water and allowed to cool and stand overnight. The dark semi-crystalline material which had separated was recrystallized from acetic acid. The resulting crystalline solid was triturated with concentrated aqueous potassium carbonate. Extraction of the mass with ether left the **potassium salt** of the desired acid. (Occasionally the solid dissolved completely in ether, but the potassium salt separated immediately on stirring the ethereal solution.) The salt was crystallized directly from acetic acid and the crude product, m. p. 215–220° (dec.), was recrystallized from absolute alcohol. **3-Acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic acid** (0.5 g.) separated in fine, fluffy, white needles, m. p. 232–233.5° (cor.).

On careful addition of an alcohol solution of the acid to aqueous–alcoholic potassium carbonate, carbon dioxide was evolved and the potassium salt precipitated.

Absorption data (see Fig. 1 in the theoretical part), $\lambda_{\text{max.}} < 230$ mμ; log ϵ_{228} mμ = 3.95 (dioxane + ethanol) (Heilbron, *loc. cit.*, log ϵ_{228} mμ = 3.9 (ethanol)).

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.97; H, 10.08. Found: C, 75.90; H, 10.00.

Ethyl 3-Hydroxy-Δ^5-(6)-*nor*-cholestene-7-carboxylate.—A solution of 1 g. of the above acid in 20 cc. of ethanol containing 0.5 g. of sulfuric acid was heated under reflux for one hundred and twenty hours. After addition of water, the precipitated solid was collected and crystallized from aqueous methanol, from which the ester (650 mg.) separated in needles, m. p. 112–113°; mixed with a sample of "3-hydroxy-7-ethoxy-6-keto-Δ^4-cholestene" prepared according to Heilbron,[1] m. p. 112–113°.

Ethyl 3-Acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylate.—The above ester (0.6 g.) was boiled for three hours with 6 cc. of acetic anhydride. After removal of the excess reagent *in vacuo*, the residue was crystallized from ethanol. The acetoxy ester (0.5 g.) was obtained as fine needles, m. p. 119.5–121°. Mixed with a sample of the substance obtained according to Heilbron by the action of sodium acetate in alcohol on 3-acetoxy-5′,7-dibromo-6-ketocholestane, m. p. 119–120°.

3-Hydroxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic Acid.—One gram of the hydroxy-ester was boiled with aqueous–alcoholic potassium hydroxide (10%, 1:1) for twenty-four hours. The reaction mixture was then poured into iced diluted hydrochloric acid, and the organic product extracted with ether. The residue after removal of the ether was recrystallized from aqueous methanol, from which the hydroxy-acid (300 mg.) separated in fine needles, m. p. 225–226° (cor.) identical with the "3,7-dihydroxy compound" of Heilbron.[1]

$\Delta^{3,5}$-(6)-*nor*-Cholestadiene.—3-Acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic acid (400 mg.) was distilled slowly from a small retort at *ca.* 320° (25 mm.). A yellow oil collected and solidified in the neck of the retort. The distillate was absorbed in ether, the ethereal solution was washed twice with sodium hydroxide solution, once with water and the ether was removed. The residue was crystallized twice from ethanol. $\Delta^{3,5}$-(6)-*nor*-Cholestadiene (250 mg.) separated in splendid needles, m. p. 74–76°; mixed with an authentic sample,[5] m. p. 74–76°.

Summary

The action of basic reagents on 3-acetoxy-5(*or* 5′)-7-dibromo-6-ketocholestane proceeds with the formation, in part, of substances whose skeletal structure is that of (6)-*nor*-cholestane. Thus, either dibromoketone, on boiling with pyridine, is transformed into 3-acetoxy-Δ^5-(6)-*nor*-cholestene-7-carboxylic acid, while the 5′,7-dibromoketone with sodium acetate in ethanol gives the ethyl ester of this acid. The relation between these compounds has been demonstrated, and the carbon skeleton has been shown by degradation to the known hydrocarbon, $\Delta^{3,5}$-(6)-*nor*-cholestadiene.

This formulation is supported by the absorption spectra of the substances. Since the view of previous workers that these substances were α,β-unsaturated ketones is no longer tenable, the compounds do not constitute an exception to the rules correlating the position of the wave length of maximum absorption with the extent of substitution of the carbon–carbon double bond in an α,β-unsaturated carbonyl system.

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