This is possible if the resonance form (b) contributes appreciably to the structure of the boron trifluoride-ester complex, or if the complex acquires the structure of resonance form (b) during condensation. Thus resonance form (b) with the positive charge on the carbonyl carbon may be regarded as the "active" acylating component in acylations.

Experimental

Alkylation of Ethyl Acetoacetate with Isopropyl Acetate.—A solution of 26.0 g. (0.20 mole) of purified ethyl acetoacetate (b. p. 180–181°) and 20.4 g. (0.20 mole) of purified isopropyl acetate (b. p. 87–88°) was chilled in an ice-bath and saturated with boron trifluoride as previously described,[7] 28.0 g. (0.41 mole) of boron trifluoride being absorbed. A mixture of yellow solid and liquid formed, which turned to a clear orange solution on stirring at room temperature for thirty hours. The reaction mixture was hydrolyzed by pouring it into a solution of 80 g. of anhydrous sodium bicarbonate in 500 cc. of water. The hydrolyzed solution was extracted several times with ether and the combined ether solutions dried over "Drierite." The ether was distilled off through a short Widmer column and the residue distilled at atmospheric pressure, the fraction boiling at 201–203° being collected. It was identified as ethyl α-isopropylacetoacetate by hydrolysis to methyl isobutyl ketone as previously described.[8]

The yield of ethyl α-isopropylacetoacetate was 14.4 g. or 42.1% of the theoretical amount.

Summary

1. Ethyl acetoacetate has been alkylated with isopropyl acetate in the presence of boron trifluoride.

2. The mechanism of alkylation and of acylation by means of esters in the presence of acidic reagents is discussed.

DURHAM, NORTH CAROLINA RECEIVED JULY 17, 1940

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[7] Breslow and Hauser, THIS JOURNAL, **62**, 2385 (1940).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON BIOPHYSICAL INSTITUTE]

Photodehydrogenation of Steroids. I. 2,4-Cholestadiene

BY ROBERT P. JACOBSEN AND C. Z. NAWROCKI

An investigation of the formation and properties of certain bimolecular photodehydrogenation products of sterol and bile acid derivatives has been undertaken partly with the hope of learning more about the character of this rather unique group of compounds and partly with the idea of examining them for possible physiological activity.

During the past several years the preparation by photodehydrogenation of a number[1–12] of bisteroids[13] has been reported. In every case the key system which seems to be necessary in order that such photodehydrogenation may occur is a conjugated system of double bonds in Ring B at the 5,7- or 6,8-positions, and, in the former case, the additional requirement of a *trans* orientation[10] of the hydrogen at C_9 with respect to the methyl group at C_{10}. It seemed of particular interest to see whether compounds possessing conjugation in Ring A might undergo similar photodehydrogenation. From preliminary experiments with cholestadiene mixtures rich in 2,4-cholestadiene, this indeed appears to be the case. Although a decision regarding the structure of the hydrocarbon obtained must await further investigation, it seemed desirable in view of the recent appearance of papers by Ando[4] and Tominaga,[11] to make a preliminary report of the investigations which have been undertaken in this Laboratory.

For the photodehydrogenation of steroid dienes

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[1] Windaus and Borgeaud, *Ann.*, **460**, 235 (1928). Inhoffen, *Naturwissenschaften*, **25**, 125 (1937), has tentatively proposed a 7,7'-structure for this substance from ergosterol.

[2] Ando, *Bull. Chem. Soc. Japan*, **14**, 285 (1939).

[3] Windaus and Linsert, *Ann.*, **465**, 148 (1928).

[4] Ando, *Bull. Chem. Soc. Japan*, **14**, 482 (1939).

[5] Windaus and Langer, *Ann.*, **508**, 105 (1933).

[6] Schenck, Buchholz and Wiese, *Ber.*, **69**, 2696 (1936).

[7] Urushibara and Ando, *Bull. Chem. Soc. Japan*, **11**, 802 (1936); **12**, 495 (1937).

[8] Dimroth, *Ber.*, **69**, 1123 (1936).

[9] Wunderlich, *Z. physiol. Chem.*, **241**, 116 (1936).

[10] Haslewood, *Biochem. J.*, **33**, 454 (1939).

[11] Tominaga, *Bull. Chem. Soc. Japan*, **14**, 486 (1939).

[12] Kennedy and Spring, *J. Chem. Soc.*, 250 (1939).

[13] The prefix "bi-" is suggested as an alternative to supplant the term "pinacone" (pinacol in English usage) as applied to this group of photodehydrogenation products. To avoid confusion (see statement of Weizmann, E. Bergmann, and Hirshberg, THIS JOURNAL, **60**, 1532 (1938)) with the bimolecular reduction products of ketones the misnomer "ergopinacol" would become "biergostratrienol." The "Δ^4-cholestenone pinacone" of Windaus, *Ber.*, **39**, 518 (1906), Krekeler, Dissertation, Göttingen, 1937, and of Galinovsky and Bretschneider, *Monatsh.*, **72**, 190 (1938), is probably a true pinacol and its dissimilarity to the aforementioned group of bimolecular photodehydrogenation products is at once apparent on the basis of proposed change in nomenclature. The interesting bimolecular products of the ultraviolet irradiation of α,β-unsaturated steroid ketones [E. Bergmann and Hirshberg, *Nature*, **142**, 1037 (1938); Inhoffen and Huang-Minlon, *Naturwissenschaften*, **27**, 167 (1939); Butenandt and Wolff, *Ber.*, **72**, 1121 (1939)] may possess 4,4'-linkages or may be joined through the oxygen function at C_3. The bimolecular steroid of Petrow and Starling, *J. Chem. Soc.*, 60 (1940), is assumed to have a 6,6'-linkage between molecules.

in the present work, the usual[14] method has been improved by using different sensitizers with the light from tungsten filaments.

In trial runs, ergosterol was irradiated using a sensitizer[15] consisting of a mixture of fluoresceins to give biergostatrienol in improved yield at the rate of 10 g. in forty-eight hours irradiation time. The absorption data for the compound (Fig. 1) and its diacetate are in accord with the observations of Buchholz,[16] regarding the disappearance of the absorption maxima characteristic of ergosterol in the process of formation of the dehydrogenation product, but apparently do not coincide completely with the report by Ando[17] of a faint maximum at 268 mμ. The presence of an inflection at 2500 Å. (Fig. 1) suggests that the long wave length portion of the absorption is contributed to by a component band in the region indicated by the Japanese investigator but no actual maximum was observed.

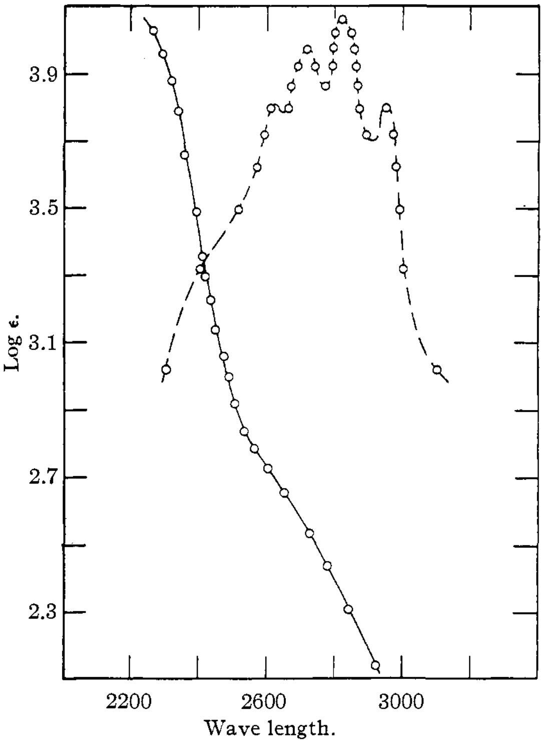

Fig. 1.—-O---O---O-, Ergosterol; -O——O——O-, biergostatrienol.

Dehydroergosterol, in a similar trial reaction using rose bengal as the sensitizer gave biergostatetraenol identical with the material prepared by Windaus and Linsert.[3] The ultraviolet absorption spectrum of this material (Fig. 2) is essentially that described for the diacetate by Ando,[4] and clearly shows[18] the presence of a double conjugated diene system in the photodehydrogenation product.

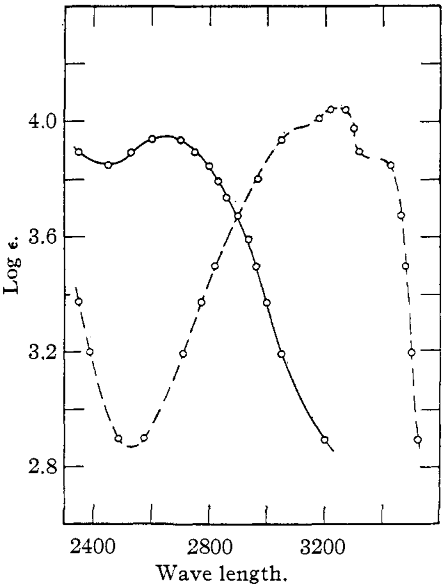

Fig. 2.—-O---O---O-, Dehydroergosterol; -O —O—O-, biergostatetraenol.

The irradiation of impure 2,4-cholestadiene with rose bengal as the sensitizer gives in poor yield a sparingly soluble hydrocarbon which no longer possesses the conjugation (maximum at 2680 Å.) of the starting material but shows (Fig. 3), like biergostatrienol, only general absorption in the ultraviolet region below 2600 Å. As might be expected, the 3,5-isomer, which is probably present in the unpurified starting material, does not interfere in the photodehydrogenation. The hydrocarbon from 2,4-cholestadiene is apparently isomeric with the compound m. p. 269–270° prepared by Tominaga[11] by the photodehydrogenation of 5,7-cholestadiene with eosin in sunlight. By analogy with the proposed 7,7′-structure for this and other photodehydrogenation products of steroid 5,7-dienes, the compound from 2,4-cholestadiene might be expected to possess the corresponding 3,3′-structure with double bonds at the 1,2- and 4,5-posi-

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[14] One or two weeks of exposure to bright sunlight using 0.004–0.01 *M* solutions with eosin as the sensitizer.

[15] A striking specificity of sensitizers in controlling the rate of photodehydrogenation has been observed in this work and the various factors involved are being made the subject of further study.

[16] Buchholz, Dissertation, Göttingen, 1937.

[17] Ando, *Bull. Chem. Soc. Japan*, **13**, 371 (1938); **14**, 285 (1939). Faint maxima at 254 and 268 mμ also reported for bicholestadienol. No curves are given.

[18] Since this report was submitted, Windaus and Roosen-Runge, *Ber.*, **73**, 321 (1940), have published a curve for biergostatetraenyl diacetate.

tions to account for the observed absorption spectrum. This possibility is being investigated.

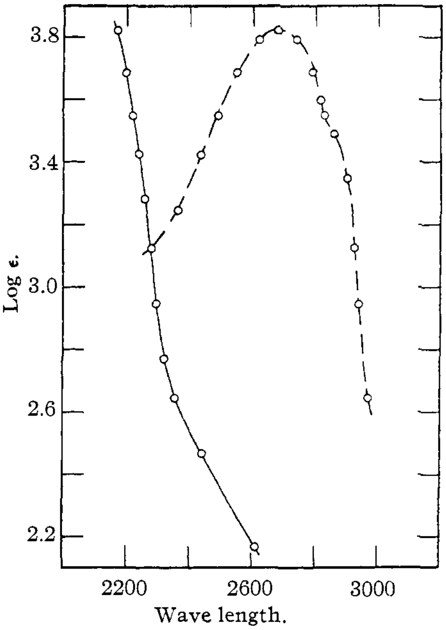

Fig.3.- -O- - -O- - -O-, 2,4-Cholestadiene; -O—O—O-, bicholestadiene.

Experimental Part[19]

Irradiation Apparatus.—The apparatus used for the photosensitized reactions consisted of a long-necked cylindrical 600-cc. flask sealed to a small reflux condenser and carrying gas inlet and outlet tubes. The reaction vessel was suspended in a 4-liter beaker fitted with a constant-level siphon so that the contents could be maintained at 20–30° during the irradiation. Surrounding the beaker was a circle of eight 200-watt tungsten-filament lamps outside which was a cylindrical radiation shield of polished aluminum. The open spaces at the bottom around the bases of the lamps and that at the top around the neck of the reaction flask were likewise fitted with aluminum shields.

Biergostatrienol.—The irradiation flask was charged with 15.6 g. of ergosterol and 16.4 g. of an equimolecular mixture of tetrabromo-, tetraiodo- and tetrachlorotetraiodofluorescein in 500 cc. of benzene and 20 cc. of ethanol. After boiling to remove dissolved oxygen and cooling under nitrogen, the solution was irradiated for forty-eight hours. The resulting thick, gelatinous mass was transferred to a 3-liter flask containing 1500 cc. of ethanol and the mixture was stirred vigorously and warmed on the steam-bath to break up the gel and form fine needles. After cooling, the solid material was collected, washed on the filter with a little warm ethanol and dried *in vacuo* at room temperature to yield 9.5–10 g. (61–64%) of fine, nearly colorless needles. This material crystallized from pyridine–ethanol or benzene–ethanol in long thin needles, m. p. 198–199° dec. The melting point lies one or two degrees higher on more rapid heating in a bath preheated to 190°. The ultraviolet absorption spectrum in dioxane (Fig. 1) or cyclohexanol showed only general absorption below 2900 Å.

Diacetate.—The diacetate prepared by acetylation with acetic anhydride in pyridine and purified by repeated crystallization from chloroform–acetone melted at 201–202° dec. after drying at 55° and 10 mm. over phosphorus pentoxide.

Anal. Calcd. for $C_{60}H_{90}O_4$: C, 82.32; H, 10.36. Found: C, 82.67; H, 10.40.

The ultraviolet absorption spectrum of the diacetate in cyclohexanol was the same as that of the free hydroxy compound.

Biergostatetraenol.—A solution of 2.3 g. of dehydroergosterol (m. p. 143–145°, broken-line curve Fig. 2) and 1.5 g. of rose bengal in 500 cc. of ethanol freed of dissolved oxygen and irradiated for thirty hours produced 1.16 g. (50%) of colorless needles. Crystallization from chloroform–methanol gave thin needles, m. p. 194–195° dec. The ultraviolet absorption spectrum of this material in dioxane (Fig. 2) showed a well defined peak at 2650 Å. (log ε 3.95). For analysis a portion of the material was acetylated in pyridine and the product was crystallized from chloroform–methanol and dried at 120° and 12 mm. over phosphorus pentoxide.

Anal. Calcd. for $C_{60}H_{86}O_4$: C, 82.70; H, 9.95. Found: C, 82.24; H, 9.94.

Bicholestadiene.—A solution of 2.33 g. of impure 2,4-cholestadiene (m. p. 62–65°, $[\alpha]^{26}_{D}$ + 132°), prepared according to the method of Skau and W. Bergmann,[20] and 0.9 g. of rose bengal in 200 cc. of ethanol and 25 cc. of benzene was refluxed and then cooled under nitrogen. On irradiation the dye was slowly decolorized and crystalline material began to separate. After fifty hours the solid was collected and crystallized from ether to give 95 mg. of colorless needles, m. p. 197–201° dec. On further crystallization from ether the material (56 mg., 2.4%) melted at 203–204° dec. In the irradiation of larger quantities the yield of pure material in several experiments was 1.1–2.4%. The ultraviolet absorption spectrum in cyclohexane showed only general absorption below 2600 Å. The sensitized irradiation of practically pure 2,4-cholestadiene (0.78 g., m. p. 67.4–68.2°, $[\alpha]^{27}_{D}$ + 161°, broken-line curve Fig. 3) gave 7 mg. (0.9%) of colorless needles, m. p. 200.5–203° dec. A single recrystallization from ether gave pure material, m. p. 203–204° dec.

Anal. Calcd. for $C_{54}H_{86}$: C, 88.21; H, 11.79. Found: C, 88.56; H, 11.65.

Summary

An improved procedure for the photodehydrogenation of steroid dienes is described. The production in poor yield of a bicholestadiene by the sensitized irradiation of a cholestadiene mixture rich in the 2,4-isomer is reported. The structures and possible physiological activity of steroid photodehydrogenation products are being investigated.

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[19] All melting points are corrected. Analyses by the Arlington Laboratories.

[20] Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).