with 50 ml. of water and extracted with three 20-ml. portions of ether. The extracts were washed with 50 ml. of 5% $NaHCO_3$, 50 ml. of water and dried. Removal of the solvent at reduced pressure left a crystalline residue which was recrystallized from methanol to yield 81 mg. (84.5%) of B-norcholesterol, m.p. 113.5–115.0°, $[\alpha]^{22}D$ −89.3° ($CHCl_3$).

A solution of 147 mg. (0.38 mmole) of the ether and 19 mg. of *p*-toluenesulfonic acid in 15 ml. of anhydrous methanol was refluxed for 4 hours and processed as above. Evaporation of the ether gave a pale-yellow oil which was crystallized from ether–methanol (1:1) to yield 138 mg. of B-norcholesteryl methyl ether, m.p. 51.8–53.2°. A further recrystallization yielded 91 mg. (62%) of material melting from 53.6–54.5° and which did not depress an authentic sample of B-norcholesteryl methyl ether. The infrared spectra of the samples were identical.

Rate Measurements. (a) B-Norcholesteryl Tosylate.—Due to the solubility of the tosylate, a solution of the material in anhydrous acetic acid was made directly. This solution was approximately 0.01 *M*. The solution was placed in a bath at 50 ± 0.05°, aliquots (10 ml.) were withdrawn at intervals and immediately cooled in an ice-bath. Titrations were conducted with 0.0554 *M* NaOAc in anhydrous acetic acid using brom phenol blue as the indicator. Infinity titer taken indicated an initial concentration of 0.0104 *M*. The results from two runs gave the following values for the rate constant: 4.44×10^{-3} min.$^{-1}$ ($\pm 0.07 \times 10^{-3}$) and 4.58×10^{-3} min.$^{-1}$ ($\pm 0.18 \times 10^{-3}$).

(b) **Cholesteryl Tosylate.**—The experiment was performed as described by Winstein and Adams.[24] A value for the rate constant of 7.9×10^{-3} min.$^{-1}$ was reported by these workers and in the present work a value of 7.75×10^{-3} min.$^{-1}$ was found.

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[CONTRIBUTION FROM CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. III. A Selective Rearrangement of Steroid Polyenes[1]

BY G. D. LAUBACH, E. C. SCHREIBER, E. J. AGNELLO AND K. J. BRUNINGS

RECEIVED APRIL 5, 1956

A rearrangement of sterol 5,7-dienes to isomeric 6,8(14)-dienes in the presence of anhydrous sulfur dioxide and pyridine has been discovered and applied to the preparation of 6,8(14),9(11),22-ergostatetraenol acetate, a useful intermediate for corticosteroid synthesis.

In the course of exploratory research directed toward new routes for corticosteroid synthesis,[2] a sulfur dioxide catalyzed rearrangement of steroid 5,7-dienes has been discovered. The rearrangement was first encountered when it was observed that ergosterol acetate (I) in the presence of liquid sulfur dioxide and pyridine had reacted to form in 70% yield a product II isomeric with starting material. The ultraviolet absorption spectrum of II was most consistent with its formulation as a 6,8(14)-diene, but the physical constants were not identical to those subsequently reported by Barton and Bruun[3] for 6,8(14),22-ergostatrienol acetate prepared by another method. Hydrogenation studies, however, confirmed the correctness of this formulation. That the product II had not undergone skeletal change was readily demonstrated by catalytic hydrogenation over platinum in ethyl acetate solution to 8(14)-ergostenol acetate (III), identical to an authentic specimen prepared by the hydrogenation of ergosterol acetate in acidic solution.[4] Since the hydrogenation was carried out under conditions known to be unfavorable to the migration of nuclear double bonds,[5] the isolation of III suggested further that the product II was a double bond isomer of ergosterol in which one of the centers of unsaturation was at the 8(14)-position. Further hydrogenation data supporting the latter conclusion were obtained by catalytic hydrogenation of II over a mild and selective Raney nickel catalyst.[6,7] The product IV resulting from the absorption of one molar equivalent of hydrogen was a dienol acetate, shown to be identical to a sample of 8(14),22-ergostadienol acetate prepared by another procedure.[8] A further result of the hydrogenation experiments was the demonstration of the 5α (allo) configuration of the AB ring juncture, which subsequently proved to be the characteristic steric result of sulfur dioxide–pyridine rearrangement of 5,7-dienes.

Rearrangement of ergosterol with strong acid has been long known.[4,9] However, no rigorously pure substance with the 6,8(14)-structure II was isolated from the complex reaction mixtures by the early workers.[4,9a] Repetition of the preparation in this Laboratory was carried out in order to confirm the non-identity of II with the 8,14,22- and 7,14,22-isomerides, and in the course of the fractionation no product identical to II was isolated. Work with the classical acid rearrangement procedures clearly demonstrated the superior specificity of the sulfur dioxide method.

The product obtained when the sulfur dioxide–pyridine rearrangement was carried out using the 9(11)-dehydro analog of I (V) was shown by analysis to be a new isomer of dehydroergosterol acetate, which in analogy to the simpler case was formulated as the 6,8(14),9(11),22-tetraene (VI).

Consistent with the formulation of VI as a re-

(1) Presented before the Division of Organic Chemistry, 124th Meeting of the American Chemical Society, September, 1953.

(2) G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, THIS JOURNAL, **75**, 1514 (1953).

(3) D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 2728 (1951).

(4) F. Reindel, E. Walter and E. Rauch, *Ann.*, **452**, 34 (1927).

(5) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 3rd Ed., 1949, p. 240.

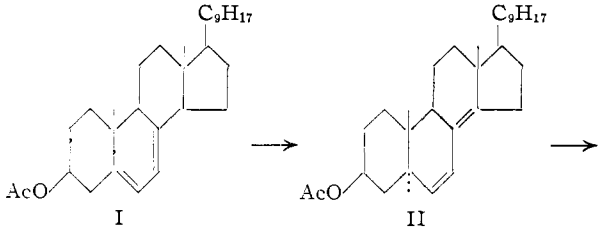
(6) (a) G. D. Laubach and K. J. Brunings, THIS JOURNAL, **74**, 705 (1952); (b) W. Ruyle, E. Chamberlin, J. Chemerda, G. Sita, L. Aliminosa and R. Erickson, *ibid.*, **74**, 5929 (1952).

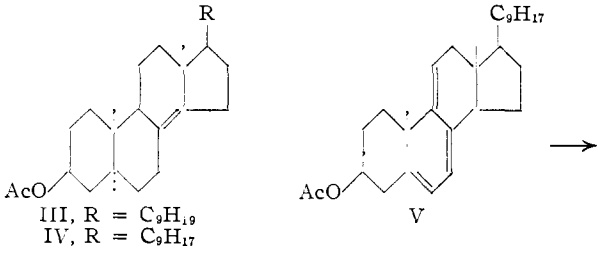
(7) Selective hydrogenation of the 6,7-double bond of 6,8(14)-diene systems in other compounds with Raney nickel are recorded: J. Cahill, N. Wolff and E. Wallis, *J. Org. Chem.*, **18**, 720 (1953); reference 10b.

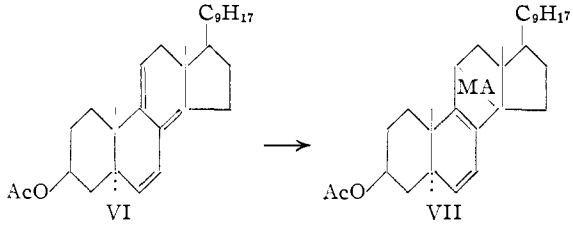
(8) W. Nes and E. Mosettig, *J. Org. Chem.*, **18**, 276 (1953).

(9) (a) A. Windaus, K. Dithmar, H. Murke and F. Suckfull, *Ann.*, **488**, 91 (1931); (b) D. H. R. Barton, *J. Chem. Soc.*, 512 (1946); D. H. R. Barton and C. Brooks, *ibid.*, 257 (1951).

arranged nuclear triene, catalytic hydrogenation over platinum catalyst (3 molar equivalents of hydrogen) led to 8(14)-ergostenol acetate (III). However, confirmation of the proposed cross-conjugated structure could not be derived from selective hydrogenation studies or from the ultraviolet spectral data.[10]







Confirmatory evidence supporting the proposed structure for VI was obtained in several ways.

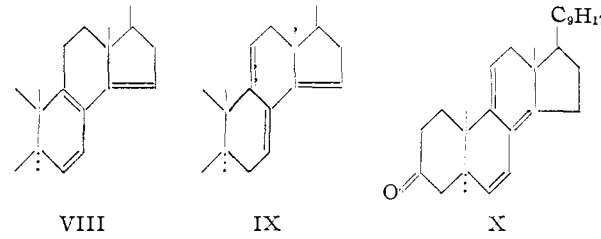
(1) Reaction with maleic anhydride yielded 71% of crystalline adduct VII diagnostic for a cisoid diene.[9b] The ultraviolet spectrum of the product, λ_{max}^{ether} 275 mμ (log ε 3.65) was precisely that expected for the 6,8-diene structure which would be derived from a 6,8(14),9(11) precursor but was different from the calculated absorption maxima of the 7,14- or the 8(14),9(11)-dienes which would be derived from the alternative structures VIII and IX, respectively.[11,12]

(2) Saponification and oxidation afforded 36% yield of a crystalline non-conjugated ketone, the unchanged ultraviolet absorption of which demonstrated that migration of the original 5,6-double bond away from the A-ring of dehydroergosterol had, in fact, occurred during the sulfur dioxide–pyridine treatment.

(10) Subsequent studies have re-emphasized the difficulties associated with attempted spectra–structure correlations of cross-conjugated unsaturated systems: (a) L. F. Fieser, K. Nakanishi and W. Huang, THIS JOURNAL, **75**, 4719 (1953). (b) G. D. Laubach, E. J. Agnello, E. C. Schreiber and K. J. Brunings, *ibid.*, **78**, 4746 (1956), paper IV of this series.

(11) L. F. Fieser and M. Fieser, ref. 5, p. 184–188.

(12) (a) Subsequent studies[10b] resulted in the actual preparation of the 7,9(11),14-trienic system (IX), which exhibited λ_{max}^{EtOH} 227 mμ (log ε 4.04), 235 mμ (log ε 3.97), 268 mμ (log ε 3.96) and its maleic anhydride adduct which displayed λ_{max}^{EtOH} 274 mμ (log ε 3.59), the latter absorption appearing at a considerably lower wave length than that calculated (295 mμ).[11] (b) Recently, R. P. Graber, *et al.*, *Chem. and Ind.*, 57 (1956), reported the synthesis of another 8(14),9(11)-diene with ultraviolet absorption spectrum (λmax 271 mμ, log ε 3.66) similar to that of the maleic anhydride adduct of IX.



That the scope of the rearrangement is limited was shown by the failure of such miscellaneous unsaturated steroids as 8(14)-ergostenol acetate (III), 7,9(11),22-ergostatrienol acetate[13,14] and 6,8(14),22-ergostatrienol acetate (II) (itself a product of sulfur dioxide rearrangement) to undergo bond migration under conditions entirely adequate for complete isomerization of ergosterol. The fact that these substances isomerize in the presence of strong acid is indicative of the fundamental difference between sulfur dioxide–pyridine and acid-catalyzed rearrangements. Further evidence arguing against involvement of proton catalysis may be cited: (a) neither boron fluoride, a strong Lewis acid, nor pyridine hydrochloride promoted rearrangement of ergosterol. (b) Best results were obtained when the sulfur dioxide isomerization was carried out in a basic (pyridine) medium. If pyridine was not present, a product similar to that obtained by acid treatment resulted. (c) Dehydroergosterol acetate was charred and underwent skeletal rearrangement under strongly acidic conditions,[15] and ergosterol acetate was isomerized non-specifically to BC and CD dienes.[16] Further experimental data cogent to any proposed mechanism for the rearrangement are the observations that tertiary amines failed to promote the reaction and that hydroquinone did not inhibit the reaction.[17]

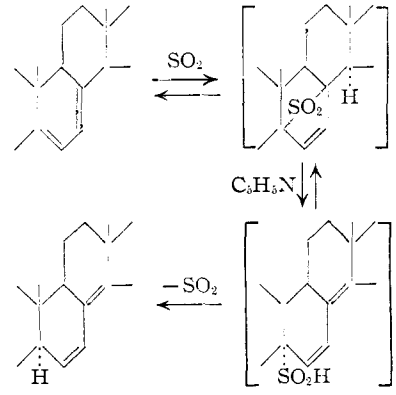
(13) W. Ruyle, T. Jacob, J. Chemerda, E. Chamberlin, D. Rosenburg, G. Sita, R. Erickson, L. Aliminosa and M. Tishler, THIS JOURNAL, **75**, 2604 (1953).

(14) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 219 (1949).

(15) W. Nes and E. Mosettig, THIS JOURNAL, **75**, 2787 (1953).

(16) An independent study of the reaction of unsaturated steroids with liquid sulfur dioxide under *non-anhydrous, non-basic* conditions has recently been published (A. Hudgell, J. Turnbull and W. Wilson, *J. Chem. Soc.*, 814 (1954)). These workers showed that, under the acidic conditions that obtained, excellent yields of 8,14,22-ergostatrienol acetate could be obtained from ergosterol acetate and that sterols with isolated double bonds, *i.e.*, 7,22-ergostadienol acetate, could be readily isomerized.

(17) One possible interpretation of the observed result is shown below, in which the well-known dienophilic properties of sulfur dioxide are suggested to rationalize the apparent inertness of non-homocyclic (and less reactive homocyclic) dienes to rearrangement with the reagent.



The obvious utility of C-ring dienes as precursors in 11-oxy steroid synthesis[2] led to the investigation of routes to the isolated C-ring diene structure, which had not been reported previously in the steroid literature.[12b] Attempted rearrangement of the 7,9(11)-diene system with sulfur dioxide has been cited as unsuccessful. An alternate attack, involving 9(11)-dehydrogenation of 8(14)-monounsaturated steroids III (in one case stabilized as the 7,15-maleic anhydride adduct) with mercuric acetate or selenium dioxide, was also unsuccessful. Attempts to selectively hydrogenate the 6-double bond of the tetraene (VI) with Raney nickel resulted in a complex product, in which the typical 7,9(11)-diene chromophore was observed.

Experimental[18]

6,8(14),22-Ergostatrienol Acetate (II).—To a solution of 4.0 g. of ergosterol acetate (m.p. 171.0–175.0°) in 20 ml. of benzene in a small glass bomb tube was added 0.200 g. of hydroquinone, dissolved in 5 ml. of pyridine. The tube was cooled in a Dry Ice-bath, and 20 ml. of anhydrous sulfur dioxide was added by condensation. The tube was sealed and then heated to 100° for 16.5 hr.

The clear red reaction mixture became almost colorless on removal of the sulfur dioxide under vacuum. Concentration to dryness and trituration with small portions of methanol afforded 2.82 g. (70%) of small yellow prisms, m.p. 115.5–117.0°, $[\alpha]^{25}D$ −91.6° ($CHCl_3$). An analytical sample was obtained as well-formed needles on recrystallization from chloroform–methanol, then ethyl acetate–methanol; m.p. 119.0–120.6°, $[\alpha]^{25}D$ −96.2° ($CHCl_3$), λ_{max}^{ether} 252 mμ (log ε 4.37). *Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.14; H, 10.57. Found: C, 82.34; H, 10.79.

The constants reported by Barton[3] were m.p. 113–114°, $[\alpha]^{26}D$ −107.0° ($CHCl_3$), λ_{max}^{ether} 253 mμ (log ε 4.23).

6,8(14),22-Ergostatrienol.—A solution of 0.300 g. of II and 0.40 g. of potassium hydroxide in 5 ml. of methanol and 0.5 ml. of dioxane was refluxed for 1 hr. On cooling, the product separated as long silky needles, m.p. 117.0–119.8°. Several recrystallizations from methanol afforded a purified sample, m.p. 123.0–124.2°, $[\alpha]^{25}D$ −101° ($CHCl_3$).

Barton[3] reported constants, m.p. 113–114°, $[\alpha]^{25}D$ −115° ($CHCl_3$).

Attempted Maleic Anhydride Adduct Formation with II.—A solution of 0.300 g. of II, m.p. 119.0–120.6°, $[\alpha]^{25}D$ −96.2° ($CHCl_3$) and 0.60 g. of maleic anhydride in 5 ml. of benzene was refluxed for 7 hr. Evaporation *in vacuo* followed by extraction with petroleum ether (b.p. 30–60°) yielded from the filtrate 0.280 g. (93%) of yellowish crystals, m.p. 111.8–116.0°. Recrystallization from ethyl acetate–methanol afforded 0.140 g. of starting material with unchanged physical constants, m.p. 118.0–120.0°, $[\alpha]^{25}D$ −97.7° ($CHCl_3$).

8(14)-Ergostenol Acetate (III).—A solution of 0.220 g. (0.0005 mole) of II, m.p. 119.0–120.6°, in 5 ml. of ethyl acetate was stirred under hydrogen at room temperature and atmospheric pressure over platinum catalyst obtained by the reduction of 0.050 g. of platinum oxide. In 10 minutes, 105% of two moles of hydrogen had been absorbed, and hydrogen uptake abruptly ceased. Evaporation of the filtered reaction mixture *in vacuo* followed by recrystallization of the residue from methanol yielded 0.175 g. (80%) of III as colorless glistening plates, m.p. 109.8–110.0°, $[\alpha]^{25}D$ +1.7° ($CHCl_3$), melting point undepressed on admixture with an authentic sample.

6,8(14),9(11),22-Ergostatetraenol Acetate (VI).—A solution of 4.1 g. of dehydroergosterol acetate (V),[19] $[\alpha]^{25}D$ +205° ($CHCl_3$), in 20 ml. of anhydrous benzene was added to 5 ml. of an anhydrous pyridine solution of 0.200 g. of hydroquinone in a small glass bomb tube. To this cooled mixture was added 20 ml. of anhydrous sulfur dioxide by condensation, the tube sealed and then heated to 100° for 16.5 hr. The deep red reaction mixture was concentrated to dryness *in vacuo*, affording crude VI as a light yellow solid, m.p. 142–146°, yield 3.01 g. (73.5%). Two recrystallizations from ethyl acetate–methanol afforded 1.69 g. (56% recovery) of nearly pure product, m.p. 146.8–150.0°, $[\alpha]^{25}D$ −74° ($CHCl_3$).

An analytical sample was obtained by several further recrystallizations of similar material from ethyl acetate–methanol and chloroform–methanol; m.p. 149.0–151.0°, $[\alpha]^{25}D$ −94° ($CHCl_3$), λ_{max}^{ether} 287.5 mμ (log ε 3.82), 232.5 mμ (log ε 4.25). *Anal.* Calcd. for $C_{30}H_{44}O_2$: C, 82.52; H, 10.16. Found: C, 82.39; H, 10.26.

Catalytic Hydrogenation of 6,8(14),9(11),22-Ergostatetraenol Acetate (VI). (a) **With Platinum Catalyst.**—A solution of 0.300 g. (0.000686 mole) of VI in 10 ml. of ethyl acetate and 1 ml. of chloroform was hydrogenated over 0.050 g. of prereduced platinum oxide catalyst. During a 50-minute period, 53 ml. (107% of 3 equivalents) of hydrogen was absorbed and hydrogen uptake ceased. The catalyst was removed by filtration through Filter-Cel and the filtrate concentrated to a colorless oil which crystallized spontaneously. The crude product amounted to 0.245 g. (80.5% of colorless platelets, m.p. 106.8–108.0°. Recrystallization from ethyl acetate afforded thin rectangular platelets of 8(14)-ergostenol acetate (III), m.p. 109.8–110.5°, $[\alpha]^{25}D$ +4° ($CHCl_3$).

The melting point on admixture with an authentic sample, prepared by the hydrogenation of ergosterol acetate over platinum in acetic acid or from the platinum hydrogenation of IV, m.p. 108.5–109.0°, was not depressed.

(b) **With Raney Nickel Catalyst.**—A solution of 0.219 g. (0.0005 mole) of VI, $[\alpha]^{25}D$ −78° ($CHCl_3$), was hydrogenated over 0.5 g. of prereduced W-2 Raney nickel catalyst[20] in 7 ml. of dioxane. In a 3-hr. period, 13.7 ml. (110% of 1 mole) of hydrogen had been absorbed and hydrogen uptake ceased. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to a mass of colorless platelets, yield 0.205 g., λ_{max}^{ether} 242.5 mμ (log ε 4.03) and 235.2 mμ (log ε 4.00) equivalent to 56% 7,9(11)-diene chromophore.

6,8(14),9(11),22-Ergostatetraenol Acetate Maleic Anhydride Adduct (VII).—A solution of 5.0 g. of VI and 4.0 g. of freshly sublimed maleic anhydride in 50 ml. of dry toluene was refluxed for 4 hr. The reaction mixture was then concentrated *in vacuo* and triturated with 150 ml. of cold petroleum ether and 30 ml. of methanol in small portions. The white residue amounted to 4.37 g. (71%), m.p. 173.2–176.4°, and on recrystallization from ether–petroleum ether afforded pure VII, m.p. 174.8–176.4°, $[\alpha]^{25}D$ +9° ($CHCl_3$), λ_{max}^{ether} 275 mμ (log ε 3.65). *Anal.* Calcd. for $C_{34}H_{46}O_5$: C, 76.37; H, 8.67. Found: C, 76.47; H, 8.79.

Tetrahydromaleic Anhydride Adduct.—To 0.100 g. of platinum oxide, prereduced in 5 ml. of glacial acetic acid, was added 0.200 g. of the maleic anhydride adduct VII in 10 ml. of acetic acid. In 40 minutes, two moles of hydrogen was absorbed and hydrogen uptake then ceased. Filtration and concentration yielded a white solid, m.p. 171.4–172.0°, which was shown to be the desired product by lack of ultraviolet absorption.

6,8(14),9(11),22-Ergostatetraen-3-one (X).—6,8(14),9(11),22-Ergostatetraenol (m.p. 129.0–131.8°, $[\alpha]^{25}D$ −93.3° ($CHCl_3$), prepared by saponification of VI in potassium hydroxide–dioxane–water) 10 g. was dissolved in 300 ml. of redistilled toluene and 50 ml. of cyclohexanone. The solution was partly distilled to remove water and then refluxed for 30 minutes with addition of 10 g. of aluminum isopropoxide in 250 ml. of toluene. The reaction mixture was cooled in ice and decomposed with 13.5 g. of Rochelle salts in 350 ml. of water. The residue, after steam distillation of the organic solvents, was extracted with ether, washed with water and concentrated *in vacuo* to 8 g. of oily solid.

Chromatography over 250 g. of alumina yielded in the benzene–petroleum ether eluates 3.58 g. (36%) of yellow solid which, after recrystallization, melted at 126.4–128.8°. An analytical sample obtained from ethanol had constants, m.p. 133.0–136.8°, $[\alpha]^{25}D$ −89.9° ($CHCl_3$), λ_{max}^{ether} 287.5 mμ (log ε 4.01), 231 mμ (log ε 4.24). *Anal.* Calcd. for $C_{28}H_{40}O$: C, 85.68; H, 10.27. Found: C, 85.62; H, 10.28. Infrared λ_{max} 5.9 μ.

Attempted Sulfur Dioxide Rearrangements. (a) **7,9(11),-22-Ergostatrienol Acetate** (**Ergosterol-D Acetate**).—Ergosterol-D acetate, m.p. 168.5–174.0°, $[\alpha]^{25}D$ +22.4° ($CHCl_3$), prepared by the method of Barton,[14] 0.35 g., was dissolved in 2 ml. of benzene and treated with 0.5 ml. of pyridine, 0.020 g. of hydroquinone and 2 ml. of sulfur dioxide in a

(18) Melting points are uncorrected.

(19) W. Bergmann and P. G. Stevens, *J. Org. Chem.*, **13**, 10 (1948).

(20) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

sealed tube at 100° for 16 hr. Concentration *in vacuo*, trituration and recrystallization from ethyl acetate–methanol afforded 0.16 g. (46%) of recovered starting material, m.p. 170.0–173.2°.

(b) **8(14)-Ergostenol Acetate** (III).—One gram of III was treated for 16 hr. in a medium consisting of 0.050 g. of hydroquinone, 1.25 ml. of pyridine, 5 ml. of benzene and 5 ml. of sulfur dioxide. Concentration of the reaction mixture yielded 0.92 g. of yellow crystals, m.p. 109.2–110.0°, undepressed on admixture with starting material.

Attempted Basic and Acidic Rearrangements. (a) **Sulfur Dioxide in Non-basic Medium.**—To a suspension of 1 g. of ergosterol in a small bomb tube in 5 ml. of chloroform containing 0.050 g. of propyl gallate as a stabilizer was added 5 ml. of liquid sulfur dioxide by condensation at −70° without special precautions to exclude moisture. The reaction mixture was heated to 90° for 2 hr., then allowed to stand at room temperature overnight. The dark yellow solution was evaporated *in vacuo* and the green tarry residue was triturated with 15 ml. of methanol to yield 0.58 g. of white granular residue m.p. 135–136°. Recrystallization from ether–methanol yielded 0.225 g., m.p. 137.5–139.5°, $[\alpha]^{25}D$ −39.9° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 250.5 mμ (log ε 4.17).

(b) **Hydrochloric Acid.**—A solution of 0.5 g. of dehydroergosterol acetate (V), m.p. 148.2–151.0°, was dissolved in 15 ml. of dry chloroform and treated with gaseous hydrochloric acid for 15 minutes at 0°. Concentration afforded a black tar, which was not brought to crystallization by trituration or chromatography.

(c) **Boron Fluoride Etherate.**—A solution of 0.50 g. of V in 10 ml. of ether containing 0.5 ml. of boron fluoride etherate was refluxed for 13 hr. Extraction and concentration afforded 0.47 g. of impure starting material, $[\alpha]^{25}D$ +94° ($CHCl_3$), λ_{max}^{ether} 326 mμ (log ε 3.86).

(d) **Pyridine.**—A solution of 1.0 g. of V in 5 ml. of pyridine and 5 ml. of benzene containing 0.1 g. of hydroquinone was refluxed for 20 hr. Concentration *in vacuo* followed by trituration with cold methanol yielded 0.920 g. of starting material, $[\alpha]^{25}D$ +142.5° ($CHCl_3$).

(e) **Pyridine Hydrochloride.**—Addition of 0.5 g. of pyridine hydrochloride to the reaction mixture (d) resulted in an identical product, 0.925 g., $[\alpha]^{25}D$ +144.5° ($CHCl_3$).

Attempted Dehydrogenation of 8(14)-Ergostenol Acetate (III).—A solution of 3.25 g. of mercuric acetate and 2.0 g. of III in 50 ml. of glacial acetic acid and 25 ml. of chloroform was stirred for 1.5 hr. in a closed flask without evidence of reaction. The solution was then refluxed for 20 hr., the precipitated mercury salts filtered off and the black filtrate concentrated to dryness *in vacuo*, weight 1.78 g., m.p. 100–105°. Recrystallization from methanol afforded 1.0 g. (50% recovery) of pure starting material, m.p. 110–111°, melting point not depressed on admixture with an authentic sample.

Attempted Dehydrogenation of 7,14,22-Ergostatrienol Acetate 7,14-Maleic Anhydride Adduct.—7,14,22-Ergostatrienol acetate, m.p. 131.0–132.2°, $[\alpha]^{25}D$ −17.6° ($CHCl_3$), was prepared in 29% yield by the method of Windaus.[9a] Reaction with maleic anhydride afforded the 7,14-adduct, m.p. 191.0–195.2°.

A solution of 0.300 g. of the adduct and 0.49 g. of mercuric acetate in 3.75 ml. of chloroform and 7.5 ml. of glacial acetic acid was stirred for 19 hr. without evidence of reaction. The reaction mixture was evacuated to dryness, extracted with benzene and reconstituted in 25 ml. of dioxane containing 0.30 g. of freshly sublimed selenium dioxide. The mixture was heated at reflux temperature for 70 minutes without evidence of reaction.

BROOKLYN 6, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. IV. Synthesis of 11-Oxygenated Steroids from Ergosterol

BY G. D. LAUBACH, E. C. SCHREIBER, E. J. AGNELLO AND K. J. BRUNINGS

RECEIVED APRIL 5, 1956

A new route for the synthesis of 11-ketoergostenol from ergosterol involving 11,14-epidioxide and ketol intermediates has been developed.

The discovery of a selective rearrangement of steroid polyenes[1] made available from simple sterols a new type of C-ring unsaturated intermediate which appeared to be functionally adaptable to corticosteroid synthesis. Like the 7,9(11)-diene precursors which have been successfully transformed to 11-oxygenated derivatives in the bile acid, sterol and genin series,[2,3] the trienic intermediates from the rearrangement reaction possess a double bond at the 9(11)-position potentially suitable for the introduction of the 11-oxygen function. However, the unique structural feature of the 6,8(14),9(11)-triene I on which the present work is based is the presence in the C-ring of a homoannular diene system. Such steroidal diene systems are known to undergo photochemical 1,4-addition of molecular oxygen[4] under mild conditions with yield and a degree of facility that has been rarely observed in non-steroid series. The photoöxidation reaction has already been made the basis of an efficient preparation of a 7,9(11)-intermediate for cortisone synthesis.[5] The goal of the present work was to explore the possibility of using the photoöxidation reaction applied in the C-ring as a means of actually introducing the 11-oxygen function.

The C-Ring Epidioxide and Derived Diols.—The classical photoperoxidation reaction as applied to sterol dienes is in general carried out by lengthy irradiation of dilute alcoholic solutions of the diene and a photosensitizing dye with visible light. The earliest attempts to prepare the C-ring peroxide from I by such methods resulted in disappointing yields, a result in harmony with the distinct instability which was later demonstrated to be the most salient characteristic of the desired product. Studies directed to the systematic variation of the several parameters of the photoperoxidation reaction met with only moderate success,

(1) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, THIS JOURNAL, **78**, 4743 (1956).

(2) C. Djerassi, *Vitamins and Hormones*, **11**, 205 (1953).

(3) G. Rosenkranz and F. Sondheimer, *Fortschritte Chem. Org. Naturstoffe*, **10**, 274 (1953).

(4) W. Bergmann and M. J. McLean, *Chem. Revs.*, **28**, 367 (1941).

(5) P. Bladon, R. B. Clayton, C. W. Greenhalgh, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. Silverstone, G. W. Wood and G. F. Woods, *J. Chem. Soc.*, 4883 (1952); P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell and G. F. Woods, *Chem. and Ind.*, 945 (1953).