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THE ISOMERIZATION OF $\Delta^{7,22}$-ERGOSTADIENOL WITH COPPER CHROMIUM OXIDE

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Nearly twenty-five years ago Reindel and Walter (1) discovered that $\Delta^{5,7,22}$-ergostatrienyl acetate (Ib, ergosteryl acetate) absorbed two moles of hydrogen when reduced in ethereal solution, with platinum black as catalyst, to give $\Delta^{8(14)}$-ergostenyl acetate (Vb, α-ergostenyl acetate). Simultaneously with the saturation of the 5,6 and 22,23 double bonds a shift of the double bond from 7,8 to 8,14 took place. The isomerization has also been effected (2) starting with Δ^{7}-ergostenol (VIa, γ-ergostenol). Despite the more recent and rather extensive investigations of this subject, notably by Wieland and Benend (3) and by Barton and co-workers (4, 5, 6), the rearrangement of the nuclear double bond has not been accomplished without hydrogenation of the side chain double bond. Indeed, the expected product, namely $\Delta^{8(14),22}$-ergostadienol (IIIa, β-dihydroergosterol), has not been obtained in a pure state by any isomerization procedure. Heilbron and co-workers (7) and Dithmar and Achtermann (8) reported its preparation by isomerization with dry hydrogen chloride, but Barton and co-workers (6) have shown that under these conditions the product obtained is an inseparable equimolecular mixture containing the further isomerized compound, $\Delta^{14,22}$-ergostadienol.

We have been able to obtain $\Delta^{8(14),22}$-ergostadienol (IIIa) in a 54% yield by direct isomerization of $\Delta^{7,22}$-ergostadienol[1] (IIa, α-dihydroergosterol) using a copper chromiun oxide catalyst (10) in the presence of hydrogen. The compound was accompanied by a crystalline by-product which probably has a 3-α-hydroxyl group. The complete structure of this latter material is under investigation. The structure of IIIa was indicated by its hydrogenation to $\Delta^{8(14)}$-ergostenol (Va) under conditions which do not normally lead to isomerization, and by the agreement of its molecular rotation with the calculated value.[2] While this work was in progress, Laubach and Brunings (9c) reported the preparation of $\Delta^{8(14),22}$-ergostadienyl acetate (IIIb) by 1,2 addition of hydrogen to $\Delta^{6,8(14),22}$-ergostatrienyl acetate (ergosteryl-B_2 acetate) using Raney nickel in dioxane. The acetate (IIIb) of our compound, prepared with acetic anhydride and pyridine at room temperature, proved to be identical with a sample kindly supplied by by Dr. G. D. Laubach of Chas. Pfizer and Company, Inc.

We have also isolated $\Delta^{8(14),22}$-ergostadienol (IIIa) in a 17% yield from the mixture obtained in the hydrogenation of ergosterol (Ia) with platinum oxide in

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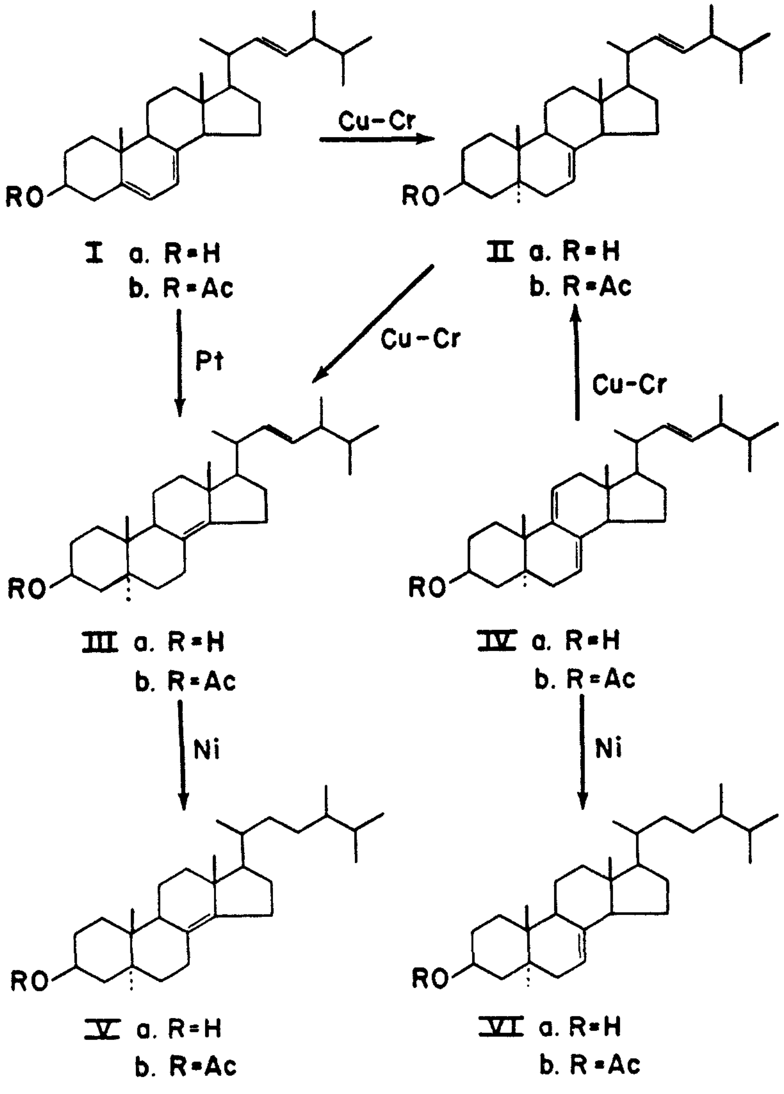
[1] Hydrogenation of ergosterol (Ia) or its acetate (Ib) leads to the corresponding derivative of $\Delta^{7,22}$-ergostadienol (IIa or IIb) in nearly quantitative yields using Rupe nickel (9a) or Raney nickel (9b, 9c).

[2] Using the molecular rotation of +44° for $\Delta^{8(14)}$-ergostenol (11) and −103° for the contribution of the Δ^{22}-bond (6), the calculated value is $[M]_D$ −59°, or $[\alpha]_D$ −14.7°. Our experimental value for $[\alpha]_D$ is −14°.

ethyl acetate. This corroborates the findings of Stavely and Bollenback (12) who have similarly isomerized Δ^7-cholestenyl acetate with platinum in ethyl acetate.



REACTION CHART

Cu-Cr = copper chromium oxide
Pt = Adams platinum oxide
Ni = Raney nickel

It has been assumed by some investigators[3] that platinum under these conditions would not cause bond migration. A survey of the literature indicates that

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[3] See references 6, 5, and 3 as well as L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd edition, Reinhold Publishing Corporation, New York, N. Y., 1949, page 240.

Raney nickel and Rupe nickel are the only catalysts that have been used without inducing isomerization at room temperature and atmospheric pressure.[4] At elevated temperatures and pressures, as shown by Bladon and co-workers (13), even Raney nickel will cause the Δ^7-bond to migrate.

In an effort to prepare $\Delta^{9(11),22}$-ergostadienol, we studied the effect of copper chromium oxide on the hydrogenation of $\Delta^{7,9(11),22}$-ergostratrienol (IVa, ergosterol-D). We found, however, that the reaction mixture consisted chiefly of $\Delta^{7,22}$-ergostadienol (IIa). A similar hydrogenation of ergosterol (Ia) resulted in a 60–70% yield of IIa.

When we reduced $\Delta^{7,9(11),22}$-ergostatrienyl acetate (IVb) with Raney nickel in xylene at room temperature and atmospheric pressure, we obtained Δ^7-ergostenyl acetate (VIb) in an 80% yield.[5, 6]

EXPERIMENTAL[7]

$\Delta^{8(14),22}$-*Ergostadienol* (IIIa). *a. From* $\Delta^{7,22}$-*ergostadienol*[8] (IIa) *with copper chromium oxide.* Into a stainless steel bomb of 300 cc. capacity was placed 5.00 g. of IIa,[8] 5.00 g. of copper chromium oxide (10), and 150 cc. of dry xylene. The mixture was shaken (60 cycles per minute) under 500 p.s.i. pressure of hydrogen for four hours at 150°. The system was allowed to cool to below the boiling point of the solvent, and the bomb was opened while hot. The catalyst was filtered off with the aid of Celite and the solvent removed completely in a vacuum. The residue was dissolved in 200 cc. of hot 95% ethanol and added to a hot solution of 15 g. of digitonin in 700 cc. of the same solvent. Precipitation occurred immediately. The mixture was allowed to cool to near room temperature and was then filtered. The resulting digitonide, after being dried in a vacuum, weighed 14 g. (67%). It was decomposed by dissolving in 200 cc. of pyridine at room temperature and adding 800 cc. of ether. The precipitated digitonin was filtered off with the aid of Celite and the mother liquor concentrated to a very small volume. Remaining traces of digitonin were removed by adding a small volume of ether and filtering again. The solvents were then completely removed in a vacuum and the solid residue crystallized from 60 cc. of boiling methanol. The product consisted of needles melting at 129–130° (becoming opaque by 115°). After

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[4] This is evidenced by the excellent yields of the $\Delta^{7,22}$-steroid which can be obtained from ergosterol (Ia) or its acetate (Ib) with these catalysts (9). Also Bladon and coworkers (13) have converted $\Delta^{7,22}$-ergostadienyl acetate (IIb) to Δ^7-ergostenyl acetate (VIb) in 91% yield using Raney nickel in ethyl acetate solution; similar hydrogenation of ergosterol gave the same product.

[5] Laubach and Brunings (9c) have reported that $\Delta^{7,9(11),22}$-ergostatrienyl acetate (IVb) is completely unattacked by hydrogen in dioxane solution using Raney nickel.

[6] Barton and Cox (14) have obtained $\Delta^{8(14)}$-ergostenyl acetate (Vb) from $\Delta^{7,9(11)}$-ergostadienyl acetate (IVb) using PtO_2 in ether-acetic acid.

All melting points have been taken on an electrically heated block and are uncorrected. Rotations were taken in chloroform in approximately 1% solutions at 20° and are accurate to ±2°. Ultraviolet spectra were determined either on a Beckman (Model DU) or a Cary spectrophotometer. Infrared spectra were determined in carbon disulfide solution on a Perkin-Elmer double beam spectrophotometer. Microanalyses are by the Analytical Service Laboratory of this Institute under the direction of Dr. William C. Alford.

[8] The $\Delta^{7,22}$-ergostadienol (II) used in this work for comparisons and as starting material was prepared by hydrolysis of the acetate which was obtained by hydrogenation of ergosteryl acetate in benzene or toluene solution using prereduced Raney nickel (9). The alcohol melted at 176–178°, $[\alpha]_D$ −20° and the acetate melted at 177–180°. The literature (5) records respectively m.p. 176°, $[\alpha]_D$ −20° and m.p. 180–181°, $[\alpha]_D$ −20°.

being dried at 55°/*ca.* 2 mm. the now opaque crystals weighed 2.53 g. (51%), $[\alpha]_D$ −14°. The methanolic mother liquor on standing deposited an additional 150 mg. (3%) of flat long prisms, m.p. 127–128°.

Anal. Calc'd for $C_{28}H_{46}O$: C, 84.35; H, 11.63.

Found: C, 84.05; H, 11.54.

The infrared spectrum of IIIa showed a hydroxyl stretching frequency at 3550 cm^{-1}, and a band associated with the Δ^{22}-bond (16) at 968 cm^{-1}.

The filtrate from the digitonide was evaporated to dryness in a vacuum and the residue extracted with 400 cc. of boiling ether. The digitonin was filtered off and the filtrate evaporated to dryness in a vacuum. The residue was crystallized from ethyl acetate-methanol-water to give 0.96 g. (19%) of a material which after recrystallization from ethanol-water gave needles melting at 172–175°.

$\Delta^{8(14),22}$-*Ergostadienyl acetate* (IIIb). A solution of 0.39 g. of IIIa in 5.0 cc. of pyridine and 3.0 cc. of acetic anhydride was left overnight at room temperature. The solution was evaporated to dryness in a vacuum and the residue crystallized from ethyl acetate-methanol. The compound formed in lustrous, transparent flakes, m.p. 120–122°, $[\alpha]_D$ −24°, weighing 0.29 g. Lit. (9c) m.p. 122.6–124°, $[\alpha]_D$ −26.5°. An additional 40 mg. was obtained from the mother liquor. The infrared spectrum of our sample was identical with that of a sample kindly supplied by Dr. G. D. Laubach. A mixture of the two samples melted at 122–124°.

Anal. Calc'd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.97.

Found: C, 81.76; H, 10.98.

The infrared spectrum showed bands at 1733 cm^{-1} and at 1238 cm^{-1} characteristic of an ester grouping and at 968 cm^{-1} characteristic (16) of a Δ^{22}-bond.

IIIa. *b. From ergosterol* (Ia) *with platinum oxide.* Compound Ia (30 g.) (recrystallized from benzene-95% ethanol) was dissolved in one liter of ethyl acetate and was shaken with 0.65 g. of platinum oxide in a hydrogen atmosphere. The reaction was allowed to proceed until exactly one molecular equivalent of hydrogen had been absorbed (about 50 minutes) at which point the rate of hydrogenation had become very slow. The catalyst was filtered off. The filtrates from three such experiments were combined, concentrated to about one-fourth of their volume, and refrigerated. There was obtained 67 g. (74%) of impure IIa which after two recrystallizations melted at 171–173°, $[\alpha]_D$ −18°. Lit. (5) m.p. 176°, $[\alpha]_D$ −20°.

The mother liquor from the first crop of II was concentrated to a very small volume, diluted with hot methanol, and refrigerated. The resulting crystals weighed 16 g. (17%) and melted at 125–127°, $[\alpha]_D$ −15°. The infrared spectrum showed no appreciable difference from the sample of IIIa isolated in the copper chromium oxide isomerization above. The acetate melted at 119–120° and gave no melting point depression when mixed with the acetate (IIIb) from the preceding experiment; the infrared spectra also indicated the two samples were identical.

Hydrogenation of $\Delta^{8(14),22}$-*ergostadienol* (IIIa) *to* $\Delta^{8(14)}$-*ergostenol* (Va). A solution of 0.20 g. of IIIa in 30 cc. of dry toluene was hydrogenated in the presence of a small amount of prereduced Raney nickel for eight hours. The catalyst was filtered off, and the toluene was removed in a vacuum. Crystallization of the solid residue from methanol-water yielded 152 mg. of fine needles, m.p. 132–133°, $[\alpha]_D$ +10°. The melting point was not depressed by admixture with an authentic sample of Va (m.p. 132–133°) prepared according to the method of Hart, *et al.* (15). Hart gives m.p. 133° and $[\alpha]_D$ +10.5°. Also, the infrared spectra of the two preparations were identical.

Hydrogenation of $\Delta^{7,9(11),22}$-*ergostatrienol* (IVa) *to* $\Delta^{7,22}$-*ergostadienol* (IIa) *with copper chromium oxide.* A solution of 7.00 g. of the trienol (IVa) in 70 cc. of dry toluene was placed in a bomb of 110 cc. capacity with 9.0 g. of copper chromium oxide catalyst (10). The mixture was shaken for three hours under 2800 p.s.i. pressure of hydrogen at 120°. The bomb was allowed to cool to 90° and then opened. The reaction mixture was diluted with benzene, filtered with the aid of Celite, and the volume of the solution was adjusted to 700 cc. with benzene. A 1.0-cc. aliquot of this was evaporated to dryness and dissolved in isoöctane; the solution showed no maxima of absorption between 220 mμ and 300 mμ. A 100-cc. aliquot was evaporated to dryness, and the resulting material was crystallized from 30 cc. of boiling methanol and enough water to induce precipitation. The crystalline product weighed 0.73 g. (73%) and melted at 161–164°. It gave a digitonide (84%) in 95% ethanol which on decomposition in pyridine-ether yielded crystals of m.p. 167–169°, $[\alpha]_D$ −14°.[9] The literature (5) records a melting point of 176° and specific rotation of −20° for $\Delta^{7,22}$-ergostadienol (IIa) but the infrared spectra of both the crude and purified samples showed no appreciable difference from that of an authentic sample.[8] In another experiment chromatography failed to significantly improve the physical constants.

The remainder of the diluted reaction mixture was evaporated to dryness and acetylated with 15 cc. of acetic anhydride in 80 cc. of pyridine and 60 cc. of chloroform by allowing the solution to stand overnight at room temperature. The crude reaction product was crystallized from 200 cc. of ethanol to give 4.4 g. of lustrous flakes, m.p. 156–158°, $[\alpha]_D$ −14°. The infrared spectrum of this acetate also proved its identity with an authentic sample[8] of $\Delta^{7,22}$-ergostadienyl acetate (IIb). Lit. (5) m.p. 180–181°, $[\alpha]_D$ −20°. In another experiment chromatography failed to significantly improve the physical constants.

Hydrogenation of ergosterol (Ia) *to $\Delta^{7,22}$-ergostadienol* (IIa) *with copper chromium oxide.* In a bomb of 110 cc. capacity 3.0 g. of copper chromium oxide was heated to 100° with shaking for 15 minutes with 60 cc. of purified methylcyclohexane under 3000 p.s.i. pressure of hydrogen. The bomb was cooled to 50°, and 23.0 g. of Ia was added. The mixture was shaken first at 150° and then at 180° under 3000 p.s.i. pressure of hydrogen until there was no longer a pressure drop (a total of 5½ hours). After dilution of the contents of the bomb with chloroform, the catalyst was filtered off. The filtrate was diluted with 400 cc. of ethyl acetate, heated to boiling and filtered through Celite and charcoal. The addition of 400 cc. of boiling methanol and refrigeration caused the product to separate as lustrous plates, m.p. 178–179°, $[\alpha]_D$ −21°. It weighed 15.7 g. (68%). The infrared spectrum was identical with that of an authentic sample.[8] Other crops of crystals could be obtained, but their melting points were successively lower. In a larger run the yield was somewhat less.

Hydrogenation of $\Delta^{7,9(11),22}$-ergostatrienyl acetate (IVb) *to Δ^{7}-ergostenyl acetate* (VIb) *with Raney nickel.* A solution of 0.80 g. of the acetate (IVb) in 31 cc. of dry xylene was hydrogenated in the presence of a small amount of prereduced Raney nickel catalyst until one molecular equivalent of hydrogen had been absorbed. The catalyst was filtered off and the filtrate evaporated to dryness in a vacuum. The ultraviolet spectrum of the residue which was determined in isoöctane indicated that about one-third of the starting material was still present. The isoöctane solution was rehydrogenated with fresh, prereduced Raney nickel until a second molecular equivalent of hydrogen had been absorbed. The catalyst was filtered off and the ultraviolet spectrum again determined. No conjugated diene was present. The solvent was removed in a vacuum and the residue crystallized from ethyl acetate-methanol to yield 0.62 g. of lustrous flakes (80% after deduction of 3% used for ultraviolet determinations), m.p. 151–154°, $[\alpha]_D$ −4°. Lit. (4) m.p. 157–159°, $[\alpha]_D$ −4°. The infrared spectrum was identical with that of an authentic sample (3, 4) of Δ^{7}-ergostenyl acetate (VIb).

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[9] Three other products could possibly be formed in this reduction, namely, (a) $\Delta^{8(9),22}$-ergostadienol, (b) $\Delta^{9(11),22}$-ergostadienol, and (c) $\Delta^{8(14),22}$-ergostadienol. As a main constituent of the mixture, (c) is clearly ruled out by its melting point of 129–130°, and (a) and (b) are ruled out, since both would have a specific rotation of about +16° [calculated from the rotation of Δ^{22}-ergostenol (6) and from the contributions of the respective nuclear double bonds (17)]. It is possible that (b) and/or (c) are contaminants.

spectra which have been used in this work. We also thank Mr. Robert Kostic for technical assistance.

SUMMARY

1. $\Delta^{7,22}$-Ergostadienol (α-dihydroergosterol) has been isomerized in the presence of copper chromium oxide and hydrogen to $\Delta^{8(14),22}$-ergostadienol.

2. Hydrogenation with copper chromium oxide or Raney nickel reduced the $\Delta^{9(11)}$-bond of the $\Delta^{7,9(11)}$-diene system in ergosterol-D.

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