emulsion is formed it should be treated with charcoal while hot and filtered. Two grams of bromoacetic acid was dissolved in 10 cc. of water and 2 drops of phenolphthalein added; 10% potassium hydroxide solution was then added until a permanent pink color was obtained. The two solutions were then mixed and gently boiled for ten minutes. A small portion of norite was then added and the boiling continued for one minute. The mixture was filtered through a fluted filter while hot. The filtrate was allowed to cool and neutralized with concentrated hydrochloric acid. An oil separated which solidified on standing. The crystalline product was then recrystallized from water, or a mixture of benzene and ligroin. The colorless crystals were then dried in an air-bath at 110°.

The authors desire to express their appreciation to Professor Wm. C. MacTavish for the facilities placed so generously at their disposal.

## Summary

The intramolecular rearrangement of isopropyl *m*-cresyl ether, under the influence of a mixture of glacial acetic acid and concentrated sulfuric acid, was studied; thymol and *m*-methyl-*p*-isopropylphenol were the products obtained, thus furnishing a new synthesis of thymol.

Methylthymol, ethylthymol and chlorothymol were prepared in a similar manner, by the rearrangement of the corresponding isomeric ethers, illustrating that the rearrangement of secondary alkyl phenyl ethers is a general reaction.

Theories underlying such intramolecular rearrangements were discussed and a reaction mechanism based upon the considerations of Lapworth and Latimer was proposed.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, THE UPJOHN COMPANY]

# BETA-ERGOSTENOL

BY MERRILL C. HART AND HAROLD EMERSON

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It was first shown by Mauthner[1] that it is possible to isomerize certain members of the sterol group by saturating chloroformic solutions with hydrochloric acid gas. Mauthner thus converted cholestene to pseudocholestene. He also showed that it was probable that cholesterol itself could be isomerized but it remained for Windaus[2] actually to separate and describe allo-cholesterol.

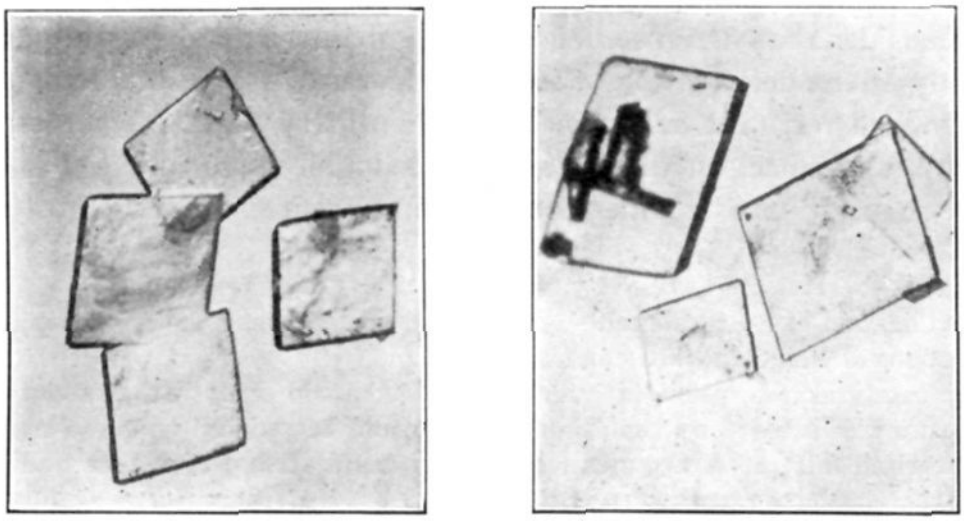
The isomerization of ergosterol by this process was first carried out by Reindel, Walter and Rauch,[3] who also studied this reaction in the case of α-ergostenol. They state that, working with α-ergostenol prepared from

[1] Mauthner, *Monatsh.*, **28**, 1113 (1907).

[2] Windaus, *Ann.*, **453**, 101 (1927).

[3] Reindel, Walter and Rauch, *ibid.*, **452**, 34 (1927); Reindel and Walter, *ibid.*, **460**, 212 (1928).

yeast ergosterol, the reaction yields 95% of the β-isomer. The acetate of β-ergostenol is said to melt at 94–95° and $[\alpha]_D$ +3.0°. This acetate upon saponification gives β-ergostenol melting at 114–118°. The corresponding chloroacetate is said to melt at 166–167°. A complete isomerization of α-ergostenol is said to result upon boiling it with chloroacetyl chloride, for the chloroacetate of β-ergostenol results.



β-Ergostenol acetate. Magnification 7×.

In a previous paper[4] we have indicated our failure to obtain β-ergostenol from the α-form prepared by the reduction of ergosterol from ergot. On every occasion that this reaction was carried out, considerable top fractions of unchanged α-ergostenol acetate could be separated with greatest ease. Furthermore, in preparing the chloroacetate we have shown that the product is largely a chloroacetate of the α-isomer.[5] The esters prepared with monochloroacetyl chloride, trichloroacetyl chloride, propionyl chloride, α-bromopropionyl chloride and butyl chloride, when saponified give obvious mixtures melting at about the same point as that given by Reindel for β-ergostenol.

β-Ergostenol, we believe, has not heretofore been isolated although its existence in the mixture is established by the fact that small amounts of the hexahydroergosterol, allo-α-ergostanol (m. p. 145°) can be prepared by the reduction of the isomerized mixtures, resulting from the above reactions, whereas from α-ergostenol itself no further reduction product can be obtained.

Since the description of the micro method for the determination of hydrogen absorption by Hyde and Scherp,[6] which we have found perfectly adapted to our problem, we have studied the isolation of β-ergostenol from

[4] Hart, Speer and Heyl, THIS JOURNAL, **52,** 2016 (1930).

[5] Hart and Heyl, *ibid.*, **53,** 1413 (1931).

[6] Hyde and Scherp, *ibid.*, **52,** 3359 (1930).

these mixtures, being able to follow the progress of the separation by the determination of the hydrogen absorption of the various fractions. In general the application of Mauthner's process to α-ergostenol yields a mixture containing somewhat less than 50% of the β-isomer, and with considerable difficulty a yield of about 5% can be isolated in pure form.

β-Ergostenol crystallizes from alcohol in plates and melts at 141°, $[\alpha]_D$ +21.2. The details of the properties will be found in the summary.

We consider that β-ergostenol is very probably a good starting point in the study of the degradation of ergosterol. Since α-ergostenol has proved to be such a resistant substance to the ordinary reactions for studying structure, and since, on the contrary, the double bond in the β-isomer is more reactive, it may be hoped to make some progress from β-ergostenol.

## Experimental

**Fractionation of β-Ergostenol.**—α-Ergostenol acetate was isomerized according to the directions of Reindel, Walter and Rauch.[3,7]

The catalytic absorption of hydrogen showed upon analysis that about 45% of the mixture was present as the β-isomer and could be reduced to allo-α-ergostanol. The isomerized mixture of acetates upon one crystallization from ether and alcohol melted at 98–100°.

It was found that the mixture could be more satisfactorily fractionated as the free sterols rather than as the acetates. Twenty-five grams of the mixture of acetates was therefore saponified by boiling with 5% alcoholic potash for thirty minutes. The following successive crops were filtered off.

| Fraction | Weight, g. | M. p., °C. | $H_2$ absorbed, % | Rotation, $[\alpha]_D$ |
|---|---|---|---|---|
| 1 | 4.1 | 100–105 | 35.4 | +14.8 |
| 2 | 7.9 | 110–115 | 41.0 | +16.0 |
| 3 | 5.75 | 120–128 | 65.6 | +21.7 |
| 4 | 0.7 | 90–125 | 56.7 | +29.5 |
| 5 | Sirup, discarded | | | |

These fractions were systematically fractionated from ethyl alcohol. Fraction 1 yielded a considerable quantity of α-ergostenol melting at 133° and forming the characteristic acetate melting at 110°. Fractions 2 and 3 yielded several crops of material of relatively low reducibility which were discarded. Fraction 4 on crystallization from the mother liquors of the above fractions yielded about 3 g. of material crystallizing in flat plates and melting at 133°. Four more crystallizations yielded 1.4 g. that melted at 137°. This material showed on quantitative reduction with hydrogen the presence of 91% of one double bond, $[\alpha]_D$ +23.5°.

This specific rotation (23.5°) is higher than that of the pure β-ergostenol (21.2°). This fact in addition to the fact that fraction 4 has a specific rotation of +29.5° indicates that there is at least one other isomer present, of higher rotation than β-ergostenol. This possibility is being investigated in this Laboratory.

[7] The result of the modification introduced by Windaus, Dithmar, Murke and Suckfüll, *Ann.*, **488**, 91 (1931), of removing the hydrogen chloride from the chloroform solution of the isomerized material before evaporation of the chloroform, is being further studied in the case of ergostenol in this Laboratory as a part of more extended investigation of β-ergostenol and its derivatives.

0.200 g. in 10 cc. of chloroform had a rotation of +0.94° in a 2-dcm. tube at 22°, $[\alpha]_D$ +23.5°. 19.800 mg. in acetic acid absorbed 0.09421 mg. of $H_2$. Calcd. for one double bond in $C_{27}H_{46}O$: $H_2$ required, 0.1033 mg. Found: 0.91 double bond.

**β-Ergostenol Acetate.**—β-Ergostenol was further purified through the acetate. One gram of β-ergostenol (m. p. 137°) was boiled for twenty minutes with an excess of acetic anhydride. The acetate separated in flat plates that melted at 107°. Repeated crystallization from acetic acid raised the melting point to 114°.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.2; H, 11.3. Found: C, 81.4; H, 11.1. 0.57 g. in 10 cc. chloroform had a rotation of +1.15° in a 2-dcm. tube at 22°, $[\alpha]_D$ 10.0°. 0.3431 g. was saponified with an excess of alcoholic potash. Calcd. for $C_{29}H_{45}OCOCH_3$: 8.01 cc. of *N*/10 acid. Found: 8.15 cc.

**β-Ergostenol.**—Pure β-ergostenol was prepared by saponification of the acetate and crystallization from alcohol. It separated in plates that melted at 141°.

0.65 g. made up to 10 cc. with chloroform had a rotation of +2.76°, $[\alpha]_D$ 21.2°. 12.882 mg. in acetic acid absorbed 0.0661 mg. of $H_2$. Calcd. for one double bond in $C_{27}H_{46}O$: $H_2$ required, 0.0672 mg. Found: 0.99 double bond.

**Preparation of Allo-α-Ergostanol from Pure β-Ergostenol.**—β-Ergostenol (1.2 g.) was reduced in acetic acid solution with platinum oxide as a catalyst. The reduced material was converted to the acetate and crystallized from acetic acid. Allo-α-ergostanol acetate was obtained in a 72% yield. This crystallized in flat plates that melted at 146° with $[\alpha]_D$ +8.00°.

*Anal.* Calcd. for $C_{29}H_{50}O_2$: C, 80.9; H, 11.7. Found: C, 81.0; H, 11.5. 0.2000 g. was saponified with an excess of alcoholic potash. Calcd. for $C_{27}H_{47}OCOCH_3$: 4.64 cc. of *N*/10 acid. Found: 4.55 cc. 0.200 g. in 10 cc. of chloroform had a rotation of +0.32° in a 2-dcm. tube at 22°, $[\alpha]_D$ +8.00°.

**Allo-α-ergostanol** prepared from the acetate by saponification with alcoholic potash and crystallization from alcohol formed flat hexagonal plates melting at 144° with $[\alpha]_D$ +15.4°.

**Allo-α-Ergostanol Chloroacetate.**—Allo-α-ergostanol (0.100 g.) was gently refluxed for fifteen minutes with an excess of chloroacetyl chloride. After crystallization from acetic acid, 0.067 g. of the chloroacetate melting at 200–201° was obtained.

*Anal.* Calcd. for $C_{29}H_{49}O_2Cl$: Cl, 7.63. Found: Cl, 7.53. 0.050 g. in 10 cc. of chloroform had a rotation of +0.09° in a 2-dcm. tube at 22°, $[\alpha]_D$ +9.0°.

**Ergostenol Chloroacetate Prepared from β-Ergostenol.**—Ergostenol chloroacetate prepared from α-ergostenol and chloroacetyl chloride has been shown[5] to be a mixture of the α- and β-derivatives. Unsuccessful attempts were made to prepare pure β-ergostenol chloroacetate. β-Ergostenol and chloroacetyl chloride yielded a mixture containing equal parts of the α- and β-isomers. The chloroacetate prepared by the use of chloroacetic anhydride was a similar mixture. The results of the action of chloroacetyl chloride and chloroacetic anhydride on α- and β-ergostenol are summarized in Table I.

TABLE I

CHLOROACETATES PREPARED FROM α- AND β-ERGOSTENOL

| Reagent | Chloroacetate M. p., °C. | Chloroacetate Rot. $[\alpha]_D$ | β-form present in reduction, % | Chlorine, % | Hydrolysate M. p., °C. | Hydrolysate Rot. $[\alpha]_D$ |
|---|---|---|---|---|---|---|
| β-Ergostenol + $ClCH_2COCl$ | 168–169 | +8.1 | 50 | 7.75 | 106–112 | +13.8 |
| β-Ergostenol + $(ClCH_2CO)_2O$ | 165–166 | +5.4 | 48 | 7.90 | 115–120 | +16.0 |
| α-Ergostenol + $(ClCH_2CO)_2O$ | 163–166 | +7.8 | 44 | 7.60 | 120–125 | +14.3 |
| α-Ergostenol + $ClCH_2COCl$ | 165–166 | +6.9 | 46 | 7.71 | 110–116 | +14.0 |

## Summary

1. Pure β-ergostenol (m. p. 141°, $[\alpha]_D$ +21.2°) and β-ergostenol acetate (m. p. 114°, $[\alpha]_D$ +10.0°) have been isolated and their properties described.

2. Both chloroacetyl chloride and chloroacetic anhydride reacting on β-ergostenol give a chloroacetyl derivative consisting of a mixture of the α- and β-forms. Approximately this same mixture of α- and β-ergostenol chloroacetates is obtained by the reaction of both chloroacetyl chloride and chloroacetic anhydride on α-ergostenol.

3. α-Ergostenol acetate isomerized by the method of Mauthner consists of a mixture of α- and β-ergostenol acetate with the acetate of at least a third isomer having a higher specific rotation than either α- or β-ergostenol.


KALAMAZOO, MICHIGAN

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, THE UPJOHN COMPANY]

# THE STEROLS OF ERGOT. III. THE OCCURRENCE OF AN ISOMER OF ALPHA-DIHYDROERGOSTEROL

BY FREDERICK W. HEYL

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Recently[1] we described the isolation of α-dihydroergosterol from the ether–petroleum ether filtrate from crude ergosterol. Not many fractions below the head fraction pure α-dihydroergosterol separated in the process of fractionation with ethyl acetate.

The subsequent fractions show a gradual lowering of the levorotation and from this series there can be repeatedly obtained magnificant plates which greatly resemble the description given for "fungisterol." We are, in fact, convinced that the "fungisterol" of Tanret ($[\alpha]_D$ 15.9°) represents one of these fractions.

From any of these fractions showing $[\alpha]_D$ −6.0° or greater, persistent fractionation, especially of the acetate from a mixture of ether and alcohol, will yield α-dihydroergosterol.

Evidence indicates that the third sterol is optically inactive and that it is practically impossible to separate it in quantity by fractional crystallization of the sterols or of the acetates.

Our purest fraction of the sterol melted at 133–134°. The corresponding acetate, $C_{27}H_{43}OCOCH_3$, melted at 143–145° and had $[\alpha]_D$ −0.5°.

It is unsaturated, giving the Liebermann–Burchard test and quantitatively absorbs two atoms of hydrogen. To color tests it responds exactly as α-dihydroergosterol, with which in fact it appears to be isomeric.

Incidentally the presence of a hydrocarbon, hentriacontane, and of an alcohol, very probably myricyl alcohol, has been observed in the unsaponifiable material from ergot fat.

[1] Heyl and Swoap, THIS JOURNAL, **52**, 3688 (1930).