Anal. Calcd. for $C_{34}H_{46}O_4N$: C, 76.8; H, 8.5. Found: (meta) C, 76.6; H, 8.9; (para) C, 76.5; H, 8.9.

When hydrolyzed, both yielded isoergosterol, as plates melting at 137° with $[\alpha]_D$ of −32.6°. Bills and Cox[1] give m. p. 140°, $[\alpha]_D$ (= $[\alpha]_{5461} \div 1.27$) = −31.2° for isoergosterol made by treatment with cinnamoyl chloride.

Chloro-acetyl Derivatives.—An attempt was made to prepare ergosteryl chloroacetate by warming ergosterol with the acid chloride in pyridine, but this resulted in a halogen-free compound, due to a further condensing effect of the pyridine. The nature of this reaction will be reported in a later paper.

Isoergosteryl chloro-acetate was readily obtained by warming 1.7 g. of ergosterol with 2 cc. of chloro-acetyl chloride on a steam-bath for three minutes. Crystallized from acetic acid and from ether it gave 1.2 g. of plates melting at 190°; $[\alpha]_D$ was −45°.

Anal. Calcd. for $C_{29}H_{43}O_2Cl$: Cl, 7.7. Found: Cl, 8.0.

Hydrolysis gave the same isoergosterol described above.

Summary

Ergosteryl acid phthalate and its silver and copper salts, ergosteryl phenylurethan and *m*- and *p*-nitrobenzoates have been prepared from the ergosterol of ergot, as well as the *m*- and *p*-nitrobenzoates and chloroacetate of isoergosterol.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY, THE UPJOHN COMPANY]

ALPHA-ERGOSTENOL AND ITS ISOMERIZATION TO BETA-ERGOSTENOL

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Since ergosterol itself and its esters, containing as they do three double bonds, are decidedly unstable and acquire a distinct yellow color on standing even in a black vacuum desiccator, we decided to continue our investigation of the ergosterol from ergot by studying its very stable tetrahydro derivatives, α- and β-ergostenol. α-Ergostenol was first prepared by Reindel and co-workers[1] from yeast ergosterol by catalytically reducing the acetate and hydrolyzing the product obtained thereby. The same compound has later been prepared by other authors with variations of the catalyst and solvents used. α-Ergostenol as we have prepared it from ergot ergosterol differs slightly in physical constants from Reindel's values, and did not react at all to his method of isomerization to the β-form (passing dry hydrogen chloride gas into a chloroform solution of α-ergostenol acetate). The statement of Reindel, Walter and Rauch that "the chloroacetyl derivative of α-ergostenol cannot be made by chloro-acetyl chloride, since thereby isomerization to β-ergostenol chloro-acetate takes place"

[1] Bills and Cox, *J. Biol. Chem.*, **84**, 455 (1929).

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

led us to attempt the preparation of β-ergostenol acetate by esterification with acetyl chloride, instead of the anhydride which is normally used to form acetates without danger of isomerization. The fact that this yielded an acetate identical in every respect with genuine α-ergostenol acetate made it seem of interest to investigate the effect of a number of acid chlorides in causing this isomerization.

Experimental

Preparation of α-Ergostenol.—Three grams of ergosterol acetate (m. p. 170–172°, $[\alpha]_D$ −74.5°) was shaken with 0.3 g. of Adams[2] platinum oxide catalyst and 300 cc. of glacial acetic acid with 2 atmospheres of hydrogen at room temperature. The acetate rapidly dissolved, and the absorption of two mols of hydrogen was complete in about fifteen minutes. Continued shaking and fresh catalyst did not cause any further absorption. After filtration from the catalyst and concentration of the solution, α-ergostenol acetate separated as plates melting at 110–111° which were optically inactive. Reindel and co-workers give $[\alpha]_D$ +5.18°; yield, almost quantitative.

Sixty grams of this material was systematically fractionally crystallized from acetic acid five times, with the results shown in Table I.

TABLE I

FRACTIONATION OF α-ERGOSTENOL ACETATE

Fraction no.	Weight, g.	M. p., °C.	$[\alpha]_D$
1	11.83	110–111	0
2	8.00	110–111	0
3	14.08	109–110	0
4	11.10	109–110	0
5	5.24	107–108	0
6	2.07	103–106	0

Fractions 1–4 gave on hydrolysis α-ergostenol melting sharply at 133° and having $[\alpha]_D$ +10.5°. Reindel and co-workers give m. p. 130–131°; $[\alpha]_D$ +17.86°. This discrepancy is most simply explained by the difference in source of the ergosterol.

α-Ergostenol was quantitatively precipitated by digitonin, and was recovered unchanged by decomposing the digitoinide with boiling xylene.

Treated in chloroform solution with dry hydrogen chloride gas according to Reindel's directions, α-ergostenol acetate was consistently recovered unchanged in better than 80% yields, although Reindel reports yields of 95% of β-ergostenol acetate. As noted in the introduction, an attempt to prepare β-ergostenol acetate by the action of acetyl chloride on α-ergostenol also failed. We could without difficulty, however, prepare the β-ergostenol chloro-acetate, m. p. 166–167° reported by Reindel, by the action of chloro-acetyl chloride on α-ergostenol. We also confirmed their observation of a "back-isomerization" upon hydrolysis, since we obtained not pure β-ergostenol but a mixture containing some α-ergostenol, from which it was impossible to separate the pure β-form by fractional crystallization.

In order to determine if possible the conditions for isomerization, we prepared a series of esters as shown in Table II by warming 0.5 g. of α-ergostenol with 0.5 g. of acid halide and recrystallizing from alcohol. Hydrolysis with alcoholic potassium hydroxide gave either the characteristic low melting mixture of α- and β-ergostenol, or the homo-

[2] Voorhees and Adams, THIS JOURNAL, **44**, 1397 (1922); Adams and Shriner, *ibid.*, **45**, 2171 (1923).

geneous sharp melting needles of α-ergostenol, according as isomerization had or had not taken place. As a control experiment, esterification was also carried out in pyridine solution,[3] resulting in every case in an α-ergostenol derivative as shown in Table III. (Compounds which were identical with those in Table II are omitted from Table III.)

TABLE II

ESTERIFICATION OF α-ERGOSTENOL WITHOUT SOLVENT

Ester	M. p., °C.	Analysis, % Calcd.	Found	M. p. of hydrolysate
Acetate	110–11			131
Monochloro-acetate	166–67	Cl, 7.69	7.71	110–12
Dichloro-acetate	114	Cl, 14.27	13.48	132
Trichloro-acetate	128	Cl, 20.01	19.66	108–11
Propionate	114–15	C, 81.36, H, 11.18	81.53, 11.02	108–12
α-Bromopropionate	104.5	Br, 15.34	15.47	112–14
Butyrate	74–75	C, 81.49, H, 11.50	81.56, 11.22	110–11
Benzoate	117.5[a]	C, 83.17, H, 10.29	82.96, 10.19	130–31
m-Nitrobenzoate	165	N, 2.61	2.38	132
p-Nitrobenzoate	178	N, 2.61	2.66	132

[a] Reindel, Walter and Rauch give 118° for α-ergostenol benzoate.

TABLE III

ESTERIFICATION OF α-ERGOSTENOL WITH PYRIDINE AS SOLVENT

Ester	M. p., °C.	M. p. of hydrolysate, °C.
Monochloro-acetate	[a]	130–131
Trichloro-acetate	133.5	129–131
Propionate	90	129–130
α-Bromopropionate	[a]	130–131
Butyrate	67–68	130–131

[a] These two compounds were not true esters of α-ergostenol, a further reaction due to the condensing effect of the pyridine having taken place. Their true nature is being investigated.

It is difficult to understand why some acid halides should cause isomerization while others do not. It cannot be explained on the basis of the "strength" of the acid involved, for acetic acid stands intermediate between butyric and the chloro-acetic acids, and dichloro-acetic acid between monochloro- and trichloro-acetic acids in strength. Likewise, the presence or absence of halogen in the acid chain cannot be made to account for the results. In every case a copious evolution of hydrogen chloride was observed, so the presence of dry hydrogen chloride alone is not sufficient to effect isomerization. We are forced to the conclusion that the reaction is one the course of which cannot be predicted with our present knowledge.

Summary

1. α-Ergostenol prepared from ergot ergosterol was found to differ slightly in physical properties, and radically in ability to isomerize, from

[3] Houben, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, 1925, Vol. II, 3d ed., p. 667.

the α-ergostenol from yeast ergosterol as described by Reindel, Walter and Rauch.

2. The effect of a number of acid halides in causing isomerization of α-ergostenol to β-ergostenol has been investigated; no single factor could be made to account for isomerization in some cases and not in others.

3. A number of new esters of α- and of β-ergostenol are described.

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[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES]

AROMATIC AMIDES OF N-ARYLGLYCINE ARSONIC ACIDS

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In the search for therapeutic arsenical compounds, used in the treatment of syphilis, Jacobs and Heidelberger[1] deviated from the usual experimental lines, which involved changes in the aromatic nucleus containing arsenic. These older researches had involved changes in the structure of salvarsan base (diamino-di-hydroxy-arsenobenzene) and this field of study has been fairly well exhausted.

The above authors synthesized a new series of compounds utilizing the reaction between chloro-acetyl-alkyl or chloro-acetyl-aryl amines and arsanilic acid (*p*-aminophenylarsonic acid). The aromatic series furnished a new field for work inasmuch as the non-arsenical benzene nucleus could be still further substituted, giving rise to compounds of substituted chloro-acetyl-aryl amines and arsanilic acid. A large number of such compounds were prepared.

It is our purpose to add further to this series and in doing so we have used the chloro-acetyl derivatives of amines which in themselves are therapeutic to some degree. We have also obtained some compounds involving 3-methylarsanilic acid (*m*-methyl-*p*-amino-arsonic acid) which correspond to the known derivatives of arsanilic acid.

The intermediate compounds used by us in the preparation of the arsonic acids are chloro-acetyl derivatives of amines. In most of the experiments these were prepared by methods employed by Jacobs and Heidelberger;[2] the few exceptions will be described later.

Jacobs and Heidelberger in their experiments[3] employed arsanilic acid, and its corresponding derivatives, in the form of its sodium salt (*i. e.*, in alkaline solution). For several of our experiments this was not practicable inasmuch as the chloro-acetyl compounds were oxidizable in alka-

[1] Jacobs and Heidelberger, THIS JOURNAL, **41**, 1581 (1919).

[2] Jacobs and Heidelberger, *ibid.*, **39**, 1439 (1917); **41**, 458 (1919); *J. Biol. Chem.*, **20**, 686 (1915).

[3] Jacobs and Heidelberger, THIS JOURNAL, **41**, 1587 (1919).