

PATENT SPECIFICATION

NO DRAWINGS

1103.984

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Date of Application and filing Complete Specification: March 29, 1965.

No. 36702/67.

Application made in United States of America (No. 400206) on Sept. 29, 1964.

(Divided out of No. 1103574).

Complete Specification Published: Feb. 21, 1968.

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Index at acceptance: —C2 C(3A19A3, 3A19B1, 3A19C1, 3A19D1)

Int. Cl.: —C 07 c 61/12

COMPLETE SPECIFICATION

3,5-Seco-A-Norandrostan-3-Oic Acids

We, F. HOFFMANN-LA ROCHE & Co.,
AKTIENGESellschaft, a Swiss Company
of 124—184 Grenzacherstrasse, Basle,
Switzerland, do hereby declare the invention,

for which we pray that a patent may be
granted to us, and the method by which it
is to be performed, to be particularly de-
scribed in and by the following statement:—

The present invention is concerned with
novel 3,5 - seco - A - norandrostan - 3 -
oic acids.

The novel 3,5-seco-A-norandrostan-3-oic
acids provided by the invention are the
17 α - (lower alkyl) - 17 β - hydroxy - 5 -
oxo - 3,5 - seco - A - norandrostan - 3 - oic
acids. These acids are valuable intermediates
for the manufacture of 9 β ,10 α -steroids of
the androstane series; for example, via the
desA-steroids which form part of the sub-
ject matter of our copending Application for
Letters Patent no: 36705/67 (now serial
no: 1103987).

The novel 3,5 - seco - A - norandrostan -
3 - oic acids aforesaid can be prepared by
the oxidative ring-opening of ring-A of a
17 α - (lower alkyl) - 17 β - hydroxy - an -
drostan - 4 - en - 3 - one. This oxidative
ring-opening can be performed by a variety
of methods. In a preferred embodiment, it
is effected by ozonolysis. The ozonolysis is
suitably carried out in an organic solvent;
for example, acetic acid, ethyl acetate,
methanol, chloroform or methylene chloride
or a mixture of two or more of such solvents
such as (ethyl acetate)/(acetic acid) or
(ethyl acetate)/(methylene chloride). How-
ever, the ozonolysis is advantageously con-
ducted at below room temperature. Thus,
it is advantageously conducted at a tempera-
ture between about -70°C and 25°C. The
resulting ozonides can be decomposed by
conventional means; for example, by treat-
ment with water, hydrogen peroxide in water,

acetic acid or ethyl acetate. The oxidative
ring-opening can also be effected by other
oxidation methods; for example, by treat-
ment with hydrogen peroxide. It should be
noted that the oxidative ring-opening either
by ozonolysis or by treatment with hydrogen
peroxide does not require protection of the
17 β -hydroxy group. However, it may in some
cases be desirable to protect this group. On
the other hand, the oxidative ring-opening
can also be effected by oxidation with
chromium trioxide or by treatment with
sodium periodate and potassium permanga-
nate in potassium carbonate solution, but,
if these oxidation agents are used, it is
necessary to protect the 17 β -hydroxy group.
The 17 β -hydroxy group can be protected
by esterification or etherification. Any avail-
able acid which will form an ester that can
subsequently be hydrolysed to regenerate
the hydroxy group is suitable. Examples of
acids which are useful for this purpose are
alkanoic acids containing not more than six
carbon atoms (e.g. acetic acid), caproic acid,
benzoic acid, phosphoric acid and alkane
dicarboxylic acids containing not more than
six carbon atoms (e.g. succinic acid). A suit-
able ether protecting group is, for example,
the tetrahydro-pyranyl ether group. These
protecting groups can be removed by
methods known *per se*; for example, by
mild acid hydrolysis.

It will be appreciated that the term 'lower
alkyl' is used in this description and in the
claims appended hereto to mean both
straight-chain and branched-chain alkyl
groups containing not more than seven carbon
atoms (e.g. methyl, ethyl, propyl and *iso*-
propyl).

The following Examples illustrate the
manner in which the novel 3,5 - seco -
norandrostan - 3 - oic acid provided by the
invention can be prepared:

[Price 4s. 6d.]



EXAMPLE 1

A solution of 3.2 g of 17 α - ethyl - testosterone in 50 ml of methylene chloride and 25 ml of ethyl acetate was ozonized at -70°C [acetone/(dry ice)bath] until the solution was blue in colour. After oxygen had been passed through, the solution was evaporated *in vacuo* at room temperature. The syrupy residue was then dissolved in 100 ml of glacial acetic acid and, after addition of 5 ml of 30 per cent hydrogen peroxide, left for 24 hours at 0°-5°C. Following this time, it was evaporated to dryness, dissolved in 1500 ml of ether, and extracted with 2-N sodium carbonate solution. The alkaline extract was poured in ice-cold hydrochloric acid. The resulting crystalline 17 α - ethyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid was filtered, washed with water and dried. After recrystallization from acetone, it melted at 196°-197°C.

A solution of 1.5 g of 17 α - ethyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid in 100 ml of methanol was titrated with 2-N sodium methoxide to the reddish colour of phenolphthalein, and then evaporated to dryness *in vacuo*, giving the sodium salt of 17 α - ethyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid as the residue.

EXAMPLE 2

7 α ,17 α - Dimethyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid was prepared from 7 α ,17 α - dimethyl -

testosterone by ozonolysis of the latter according to the procedure of the first paragraph of Example 1.

7 α ,17 α - Dimethyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid was converted into its sodium salt according to the procedure of the second paragraph of Example 1.

EXAMPLE 3

17 α - Methyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid was prepared from 17 α - methyl - testosterone by ozonolysis according to the procedure of the first paragraph of Example 1. The so-obtained product melted at 191°-194°C; $[\alpha]_D^{25} = +9.8^\circ$ $c=1$ in chloroform).

17 α - Methyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid was converted into its sodium salt according to the procedure of the second paragraph of Example 1.

WHAT WE CLAIM IS:—

1. A 17 α - (lower alkyl) - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid.

2. 17 α - Ethyl - 17 β - hydroxy - 5 - oxo - 3,5 - seco - A - norandrostan - 3 - oic acid.

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For:
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EXAMPLE 1

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.

Published by the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.



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