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4-ANDROSTEN-3,17-DIONE FROM CHOLESTEROL, ß-SITOSTEROL, AND CAMPESTEROL BY CHEMICAL DEGRADATION

Peter Welzel*, Kurt Hobert, Aranka Ponty
Abteilung für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum, West Germany

Tsenka Milkova
Institute of Organic Chemistry
Bulgarian Academy of Sciences
1113, Sofia, Bulgaria

Abstract: 1 was degraded to 24 in good overall yield via 7,10,16,21,19 and 20; similarly, 24 was obtained from 2 and 3.

For many years diosgenin, deoxycholic acid, and stigmasterol served as the most important raw materials for the commercial partial synthesis of steroid hormones.[1] As a result of a shortage of diosgenin several economic processes have been developed for the microbial conversion of abundant naturally occuring sterols, e.g. cholesterol (1), ß-sitosterol (2), and campesterol (3), into useful steroid hormone intermediates such as 4-androsten-3,17-dione (24).[1,2,3] An analogous degradation of the saturated hydrocarbon side chain by conventional chemical methods can be accomplished only with unacceptably low yields even after protection of the Δ^5 double bond.[4] Site-specific introduction of a Δ^{16} double bond into saturated steroids by remote functionalisation has been achieved by both Breslow[5] and Baldwin[6]. The "reagent" capable of abstracting 17α-H selectively was attached to the steroid nucleus by either a 3α- or 7α-ester linkage. After transfer of the unsaturation from the 16- to the 17(20) position the side chain could be cleaved off. By application of this procedure 5α-cholestan-3α-ol was degraded to 3α-hydroxy-5α-androstan-17-one.[7]

We describe herein a short and efficient chemical method for degrading sterols 1,2, and 3 to the important compound 24 using remote halogenation in one of the key steps.

Acetates 4 and 5/6 (obtained from a commercial 6:4 mixture of 2 and 3) furnished the 5α-hydroxy compounds 7 and 8/9, respectively, in an overall yield of 74% on sensitized photooxygenation followed by catalytical hydrogenation of the intermediate 5α-hydroperoxy-Δ^7-ene allylic hydroperoxides.[8] This method for the conversion of 5-olefins into 5α-hydroxy steroids compares favourably with the standard method via the 5α,6α-epoxide[9] because of its simplicity. Esterification of the 5α-OH group in 7 and 8/9, respectively, caused more difficulties than anticipated. After much experimentation it was found that a modification of the Oppenauer method[10] (refluxing a toluene solution of the alcohols with a 3- fold excess of 4-iodophenylacetyl chloride and calciumhydride in the presence of a catalytical amount of tetra-n-butylammonium iodide) gave the desired esters 10 and 11/12 in about 80% yield.[11] Molecular models suggest that in 10, as well as in 11/12 the geometrical demands for the relay chlorination at C-17 are perfectly met.[12] Thus, irradiation of a CCl_4 solution of 10 (0.12 mmol) in the presence of sulfuryl chloride (0.87 mmol) and azobis (isobutyronitrile) (0.36 mmol) at -10°C with UV light (Philips HPK 125, pyrex filter) for 150 min or of a $CHCl_3$ solution of 10 (0.14 mmol) and freshly prepared iodobenzene dichloride (0.16 mmol) at 20°C with a 300 W sun lamp for 5 min furnished the desired 17α-chloro compound 16. After chromatographic separation the somewhat unstable 16 was obtained in 53% yield. When 16 was heated in pyridine solution only the 16-olefin 13 was formed. This finding is consistent with Breslow's report that dehydrochlorination of 17-chloro compounds of this type with hot alkali leads exclusively to 16-olefins. Unfortunately, from these olefins the side chain can be degraded only in a sequence of several steps.[7] To our delight we found that treatment of 16 with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) at 90°C gave a 4:1 mixture of olefins in which the 17(20) isomer 21 was the main component. When the chlorination and elimination steps were performed without purification of the intermediate 16 the overall yield of the 4:1 mixture of 21 and 13 was 64%. Simple treatment of the olefin mixture with ozone (trimethyl phosphite workup) gave 17-ketone 19 quantitatively (based on 21). By the same sequence of reactions the mixture of 11 and 12 was transformed into 19. Heating of a THF solution of 19 (0.02 mmol) in 1 ml THF with aqueous 0.15 molar lithium hydroxide (0.2 ml) under reflux for 4 h effected clean hydrolysis of the acetate group at C-3. 20 was obtained in 86% yield. Finally, pyridinium chlorochromate oxidation[13] and brief treatment of the resulting 3-ketone in THF solution with 0.15 molar aqueous lithium hydroxide at 20°C provided 24 in quantitative yield.[14]

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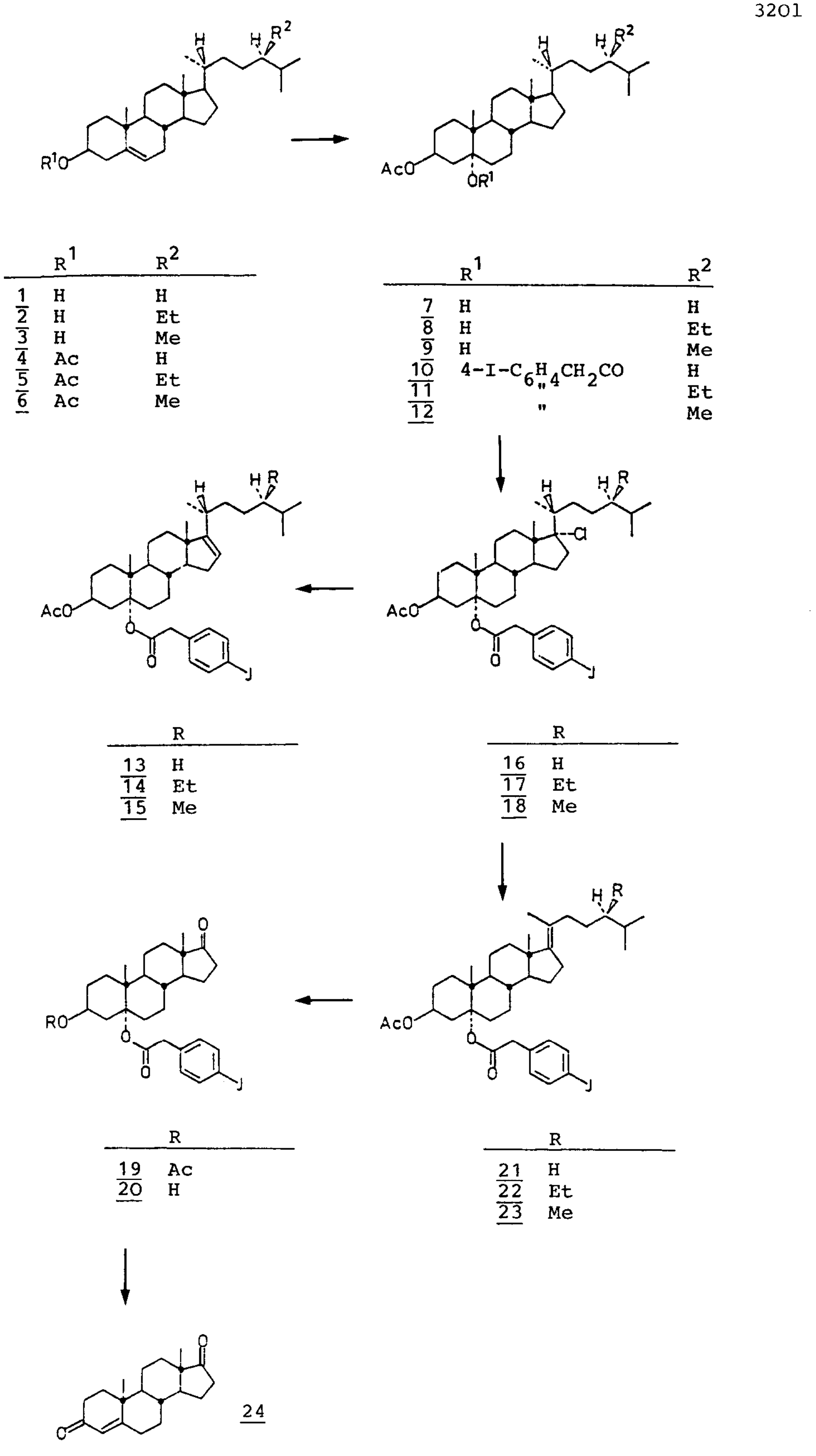

	R^1	R^2
1	H	H
2	H	Et
3	H	Me
4	Ac	H
5	Ac	Et
6	Ac	Me

	R^1	R^2
7	H	H
8	H	Et
9	H	Me
10	$4\text{-I-C}_6H_4CH_2CO$	H
11	"	Et
12	"	Me

	R
13	H
14	Et
15	Me

	R
16	H
17	Et
18	Me

	R
19	Ac
20	H

	R
21	H
22	Et
23	Me

24

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