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OXIDATIVE DECARBOXYLATION OF 17(20)-DEHYDRO-23,24-DINORCHOLANOIC ACIDS

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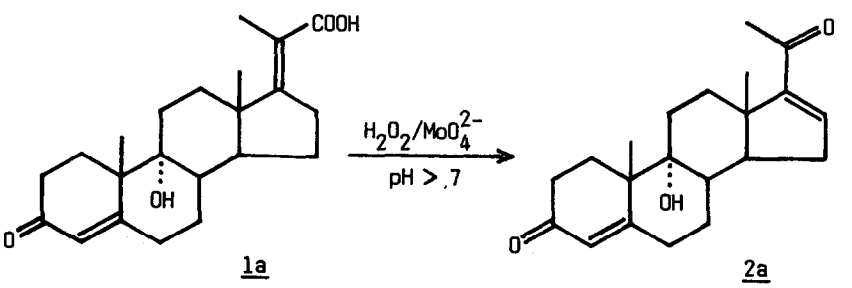
Summary: 17(20)-dehydro-23,24-dinorcholan-22-oic acids, derived from natural sterols are converted with H_2O_2 in the presence of molybdate or tungstate ions into 16-unsaturated 20-oxo-pregnanes, which are useful intermediates of corticosteroid hormones and drugs.

16-Dehydro-20-oxo-pregnane derivatives used as intermediates in the synthesis of corticosteroids have been produced industrially by oxidative degradation of diosgenin[1]. Now we report a convenient process which yields 16-dehydro-20-oxo-pregnane derivatives by catalytic oxidative decarboxylation of 17(20)-dehydro-23,24-dinorcholan-22-oic acids obtained from sterols[2].

9α-Hydroxy-3-oxo-23,24-dinor-4,17(20)-choladien-22-oic acid (1a), produced from sitosterol by microbial side chain degradation[3] transformed readily into 9α-hydroxy-4,16-pregnadiene-3,20-dione (2a) by reaction with H_2O_2 in the presence of the salt of a transition metal oxoacid, such as ammonium paramolybdate or sodium tungstate in an alkaline aqueous medium[4].



1a 2a

Using this reagent Payne and Williams[5] prepared epoxy-derivatives from α,β-unsaturated aliphatic acids in an acidic medium. We did not observe the formation of 17,20-epoxydes from 1a during the preparation of 2a, although epoxidation of the 4(5)-double bond of 2a occured to a small extent. The products and yields obtained by this decarboxylation of 1a and some modified derivatives (1b-e) are compared in Table I.

Table I

Starting material	Reagent	Product	Yield(%)
9α-hydroxy-3-oxo-23,24-dinor-4, 17(20)-choladien-22-oic acid (1a)	H_2O_2/MoO_4^{2-}	9α-hydroxy-4,16-pregnadiene-3,20-dione (2a)	66
3-oxo-23,24-dinor-4,9(11),17(20)-cholatrien-22-oic acid (1b)	H_2O_2/MoO_4^{2-}	4,9(11),16-pregnatriene-3,20-dione (2b)	63
3-oxo-23,24-dinor-1,4,9(11),17(20)-cholatetraen-22-oic acid (1c)	H_2O_2/WO_4^{2-}	1,4,9(11),16-pregnatetraene-3,20-dione (2c)	58
3,3-ethylenedioxy-23,24-dinor-5,9(11), 17(20)-cholatrien-22-oic acid (1d)	H_2O_2/MoO_4^{2-}	3,3-ethylenedioxy-5,9(11),16-pregnatrien-20-one (2d)	70
3-methoxyimino-23,24-dinor-4,9(11), 17(20)-cholatrien-22-oic acid (1e)	H_2O_2/WO_4^{2-}	3-methoxyimino-4,9(11),16-pregnatrien-20-one (2e)	95

By protecting the 3-oxo-group the unwanted epoxidation of the 4(5)-double bond can be avoided. The presence of the 9(11)-double bond in 2b-e affords a possibility for the introduction of an 11β-hydroxyl group as well as a 9α-fluoro substituent in the course of the synthesis of corticosteroid hormones and drugs.

For studying the mechanism of this reaction we attempted the decarboxylation of 3-oxo--1,4,9(11),16-androstatetraene-17-carboxylic acid (3) and 3-oxo-16-methyl-1,4,9(11),16--androstatetraene-17-carboxylic acid (4) prepared from prednisolone. Compound 3 is not decarboxylated while 16-methylene-1,4,9(11)-androstatriene-3,17-dione (5) is formed from compound 4. Thus, a (Z)-arrangement of the carboxyl group and the bond from which the new double bond is formed is required for a successful decarboxylation. We assume that the transformation preceeds via a cyclic intermediate formed by the assistance of an activated catalyst.

The transformation of 17(20)-dehydro-23,24-dinorcholan-22-oic acids into 16-dehydro--20-oxopregnane derivative is a simple, one step reaction. It affords a new, useful tool for the synthesis of corticosteroids from the cheap, easily available plant sterols.

References and notes

1. R.E. Marker, T. Tsukamoto, D.L. Turner: J. Am. Chem. Soc., 62, 2525 (1940).
2. A. Toró, I. Pallagi, N. Makk, G. Ambrus: XIII. Conference on Isoprenoids, Poznan, 1989. Abstracts p. 86.; G.B. Pat. Appl. No. 2.199.325A (1987).; (C.A. 109: 190.659m).
3. A. Jekkel, É. Csajági, É. Ilkőy, G. Ambrus: J. Gen. Microbiol., 135, 1727 (1989).
4. Preparation of 2a: A solution of 1a (1075 mg, 3mMol) in 0.1 N NaOH (30 ml) is combined with a solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (351 mg) in water (6 ml) then pH is adjusted to 9.0 with cc. NH_4OH. 12 ml 30 % H_2O_2 is added dropwise at 30° within 1 hour, while 2a (705 mg) is precipitated. Mp. 186-192°C (acetone).
5. G.B. Payne, P.H. Williams: J. Org. Chem., 24, 54 (1959).

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