Delta 5-sterol en provitamiene D met vertakte sykettings
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1953

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Windaus, Lettré and Schenck synthesized 7-dehydrocholesterol (I) by pyrolysis of the dibenzoate of 7-hydroxycholesterol. On comparing this synthetic provitamin D with ergosterol (II) they came to the conclusion that a number of steroids differing in the degree of unsaturation and in the length of the side chain, but having the same system of conjugated double bonds in ring B of the nucleus, would be convertible to antirachitic substances (vitamins D) by irradiation with ultra-violet light.

To investigate the validity of this hypothesis De Vries prepared various provitamins D with side chains differing in length. All those having straight hydrocarbon side chains were inactive after irradiation, but 3β-hydroxy-17-(1-methyl-5-phenylpentyl)-A5,7-androstadiene (III) showed feeble antirachitic activity (< 3.5% of vit. D3). The conclusion was drawn that the side chain and especially the isopropyl group has a predominating influence on the antirachitic properties of the vitamins D.

The object of the present research, which originated from De Vries' assumption, was to prepare various provitamins D in which branched (swallow-tailed) side chains occur and to compare the properties of their irradiation products with a standard solution of vit. D3.

Two series of compounds were synthesised viz.:

10. A5-steroids and provitamins D having a swallow-tailed carbon atom at the end of the side chain attached to C17;

20. Similar compounds having a side chain ending in a swallow-tailed nitrogen atom.

Using 3β-acetoxy-A5-cholenic acid (IV) and bisnorcholeenic acid (V) as starting materials, acid chlorides were prepared from which C24- and C22-ketones could be obtained by interaction with suitable dialkylcadmium compounds. Allowance had to be made for the varying reactivity of the cadmium derivatives having branched alkyl groups. The instability of these cadmium-dialkyls necessitated for their synthesis the use of anhydrous CdBr2, which reacted much more quickly than CdCl2.

Because of steric hindrance reaction of C22-ketones with dithioglycol proved impossible and ethylene mercaptals could only be prepared from two C24-ketones. The low melting point and poor crystallising qualities of 3β-acetoxy-A5-norcholenyl-pentyl-3 ketone made it unsuitable for the further conversions.

The mercaptals were reductively desulphurised with Raney nickel and A5-steroids with branched hydrocarbon side chains were thus

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obtained. Allylic bromination with N-bromosuccinimide (NBS) according to the method of Ziegler and dehydrobromination with s-collidine resulted in the corresponding provitamins D (VI and VII), which were separated and purified as 3,5-dinitrobenzoates.

The acids IV and V were also converted into the acid chlorides, which furnished amides on reaction with (CH₃)₂NH and (C₂H₅)₂NH. These amides having swallow-tailed nitrogen atoms, were converted into provitamins D with NBS and s-collidine. Only in the case of the dimethylamide of 3β-acetoxy-Δ⁵,7-bisnorcholeadienic acid (VIII) could this compound be separated by recrystallisation from the simultaneously formed Δ⁴,6-isomer.

Reduction of the amide with an ethereal LiAlH₄ solution resulted in 3β-hydroxy-Δ⁵,7-bisnorcholeadienic-22-dimethylamine (IX).

All Δ⁵-amides previously prepared were also reduced to the corresponding amines in a similar way. It proved impossible to convert these Δ⁵-steroid amines into their 7-dehydro derivatives, because a considerable quantity of the basic material was precipitated as the hydrobromic acid salt on reaction with NBS in CCl₄. The origin of the hydrobromic acid has not been elucidated but it is probable that an originally brominated molecule was dehydrobrominated by still unchanged basic compound.

Altogether four new provitamins D (VI, VII, VIII, IX) were prepared. Their irradiation and the examination of the antirachitic properties were conducted by courtesy of Philips-Roxane Ltd, Weesp.

The antirachitic properties of the irradiation products of VI, VII, VIII and IX were determined and compared with those of standardised doses of vitamin D₃. The following activities were deduced: 1.8%, 0.9%, 0.4% and 1.9% respectively.

We may therefore conclude that not only is the swallow-tailed side chain of importance, but that the position of the branched atom in the chain is supremely significant. Attention is drawn to the higher activity of the amine IX in comparison with the corresponding amide VIII.