Synthese van nieuwe sterolen en provitamines D met gewijzigde zijketen

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VIII. SUMMARY.

All sterols which obtain antirachitic activity by ultraviolet irradiation show a conjugated system of double bonds (5,7) in ring B and a hydroxyl group at C_3 in the cyclopentanoperhydrophenanthrene skeleton.

Moreover, the nature of the side chain proves to be of great importance. The number of suitable side chain homologues however, was insufficient to relate structure with antirachitic activity. Some 7-dehydrocholesterols with various side chains were therefore synthesised.

Ergosterol was considered the best starting material, but the necessary protection of the conjugated double bonds proved to be rather complicated.

Maleic anhydride, the usual protecting agent, requires a temperature of 130° C for complete reaction with ergosteryl acetate. From the reaction mixture however, only 15-20 % of the required adduct (m.p. 217°) can be isolated. It was found that the residue contained isomeric addition products, together with some isomerised ergosteryl acetate which has a single absorption maximum at 251.3 mμ.

Since sulphur dioxide by reversible addition can block the conjugated system of simple butadienes, it was reacted with ergosteryl acetate. From this reaction we could only isolate isomers, no more than a very small part of which gave a maleic anhydride adduct. The absorption spectrum of the isomers again shows a single maximum at 251.3 mμ.

Ergosterol being therefore unsuitable as starting material for our syntheses, we used 3β-acetoxy-Δ5-cholenic and -bis-nor-cholenic acid chlorides, which give with dialkylcadmium 24- and 22- ketosteroids respectively.

To reduce the carbonyl groups to methylene, we prepared the ethylene mercaptals, which, by reductive desulphurisation with Raney nickel, gave 3β-acetoxy-17-alkyl-Δ5-androstenes with a good yield.

Several steryl esters, in particular bis-nor- and nor-cholesteryl acetate give brightly coloured liquid crystals. The physical study of this phenomenon (by Hl de Vries) has revealed the probability, that the molecules form screwed piles.

From the fact that cholesterol synthesised in this way is identical

with natural cholesterol, we conclude that there is no change whatever in the configuration at the asymmetric carbon atoms.

We prepared from the sterols, using N-bromosuccinimide, the 7-bromo derivatives, which lose HBr under the influence of collidine, giving rise to sterols with the required conjugated system of double bonds in ring B.

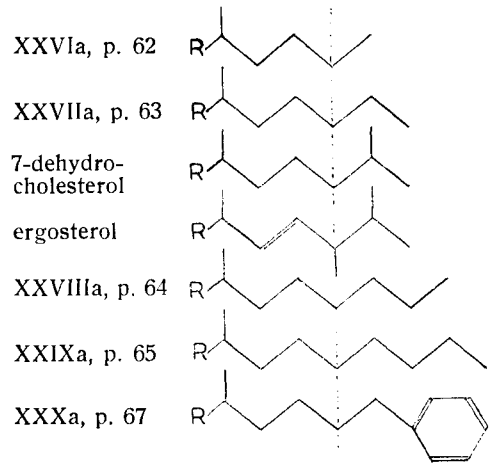
The irradiation of the new provitamins D and the examination of the pharmacological properties of the products have been made possible by the courtesy of Philips-Roxane Ltd in Weesp.

The irradiated provitamins were administered to rachitic rats. Their recovery after 14 days was evaluated by means of an X-ray photo of the knee joint.

Four of the five irradiated products have proved to be antirachitically inactive.

Irradiated 3β-hydroxy-17-(1-methyl-5-phenylpentyl)-Δ5,7-androstadiene (XXXa), however, shows a feeble antirachitic activity. This result is of some importance, because the phenyl group attached to C_{25}, in spatial configuration, recalls the terminal isopropyl group of which, in the active vitamins, C_{25} forms the central atom.

Thus the side chain — and especially the isopropyl group — seems, in contradistinction to the current opinion, to have a predominant influence on the antirachitic properties of the vitamins D.



The modifications made in the side chain of the common provitamins D (7-dehydrocholesterol and ergosterol) appear from a comparison of the formulas (R = $C_{19}H_{27}O$). The side chain of cholenic acid has been extended, by synthesis, with the hydrocarbon rests to the right of the dotted line.