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STEROIDS. PART VII [x/]

A CONVENIENT SYNTHESIS OF STEROID 3β-HYDROXY-4,6-DIENES

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In the course of our work on industrial synthesis of vitamin D_3 we investigated dehydrobromination of 7-bromocholesterol esters to the corresponding 7-dehydrocholesterol derivatives.

It is known, that dehydrobromination of esters of 3β-hydroxy-7-bromo-Δ^5--steroids gives a mixture of products, in which either a 4,6-diene (III) or a 5,7-diene (IV) predominates, depending on the nature of the dehydrobrominating agent. Organic and inorganic bases do not act selectively, and give mixtures of isomers. The yields of individual isomers obtained by dehydrobromination in the presence of the bases were invariably lower than 65% (1). This can be explained in terms of the classical E_1 mechanism (2,3). The formation of the allylic carbonium ion (II) is followed by the loss of a proton either from position 7 to give the diene (IV) or from position 4 to give the diene (III) resp.

However, the dehydrobromination reaction could also fellow the E_2-rule (bimolecular elimination), which means that it would depend on the concentration of alkali. In this case also an additional condition must be fullfilled. The attacking base, the atoms to be eliminated and both carbon atoms must be in the

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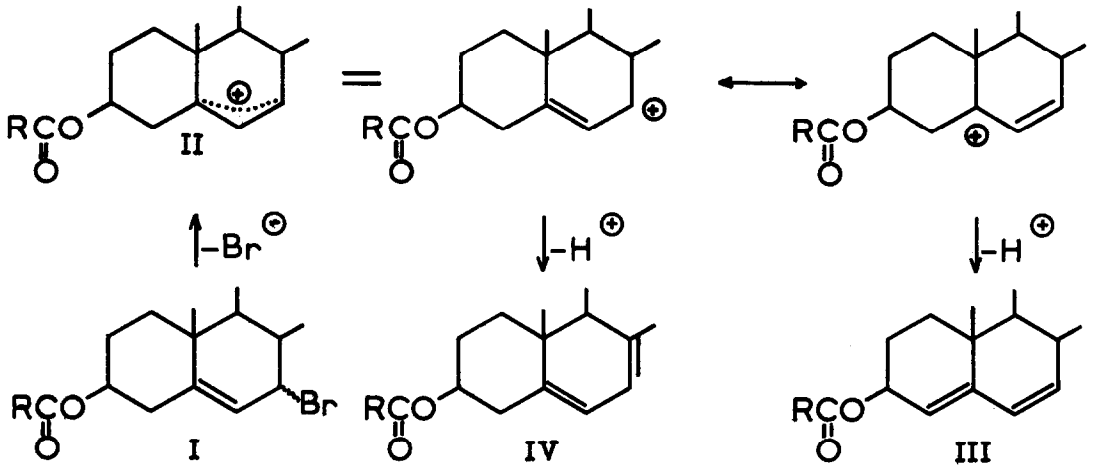
same plane, consequently in the case of cyclic compounds both hydrogen and bromine atoms should have the transdiaxial configuration.



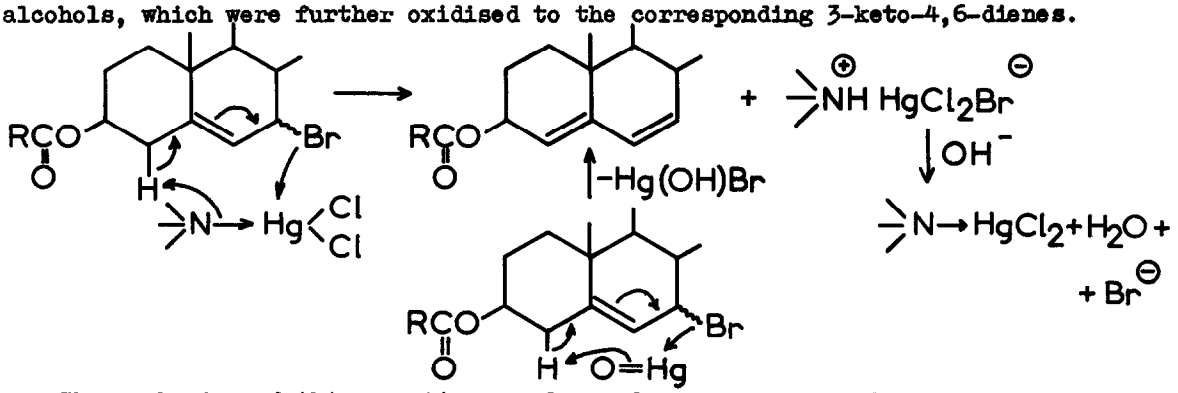
In our case it would mean that a 5,7-diene would be formed when the bromine atom on carbon atom in position 7 is α (axial), since hydrogen linked with carbon atom in position 8 is always β (axial). In fact no relation between the configuration of bromine atom in position 7 and the yield of 5,7-diene was observed.

We considered a possibility that a rapid epimerisation of Br-atom may facilitate the reaction and as a result better yields of one isomer could be obtained. It is known (4), that mercury salts cause epimerisation of both isomers, and therefore we used them as dehydromination catalysts.

In order to keep the concentration of alkali very low and constant we attempted to carry out the dehydrobromination with inorganic bases dispersed in a nonpolar solvent in the presence of catalytic amount of mercuric chloride and catalytic amount of organic base. Surprisingly only one product i.e. 3β -acyloxy-4,6-diene (III) could be isolated from the reaction mixture in very good yield(up to 90%).

We carried out this reaction not only with 7-bromocholesterol esters but also with the corresponding derivatives of sitosterol and androstane, and in all cases we obtained the same result i.e. the 4,6-diene in excellent yield (70-90%).

The isolation of the product was very simple and consisted of filtration of the reaction mixture, evaporation of the filtrate to dryness under reduced pressure and crystallisation of the crude product from acetone. The 4,6-diene--esters thus obtained were converted by alkaline hydrolysis to the free alcohols, which were further oxidised to the corresponding 3-keto-4,6-dienes.



The mechanism of this reaction can be explained in the following way : organic bases like pyridine, collidine, quinoline etc. and mercuric salts form complexes, in which the mercury atom coordinates with the nitrogen atoms. The large size of these complexes prevents their attack on hindered positions in the steroid nucleus, such as position 8. On the other hand the mercury salts promote the loss of the bromide ion. The resulting carbonium ion rearranges to the more stable tertiary carbonium ion. The loss of the C_4-proton and the migration of the double bond result in the formation of the 4,6-diene.

This mechanism would mean, that the reaction is in principle an E_1-elimination, but the stereochemical factors play a very important part, and the whole mechanism is a concerted one.

We also observed that when an excess of the organic base was used in the presence of small amounts of mercuric chloride, both dienes were formed. This indicates that a competetive E_2-reaction also took place.

Of course the mercury - organic base complex decomposes during the reaction, and a quaternary bromide and mercuric chloride are formed, but the inorganic base regenerates the organic base, which again forms the complex with mercuric chloride.

We also observed that exactly the same result can be obtained when the

7-bromosteroid is refluxed in benzene with an excess of mercuric oxide alone. This must be a heterogenous reaction, but its mechanism is very similar to that described above. Mercuric oxide, acting as a base, can attack the hydrogen only from the side of carbon atom 4; at the same time mercury combines with the negative bromine atom, and after the migration of the double bond and the loss of proton the same 4,6-diene is formed.

The yields of this dehydrobromination are very high and the reaction should be applicable to cyclic systems in general.

A detailed report on this work will be published soon elsewhere.

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