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(Hydroxyalkyl)pyridines as Bifunctional Catalysts. Dehydrobromination of 7-Bromocholesterol

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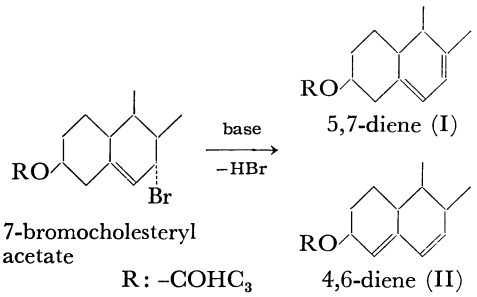
Synopsis. In the dehydrobromination of 7-bromocholesterol, the reactions catalyzed by 2- and 3-(hydroxyalkyl)-pyridines afforded 5,7-diene and 4,6-diene as the main product, respectively. The relative isomer ratio has been related to the position of the hydroxyalkyl group of the (hydroxyalkyl)pyridines. The results have been interpreted in terms of a concerted mechanism through a cyclic intermediate.

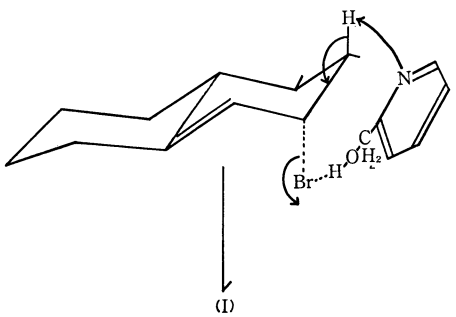
Increased attention has been paid to bifunctional catalysts in connection with biochemical reactions.[1-6] A selective rearrangement of penicillin *S*-oxide to isothiazolone using (hydroxyalkyl)pyridines as catalysts has been reported and the mechanism interpreted as a concerned reaction through a cyclic intermediate.[7] In the course of studies on the catalytic activities of (hydroxyalkyl)pyridines, it has been found that 2- and 3-(hydroxyalkyl)pyridines act as bifunctional catalysts in the dehydrobromination of 7-bromocholesterol.



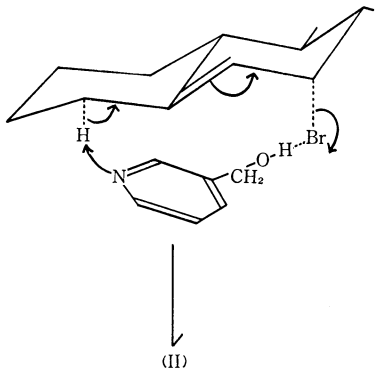
7-bromocholesteryl acetate

R: $-COHC_3$

It is known that the dehydrobromination of esters of 3-β-hydroxy-7-bromo-Δ^5-steroids gives a mixture of products, in which either a 5,7-diene or a 4,6-diene predominates, depending on the nature of the dehydrobrominating agent. Organic and inorganic bases do not act selectively and give mixtures of isomers.[8-10] When the dehydrobromination was carried out in the presence of 2-(hydroxyalkyl)pyridines, the 5,7-diene (I) was obtained as the main product. The reaction catalyzed by 3-(hydroxyalkyl)pyridines, on the other hand, afforded the 4,6-diene (II) selectively. The employment of 4-(hydroxyalkyl)pyridines showed no selectivity in the formation of (I) or (II) compared with the 2- and 3-(hydroxyalkyl)pyridines. The results are summarized in Table 1.



(I)



(II)

Table 1. Yield and relative ratio (I/II)

Base	Yield(%)[a] (I)	Yield(%)[a] (II)	Relative ratio[b] (I/II)
2-(Hydroxymethyl)pyridine	43.9	31.1	1.41
2,6-(Dihydroxymethyl)pyridine	44.1	30.8	1.43
2-(2-Hydroxyethyl)pyridine	46.1	29.0	1.59
2-(3-Hydroxypropyl)pyridine	41.9	31.2	1.34
Pyridine	23.4	35.4	0.66
2-Ethylpyridine	26.5	31.2	0.84
2-Propylpyridine	26.8	27.8	0.96
3-(Hydroxymethyl)pyridine	19.7	56.3	0.35
3-(3-Hydroxypropyl)pyridine	20.5	54.0	0.38
3-Ethylpyridine	22.6	35.9	0.63
4-(Hydroxymethyl)pyridine	24.6	49.3	0.50
4-(3-Hydroxypropyl)pyridine	25.8	49.7	0.53
4-Ethylpyridine	23.7	42.1	0.56
4-Propylpyridine	22.8	42.1	0.54

a), b) Yield and relative ratio were determined by GLC.

The interpretation is that a 5,7-diene (I) would be formed when the bromine atom on the carbon atom in position 7 is α, since hydrogen linked with the carbon atom in position 8 is always β. 7-Bromocholesteryl acetate employed in the reaction is considered to consist primarily of 7-α-bromocholesteryl acetate as suggested by Bernstein.[9] However, Jaworeska observed no relation between the configuration of the bromine atom in position 8 and the yield of 5,7-diene(I), and suggested the possibility of a rapid epimerization of the bromine atom.[11]

As can be seen in Table 1, 2- and 3-(hydroxyalkyl)-pyridines showed selectivity in the formation of (I) and (II) compared to the corresponding alkylpyridines. This

suggests that the steric and inductive effects are excluded and the hydroxyl group plays an important role in the selective formation of (I) and (II). The reported results above are most readily rationalized by a concerted mechanism involving a cyclic intermediate. The reaction may be initiated by the abstraction of a proton in position 8 or 4. The abstraction of the proton in position 8 competes with that in position 4, giving rise to the 5,7-diene (I) and the 4,6-diene (II), respectively. In the case of 2-(hydroxyalkyl)pyridines, the base abstracts the proton in position 8 and the reaction is considered to proceed through the cyclic intermediate by the interaction of the hydroxyl group with the bromine atom to give (I) as the main product.

When 3-(hydroxyalkyl)pyridines are employed, the preferential formation of (II) can be interpreted by assuming the selective abstraction of the proton in position 4 followed by the formation of a cyclic intermediate as depicted in the figure. It is highly probable that 4-(hydroxyalkyl)pyridines can not form cyclic intermediates since the interaction of the hydroxyl group with the bromine atom is considered to be difficult. This explains the absence of selectivity observed in the reaction catalyzed by 4-(hydroxyalkyl)pyridines compared with 2- and 3-(hydroxyalkyl)pyridines. The most plausible mechanism explaining the catalytic activities of 2- and 3-(hydroxyalkyl)pyridines is shown below.

Further work including a extension of the reaction and a mechanistic study of the reaction is now in progress.

Experimental

GLC was recorded on a Hitachi 023 gas chromatograph equipped with a flame ionizer detector.

A typical procedure is described for the reaction of cholesteryl acetate with 2-(hydroxymethyl)pyridine; A hexane solution (100 ml) of cholesteryl acetate (4.3 g, 10 mmol), *N*-bromosuccinimide (2.1 g, 12 mmol) and a catalytic amount of benzoyl peroxide was allowed to reflux for 1 h. After the reaction, the hexane solution was filtered to remove succinimide and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in butyl acetate (50 ml) and 2-(hydroxymethyl)pyridine (1.3 g, 12 mmol) was added. The mixture was heated under reflux for 1 h. The solution was washed with dilute hydrochloric acid and water, dried over anhydrous Na_2SO_4 and the extract condensed under reduced pressure. The residue was analyzed by GLC.

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