THE SELECTIVE HYDROLYSIS OF ± 3α, 6β-DIACETOXY-TROPANE

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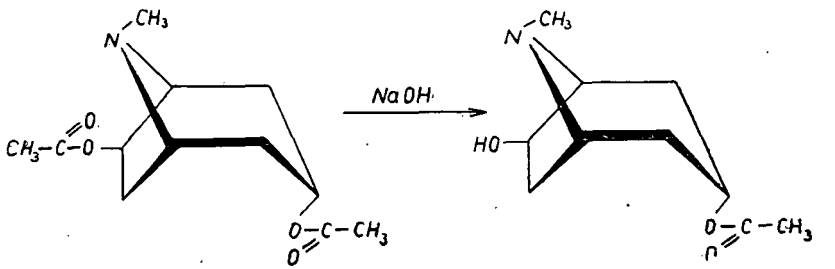
The selective hydrolysis of 3α, 6β-diacetoxy-tropane afforded 3α-acetoxy-6β-oxy-tropane. The optimum temperature and duration of the reaction were established by calculations on the basis of titrations.

The selective esterification of the hydroxyl group attached to the C_3 atom is a decisive step in the synthesis of tropane alkaloids containing an O function in position C_6. In connection with the synthesis of scopolamine and valeroidine, several unsuccessful attempts are described in literature, the majority of which failed since 3α, 6β-dihydroxy-tropane could not be selectively acylated [1], [3].

The process in question was carried out first in 1955 in this Institute indirectly by preparing 6β-hydroxy-tropinone-6-phenyl carbamate. Reduction of this compound followed by acetylation in position 3 and thermic decomposition of the phenyl carbamate bond afforded 3α-acetoxy-6β-oxy-tropane (II), the important starting material for synthesizing both alkaloids [4]. In our



I. II.

Fig. 1

first series of syntheses we were obliged to use this long and rather inconvenient chain of reactions [5], [6].

Recently, however, we observed that 3α, 6β-diacetoxy-tropane (I) loses under the experimental conditions of the KUNTZ hydrolysis first only its acetyl group in position C_6, completely deacetylated-product being isolable but after a treatment of longer duration. In order to produce the maximum quantity of monoacetyl compound (II), a series of titrations was carried out

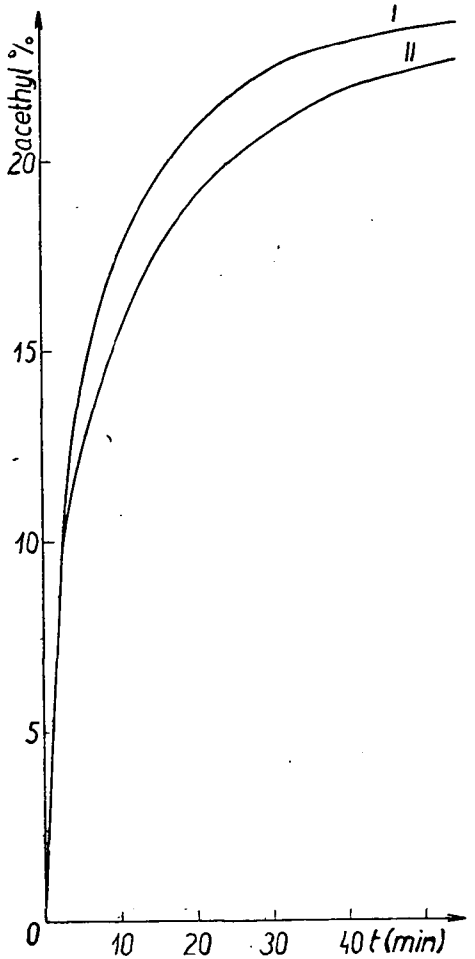


Fig. 2

at different temperatures. By calculations conducted on the basis of the results obtained, we were able to establish the optimum temperature and duration for this reaction.

The curves plotted on the basis of titration results indicate that, in the interval studied, the hydrolysis is, from the point of view of preparation, not affected decisively by temperature.

A bimolecular velocity equation was used at our calculations since the excess of alkali (40%) seemed to exclude the application of the pseudo-monomolecular equation. Thus, making use of the formula

$$k = \frac{1}{t} \cdot \frac{0{,}434}{A-B} \log \frac{B(A-c)}{A(B-c)}$$

where t is time in minutes, A the initial concentration of NaOH in millimoles/liter, B the concentration of $3\alpha, 6\beta$-diacetoxy-tropane (I) in millimoles/liter, c the actual concentration of acetyl in millimoles/liter, we obtained, on the basis of the values of curve I of Fig. 2 measured at 30,6°C, for the mean values of k

$$\overline{k} = 5{,}99 \cdot 10^{-4} (\pm 0{,}24 \cdot 10^{-4}) \text{ min}^{-1}$$

whereas use of titration values obtained at 19,9°C (curve II of Fig. 2) afforded

$$\overline{k} = 4{,}68 \cdot 10^{-4} (\pm 0{,}45 \cdot 10^{-4}) \text{ min}^{-1}.$$

In these calculations, we considered the initial section (first 20 minutes) of titration curves where no appreciable amounts of deacetylated product formed in later periods were present.

According to experiences gathered in preparative experiments, when hydrolysis is stopped in any period after the initial section of twenty minutes, always three types of products appear. Namely, besides initial compound I and expected product II, also $3\alpha, 6\beta$-dihydroxy-tropane, the completely deacetylated product, is present. We set the aim to calculate the duration of reaction at which a maximum conversion is attained, *i.e.*, at which a maximum quantity of II is present with a minimum amount of deacetylated product.

Quantities of acetyl determined by titrations at 30,6°C were plotted in millimoles/liter against the time, in curve I of Fig. 3. Curve II was obtained from values c calculated by the equation originally used for deriving values of $\bar{k}$, on substituting known values for $\bar{k}$. The difference of curves I and II, namely, curve III indicates in any moment the quantity of 3α, 6β-dihydroxy-tropane, as a product of the further hydrolysis of II formed.

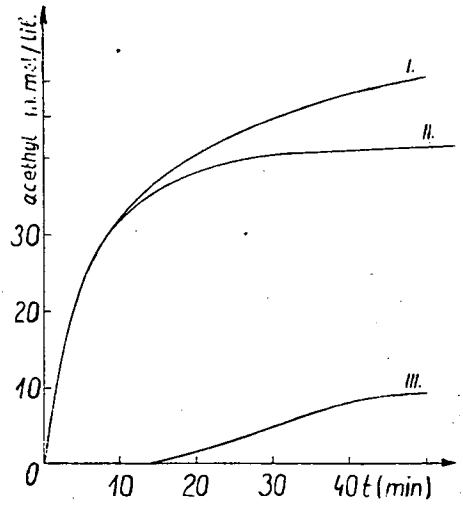


Fig. 3

Thus, in accordance with preparative experiments, it can be stated that it is practical to stop hydrolysis in the 65th minute of reaction although the quantity of monoacetyl compound shows further rise. However, unhydrolysed I can be instantaneously retransferred in the reaction, and 3α, 6β-dihydroxytropane formed in rising quantities can be isolated from the reaction mixture only with difficulty, being available for the preparation of II solely after acetylation.

Experimental

± 3α-acetoxy, 6β-oxy-tropane (II). 24 g of I was dissolved in a mixture of 700 ml of acetone and 1700 ml of 0,1 N sodium hydroxyde. The solution was kept at 30°C and 65 minutes after combining the solvents, the liquid was neutralized with 1,0 N hydrochloric acid to accurately pH 7, acetone and water removed from the reaction mixture under reduced pressure, at a temperature below 70° C. On dissolving the residue in 250 ml of distilled water, the solution was adjusted with potassium carbonate to pH 10, extracted with 2 × 100 ml and 6 × 50 ml portions of chloroform, the chloroformic solution dried over sodium sulphate evaporated to dryness under reduced pressure, and the residue treated with some waterfree ether to afford 15,6 g of white crystalline II, m. p. 116—117°C (yield 78%). Evaporation of the ethereal solution yielded further 3,84 g of a brownish oil identical with I, which could be converted by hydrolysis. (Conversion 96%). Completely deacetylated 3α, 6β-dihydroxy-tropane insoluble in chloroform was extracted by butanol from the aqueous residue of the chloroformic extract, yield 0,18 g of substance with m. p. 181°C.

Experimental conditions of titrations. 0,5028 g of 3α, 6β-diacetoxy-tropane dissolved in a mixture of 15 ml acetone and 35 ml of 0,1 N sodium hydroxide was kept in thermostat, samples of 1 ml being taken in intervals of five minutes. In order to suppress hydrolysis, 2 ml ethanol was added to each sample, then titrated with 0,01 N ethanolic hydrochloric acid in the presence of phenolphthalein as indicator.

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