A Rearrangement Occurring under the Prévost–Woodward Reaction Conditions

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MISHIMA, KURABAYASHI, and IWAI[1] recently reported that the stereochemistry of galanthamine (I) could not be that suggested by Barton and Kirby[2] since the octahydroindole (II) derived from galanthamine was not identical with the product obtained by the stepwise transformations of thebaine, although identity was to have been expected.

In contrast, one of us (S.U.)* was convinced from previous experimental findings that galanthamine was correctly represented by the stereostructure (I)[2] and, therefore, that in the course of transformation reactions carried out by the Sankyo group some unexpected reaction had led to a compound other than the octahydroindole (II). We have now carried out a joint research to establish this contention.

First, it was decided to ascertain whether the key intermediate obtained by the Prévost–Woodward reaction on 14-hydroxydeoxydihydrocodeine methine (III) had structure (V), which was assigned to it previously. If such was the case, the compound should be identical with the product of periodate oxidation of the methine (III). We have found that this product (V; R = CHO) exhibited the ultraviolet, infrared, and nuclear magnetic resonance spectra expected from its structure, and its combustion values were also in good agreement with those calculated for the formula, $C_{18}H_{23}NO_4$, but it was different from the compound obtained by the Prévost–Woodward reaction on the methine (III).

In view of this discrepancy the structure of the Prévost–Woodward oxidation product of 14-hydroxydeoxydihydrocodeine methine was reinvestigated. New analytical values for this substance and its oxime corresponded more precisely to $C_{19}H_{25}NO_4$ and $C_{19}H_{26}N_2O_4$, respectively, rather than $C_{18}H_{23}NO_4$ and $C_{18}H_{24}N_2O_4$, as previously assigned, though the respective differences of theoretical values between these pairs of formulae were within experimental error. However, convincing evidence for the higher-molecular-weight possibilities was provided by mass-spectral data. While the parent aldehyde showed a strong fragment peak at m/e 302 (M–CHO),$^+$ the benzyl alcohol obtained by catalytic reduction of the aldehyde function in this compound and the methyl derivative isolated by the Wolff–Kishner reduction of the aldehyde showed parent peaks at m/e 333 and 317, respectively. In contrast, the mass peaks for the benzyl alcohol and the methyl derivative

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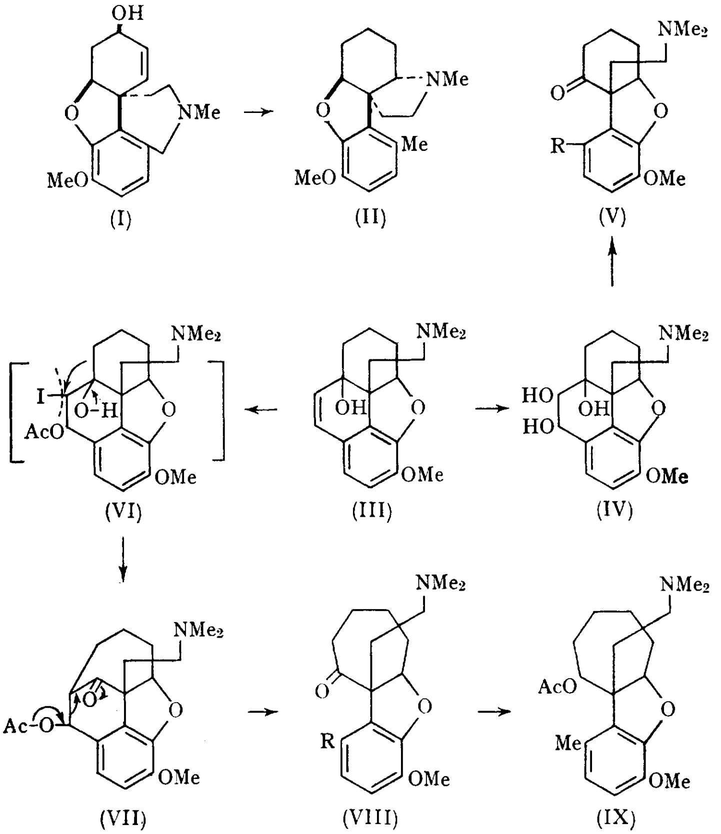
* Details of the experimental results will be published elsewhere. It may be added that D. J. Williams and D. Rogers have recently confirmed the constitution and absolute stereochemistry of galanthamine (I) by a three-dimensional *X*-ray study (*Proc. Chem. Soc.*, 1964, 357).

[1] H. Mishima, M. Kurabayashi and I. Iwai, *J. Org. Chem.*, 1963, **28**, 2621.

[2] D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806.

calculated from the formulae assigned by Mishima *et al.* should have shown peaks at *m/e* 319 and 303, respectively. These figures were in good agreement with those obtained in the mass spectrum of the benzyl alcohol (V; R = $CH_2{\cdot}OH$) and the methyl derivative (V; R = CH_3) prepared by reduction of the keto-aldehyde (V; R = CHO).



Thus it has been established that the compound obtained by Mishima *et al.* by the Prévost–Woodward reaction with the methine (III) possesses the molecular formula $C_{19}H_{25}NO_4$ and its structure can now be reformulated as (VIII; R = CHO) on the basis of the following evidence.

The n.m.r. spectrum of the methyl compound (VIII; R = Me) showed no additional methyl signals other than the one (τ 7·97 singlet) attached to the benzene ring, indicating clearly that there is no possibility that other methyl or alkyl side chains are present in the molecule. It is probable, therefore, that the cyclohexane ring in compound (III) underwent enlargement giving a cycloheptane ring as represented by formula (VIII; R = CHO). The position of the ketonic group was deduced from its unreactivity to the carbonyl reagents, and from its failure to undergo the Wolff–Kishner and the Clemmensen reactions, indicating that the ketonic function is sterically hindered as might have been expected from formula (VIII; R = CHO). Furthermore the n.m.r. spectrum of a derivative (IX) obtained by sodium borohydride reaction of the ketone (VIII; R = Me) followed by acetylation of one of the resulting epimers showed a doublet (one proton, J = 7·5 c./sec.) centred at τ 4·45 providing confirmative evidence that the position of the acetoxyl group must be adjacent to a quaternary carbon atom. We envisage the formation of compound (VIII) by the following sequence of reactions (III→VI→VII→VIII; R = CHO).

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