

The Base-Catalysed Equilibration of 6 α -Nitrocholest-4-ene and 6 β -Nitrocholest-4-ene

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Abstract

Treatment of 6 β -nitrocholest-4-ene with a catalytic amount of sodium methoxide in methanol gave an equilibrium mixture which contained the starting material and the 6 α -epimer in a 1 : 1 ratio. The unusual stability of the 6 β -epimer is explained by electronic factors.

In connection with our study of the photochemistry of 6-nitrocholest-5-ene,¹ we had reason to determine the ratio of 6 α -nitrocholest-4-ene (1) to 6 β -nitrocholest-4-ene (2) after equilibration with base. It had been shown earlier^{2,3} that 6 β -nitrocholest-5-ene is formed in high yield in a kinetically controlled protonation of the *aci*-nitronate salt formed from 6-nitrocholest-5-ene. We have recently confirmed this and shown that the epimers (1) and (2) are present in a ratio of 1 : 9.¹ McKenna *et al.*³ had shown that the 6 α -epimer (1) could be obtained in about 30% yield on treatment of (2) with a catalytic amount of sodium methoxide over 6 days, but they did not determine the composition of the equilibrium mixture. They predicted that the equilibrium concentration of (1) would 'undoubtedly be much higher' than their isolated yield.

We have reported¹ that the percentages of (1) and (2) in a mixture are readily calculated from the integrated n.m.r. spectrum and we have used this method to reexamine the base equilibration of (1) and (2). When (1) was treated with a catalytic amount of sodium methoxide in methanol under nitrogen for 5 days, the only compounds present were (1) and (2) in the ratio 45 : 55, which was unaltered by extending the reaction time to 10 days.

The 1 : 9 mixture of (1) and (2) produced on kinetically controlled protonation of the *aci*-nitronate salt has been rationalized as resulting from faster protonation at C6 on the less-hindered α -face of the molecule; however, the approximately equal stabilities of (1) and (2) are perhaps a little surprising. On the grounds of steric hindrance by the C10 methyl group, a 6 α -nitro steroid might be expected to be thermodynamically more stable than its 6 β -epimer. This expectation is confirmed for the 6-nitroprogesterones⁴ (3) and 6-nitrocholestanes² (4) with the 6 α -epimer accounting for more than 90% of the equilibrium mixture in both cases. On the

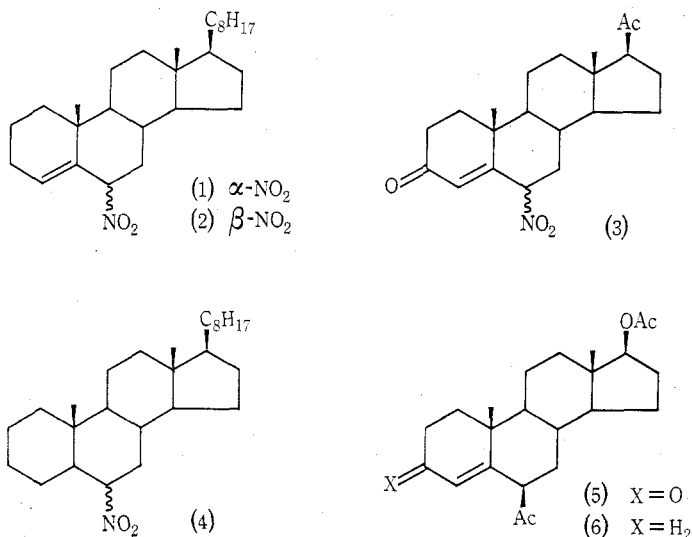
¹ Pinhey, J. T., Rizzardo, E., and Smith, G. C., *Aust. J. Chem.*, 1978, 31, 97.

² Bull, J. R., Jones, E. R. H., and Meakins, G. D., *J. Chem. Soc.*, 1965, 2601.

³ McKenna, J., McKenna, J. M., and Smith, P. B., *Tetrahedron*, 1965, 21, 2983.

⁴ Bowers, A., Sanchez, M. B., and Ringold, H. J., *J. Am. Chem. Soc.*, 1959, 81, 3702.

other hand, Gorodetsky *et al.*⁵ have found that acid-catalysed equilibration of 6 β -acetyltestosterone acetate (5), and base treatment of 6 β -acetylroast-4-en-17 β -yl acetate (6) followed by reacetylation, led to mixtures of approximately equal amounts



of the 6 α - and 6 β -epimers. The unexpected stability of these 6 β -substituted steroids has been rationalized by the authors in terms of homoconjugation between the 4,5-double bond and the carbonyl group, which is not possible in the 6 α -epimers. A similar interaction of π -orbitals is also possible in 6 β -nitrocholest-4-ene, and this may also be the explanation for the very similar stabilities of (1) and (2). Another feature of the 6-nitro compounds (1) and (2), which extends the analogy with the 6-acetyl compounds, is the similarity in the effective sizes of the nitro and acetyl groups when attached to a cyclohexane ring.⁶

As in the case of 6 β -acetylroast-4-en-17 β -yl acetate (6), support for the above suggestion is to be found in the ultraviolet spectrum of the 6 β -nitro epimer (2) which indicates coupling between the nitro group and the double bond. Whereas nitroalkanes generally display a weak $n \rightarrow \pi^*$ absorption band at 275–280 nm (ϵ 15–25),⁷ in compound (2) this band occurred at 292 nm (cyclohexane) with an enhanced absorption intensity (ϵ 90). Under the same conditions, compound (1) showed no absorption maximum in this region. Similar ultraviolet absorption data have been reported³ for compounds (1) and (2) in ethanol.

Although it is attractive to explain the stability of (2) in the above way, homoconjugation should also be possible in 6 β -nitroprogesterone, and it is not clear why a similar stabilization is not observed in that case.

⁵ Gorodetsky, M., and Mazur, Y., *J. Am. Chem. Soc.*, 1964, **86**, 5213; Gorodetsky, M., Amar, D., and Mazur, Y., *J. Am. Chem. Soc.*, 1964, **86**, 5218.

⁶ Hirsch, J. A., in 'Topics in Stereochemistry' (Eds N. L. Allinger and E. L. Eliel) Vol 1, p. 345 (Interscience: New York 1967).

⁷ Morrison, H. A., in 'The Chemistry of the Nitro and Nitroso Groups' (Ed. H. Feuer) Part 1, p. 79 (Interscience: New York 1969).

Experimental

General experimental procedures have been reported in an earlier paper.¹

Treatment of 6 β -Nitrocholest-4-ene with Sodium Methoxide

6 β -Nitrocholest-4-ene (180 mg) in methanol (40 ml) was heated under reflux in the presence of sodium methoxide (2 mg) for 5 days under nitrogen. The solution was cooled and acidified with acetic acid. Filtration and removal of the solvent gave a yellow gum which was shown by n.m.r. spectroscopy, as previously described, to contain 6 α -nitrocholest-4-ene (1) and 6 β -nitrocholest-4-ene (2) in the ratio 45 : 55.

Further treatment of the above mixture under the same conditions for another 5 days gave material in which the ratio of (1) to (2) was unchanged. In addition, thin-layer chromatography and n.m.r. and i.r. spectra of the mixture indicated that (1) and (2) were the only compounds present in the mixture.

Acknowledgment

This work was supported by a grant from the Australian Research Grants Committee.

Manuscript received 2 June 1978