Tetrahedron Letters No.1, pp. 67-69, 1968. Pergamon Press Ltd. Printed in Great Britain.

CLASSIFICATION OF STEROID ALCOHOLS BY NMR SPECTROSCOPY

I. R. Trehan and C. Monder

Research Institute for Skeletomuscular Diseases
Hospital for Joint Diseases and Medical Centre,
New York, New York 10035

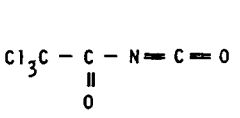
and

A. K. Bose

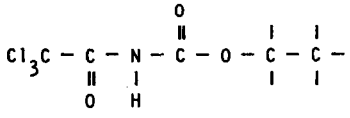
Department of Chemistry and Chemical Engineering
Stevens Institute of Technology, Hoboken, New Jersey 07030

(Received in USA 21 August 1967)

A recent communication[2] has described the use of trichloroacetyl isocyanate[3] (TAI), (I), for *in situ* reaction with alcohols for NMR studies. Since hydroxylation is a common occurrence during the metabolism of steroids, we have examined the usefulness of TAI for the NMR spectroscopy of steroid alcohols of various types. We find that, as a rule, a steroid carbamate II is formed from a steroid alcohol or phenol in a few minutes after the addition of TAI at room temperature.



I

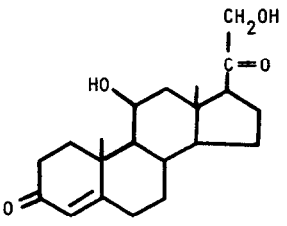


II

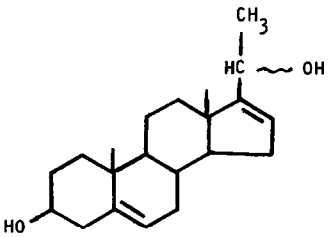
Even highly hindered hydroxy groups, such as the 11β- and 17α-hydroxy functions form carbamates without any noticeable dehydration.[4] Also, a steroid carbamate is generally more soluble than the corresponding alcohol in $CDCl_3$ or CCl_4. A polyhydroxy steroid undergoes reaction at each hydroxy group and the carbamate N − H signals appear usually in the τ 1-2 region as distinct singlets permitting the immediate determination of the total number of hydroxy functions. The area under such a singlet can serve as a convenient measure of a one-proton NMR signal for the quantitative estimation of the parent steroid. For example, a

suspension of cortisol acetate in $CDCl_3$ in an NMR tube produces a clear solution in a few minutes after the addition of a few drops of TAI (since TAI is devoid of protons, a moderate excess of the reagent is used). The NMR spectrum of this solution shows two singlets at τ 0.45 and 1.30 corresponding to the two hydroxy groups in this steroid.

Information about the environment of a hydroxy group can be obtained by comparison of the NMR spectra before and after addition of TAI.[2] Thus, the addition of TAI to 4-pregnen-11β, 21-diol-3,20-dione (III) converts the broad O — H signals in the τ 5-8 region to two one-proton singlets at τ 0.70 and 1.15 and shifts the carbinol protons downfield by characteristic amounts (0.5 - 0.9 ppm for primary alcohols and 1.0 - 1.5 ppm for secondary alcohols).[2] The C_{21}-methylene protons appears as a singlet at τ 5.20 showing that they have no vicinal proton neighbors; the primary nature of this alcohol group is indicated both by the 0.65 ppm shift to lower field and the two-proton area of the signal. The appearance of a rather broad one-proton signal at τ 5.60 (shifted downfield by 1.30 ppm) indicates the secondary nature of 11-hydroxy group and the presence of vicinal protons that are coupled with the carbinol proton.



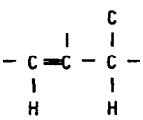
III



IV

We have found that the use of TAI reveals detailed information about allylic alcohols because the vinyl protons β to the hydroxy group are shifted downfield by about 10-15 cps on carbamate formation unlike the α-vinyl protons which suffer only a minor shift in comparison. For example, the addition of TAI to 5,16-pregnadien-3β,20ξ- diol[5] (IV) produces the following changes:

(a) a two-proton signal appears at τ 1.65, (b) two one-proton signals are shifted by 1.00 and 1.15 ppm to τ 4.62 and 5.35 (carbinol protons at C_3 and C_{16}), (c) one of the two vinyl proton signals is shifted downfield by 9 cps while the other signal is virtually unmoved. From this NMR data alone it is possible to conclude correctly that this steroid has two

secondary hydroxy groups, one of which is allylic and of the type  .

For the purpose of determining the substitution on a carbinol carbon, the use of TAI appears to have advantages over the earlier method of recording the NMR spectrum of an alcohol in DMSO.[6,7] The value of TAI for structure determination[8] and for the NMR study of amino compounds will be discussed in forthcoming publications.

Acknowledgments:- This research was supported in part by a grant from the U. S. Public Health Service (to C. Monder) and a grant from Research Corporation (to A. K. Bose).

References

1. (a) Presented in part at the 2nd Middle Atlantic Regional Meeting of the American Chemical Society, February, 1967, New York.
   (b) NMR Spectral Studies. V., for part IV, see A. K. Bose and I. Kugajevsky, Tetrahedron, 23, 1489 (1967).
2. V. W. Goodlett, Anal. Chem., 37, 431 (1965).
3. Available from Eastman Kodak Company.
4. Several of these carbamates have been characterized by elemental analysis and infrared absorption at 3.0 μ(N − H) and 5.55 μ (C=O).
5. Prepared by the reduction of 5,16-pregnadien-3β-ol-20-one acetate with $NaBH_4$ as an inseparable mixture of 20α- and 20β-isomers, see W. R. Benn, J. Org. Chem., 28, 3557 (1963).
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8. O. N. Devgan, M. M. Bokadia, A. K. Bose and M. S. Tibbetts, Tetrahedron Letters, 000 (1967).