Tetrahedron Letters No.52, pp. 3939-3943, 1964. Pergamon Press Ltd.
Printed in Great Britain.

LONG-RANGE SHIELDING EFFECTS OF THE NITRO GROUPS IN 6α- AND 6β-NITROTESTOSTERONES *

Kazuo Tori and Kaoru Kuriyama

Shionogi Research Laboratory, Shionogi & Co., Ltd.
Fukushima-ku, Osaka, Japan

(Received 11 November 1964)

HUITRIC and coworkers reported that a nitro group has the anisotropic long-range shielding effect similar to that of a carbonyl group (1, 2). Thereafter, from an NMR study of o-methyl-nitrobenzene derivatives, Yamaguchi (3) has elegantly shown that the nitro group exerts marked anisotropic shielding effect on the methyl group, and has calculated the principal magnetic susceptibilities of the nitro group. Recently, Stefaniak and coworkers (4, 5) have applied the anisotropic effect of the nitro group to the stereochemistry of some quaternary salts of 5-nitrotetrahydro-1,3-oxazines and nitropropenes. In the course of an NMR study of steroids we have also observed characteristic long-range shieldings by some nitro groups. It is believed worthwhile to add some further interesting examples of the effect of this group.

We have observed the NMR spectra of 6α-nitrotestosterone (I), 6β-nitrotestosterone (II) and its acetate (III) (6) to examine changes in the chemical shifts of the 19-methyl groups and the C_4-protons due to introduction of the C_6-nitro groups. Table I shows the NMR data, and in Fig. 1 are reproduced the signal patterns of the

---

* NMR Studies on Steroids, Part VIII. For Part VII, see K. Tori and T. Komeno, *Tetrahedron*, to be published.

TABLE I

Compound	Chemical shift (τ)[a]				
	C_{19}-H	C_{18}-H	C_6-H	C_4-H	C_3-H
I [b]	8.72 (-0.09)	9.18 (-0.03)	4.67	4.47 (+0.19)	
II [b]	8.88 (+0.07)	9.18 (-0.03)	5.16	3.92 (-0.36)	
III [b]	8.87 (+0.07)	9.14 (-0.02)	5.12	3.90 (-0.37)	
3β-Hydroxy-6α-nitro-5α-cholestane [c]	9.12 (-0.08)	9.34 (-0.02)	5.70		6.53 (+0.12)
3β-Acetoxy-6α-nitro-5α-cholestane [c]	9.10 (-0.08)	9.35 (0.00)	5.50		5.75 (+0.05)
3β-Acetoxy-5α-chloro-6β-nitro-5α-cholestane [c]	8.97 (+0.09)	9.28 (-0.06)	5.37		4.72 (+0.05)

a. Values in parentheses are the changes in the chemical shifts due to the nitro groups. Plus sign represents an upfield shift.

b: The spectra were recorded on a Varian A-60 spectrometer by using about 10% solutions in deuteriochloroform containing tetramethylsilane as an internal reference. Calibration of the spectrometer were checked by the usual side-band technique.

c. Reported values in carbon tetrachloride (10). Additional shift values in parentheses are somewhat ambiguous because the data on reference compounds employed (11) are those measured in deuteriochloroform.

C_6- and C_4-protons.

The configurations of the C_6-nitro groups in I and II were ascertained from the fact that the signals of the C_4- and $C_{6\beta}$-protons in I appear as a doublet (J=2.0 c.p.s.) and an octet (J=12.3, 4.7, and 2.0 c.p.s.), respectively, whereas those of the C_4- and $C_{6\alpha}$-protons in II appear as a singlet and a quartet (J=4.6 and 2.0 c.p.s.), respectively, as shown in Fig. 1 (7). In general, the C_4- and C_{19}-proton signals are fairly shifted downfield, at any rate, by a $C_{6\alpha}$- and a $C_{6\beta}$-substituent (CH_3, OR, SR, NRR', Hal, etc.) introduced, respectively (7). This fact has been ascribed to the magnetic anisotropy, polar and inductive effects, and the van der

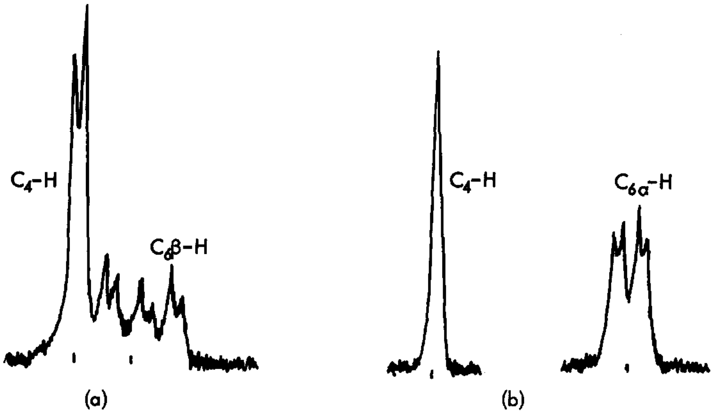

Fig. 1. Signal patterns of the C_4- and C_6-protons in I and II at 60 Mc. ((a) and (b), respectively).

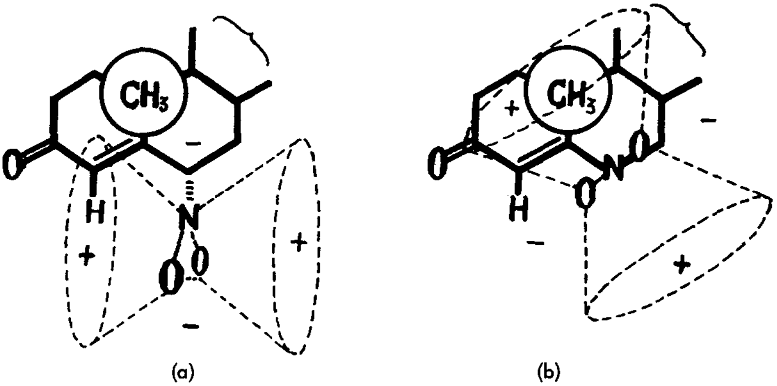

Fig. 2. An approximate representation of the long-range shielding cone of the nitro group.

Waals interaction of the substituent. However, the C_4-proton signal in I is fairly shifted upfield, whereas those in II and III are remarkably shifted downfield in comparison with those in their parent compounds, testosterone and its acetate; similarly, the 19-methyl protons in II and III are more shielded whereas those in I less shielded, as can be seen from Table I. Reported data on some other 6-nitrosteroids (10) show an analogous tendency for the effects of the nitro groups as also listed in Table I. In addition, the $C_{6\beta}$-proton signal in I appears at a remarkably lower field in comparison with the $C_{6\alpha}$-proton signal in II and III.

Of a particular interest is the fact that the C_4-proton in I and the C_{19}-protons in II and III are more shielded, although all the polar (5, 8), inductive, and van der Waals interaction effects (7, 9) should deshield the protons. This fact cannot be explained without taking into account the strong shielding effect of magnetic anisotropy of the nitro group. Inspection of molecular models suggests that both the $C_{6\alpha}$- and $C_{6\beta}$-nitro groups would not rotate freely aroung the C_6-N bond owing to the steric hindrance. Probable conformations of the nitro groups are illustrated in Fig. 2(a) and (b). In these situations, the nitro groups can exert the long-range shielding effects approximately in such a manner as shown in Fig. 2 upon the relevant protons although the shielding cone for a nitro group might not be simply illustrated. The present consideration is consistent with the observed facts.

Recent circular dichroism studies of nitrosteroids by Snatzke and coworkers (12) have conclusively demonstrated that the nitro groups in 6α- and 6β-nitrocholestanes are almost fixed in the conformations similar to those represented in Fig. 2 even at room temperature. This might amply justify our consideration.

Similar effects to the nitro group would be exerted by acetyl, formyl, and phenyl groups at the 6-position because they probably have similar conformations and long-range shielding cones. Therefore, in such a case caution must be taken when the configuration of a substituent is determined from an additional shift value of an angular methyl signal due to the substituent (13).

Acknowledgments —— We are very grateful to Dr. G. Snatzke of Organisch-Chemisches Institut der Universität Bonn for his kind sending of the manuscripts (12) prior to the publication and also to Dr. T. Sugasawa of this laboratory for providing us with the samples used.

REFERENCES

1. A. C. Huitric and W. F. Trager, *J. Org. Chem.* **27**, 1926 (1962).
2. W. F. Trager, F. F. Vincenzi, and A. C. Huitric, *Ibid.* **27**, 3006 (1962).
3. I. Yamaguchi, *Mol. Phys.* **6**, 105 (1963).
4. D. Gürne, T. Urbański, M. Witanowski, B. Karniewska, and L. Stefaniak, *Tetrahedron*, **20**, 1173 (1964).
5. Yu. V. Baskov, T. Urbański, M. Witanowski, and L. Stefaniak, *Tetrahedron*, **20**, 1519 (1964).
6. A. Bowers, M. B. Sánchez, and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3702 (1959); A. Bowers, L. C. Ibáñez, and H. J. Ringold, *Ibid.* **81**, 3707 (1959).
7. K. Tori and K. Kuriyama, *Chem. & Ind. (London)*, 1525 (1963).
8. A. D. Buckingham, *Can. J. Chem.* **38**, 300 (1960).
9. W. T. Raynes, A. D. Buckingham, and H. J. Bernstein, *J. Chem. Phys.*, **36**, 3481 (1962); T. Schaefer, W. F. Reynolds and T. Yonemoto, *Can. J. Chem.* **41**, 2969 (1963); W. Nagata, T. Terasawa, and K. Tori, *J. Amer. Chem. Soc.* **86**, 3746 (1964).
10. A. Hassner and C. Heathcock, *J. Org. Chem.* **29**, 1350 (1964).
11. K. Tori and T. Komeno, *Tetrahedron*, to be published.
12. G. Snatzke, *J. Chem. Soc.* in press; G. Snatzke, D. Becher, and J. R. Bull, *Tetrahedron*, to be published.
13. Refer to K. Tori, Y. Hamashima, and A. Takamizawa, *Chem. Pharm. Bull. (Tokyo)*, **12**, 924 (1964).