Tetrahedron, 1966, Vol. 22, pp. 1407 to 1413. Pergamon Press Ltd. Printed in Northern Ireland

NMR SPECTRA OF SOME TRANSFORMED STEROIDS

K. K. PIVNITSKY and I. V. TORGOV
Institute for Chemistry of Natural Products USSR Academy of Sciences, Moscow, U.S.S.R.

(*Received* 12 *June* 1965; *in revised form* 2 *November* 1965)

Abstract—The additive shielding of the signal from 18-methyl protons affected by some functional groups and changes in the molecules of 12 transformed steroid hormones has been deduced by means of NMR spectroscopy.

IN ORDER to clarify the configuration of D,L-$\Delta^{4,9}$-19-nor-D-homoandrostadiene-14α-ol-3,17a-dione,[1,2] the NMR spectra of some androstanes of the 19-nor, $\Delta^{4,9}$-3-oxo and D-homo series have been investigated. The data published on the NMR spectra of these steroids are fragmentary in character,[4–12] therefore, it was considered of interest to publish supplementary information and in particular the fundamental investigations carried out by Zürcher.[9]

RESULTS AND DISCUSSION

The NMR spectral data obtained and presented in Tables 1 and 2 show the effects of functional groups and changes on the chemical shift of the signal of the 18-methyl group protons (increments) in 14α-steroids. The calculated positions of signals from angular methyl groups in the steroids investigated as well as their deviations from the experimental data are presented in Table 3. These calculations are based on our own data and publications in the literature.

Regarding the increments given in Table 2 it will be noted that:

1 In the presence of the $\Delta^{5(10)}$-double bond, the increments of the substituents in the ring A of the steroids (Δ^1 and Δ^3, Δ^2, 3-methoxyl, 3-oxo groups) approximate zero.

2 These increments should be suitable for calculations and be independent of the size of ring D and the configuration at $C_{(14)}$ (as well as the increments of other substituents in the rings A, B and C of steroids[9]).

Further confirmation of conclusion 1 is offered by the results obtained by Johnson *et al.*[6] who established that the introduction of a methoxyl group at $C_{(3)}$ did not change

[1] N. N. Gaidamovich and I. V. Torgov, *Isv. Acad. Nauk SSSR. Ser. Chim.* 1803 (1961).
[2] N. N. Gaidamovich and I. V. Torgov, *Steroids* 729 (1964).
[3] N. N. Gaidamovich, K. K. Pivnitsky and I. V. Torgov, *Tetrahedron* in press.
[4] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.* **80**, 5121 (1958).
[5] N. R. Trenner, B. H. Arison, D. Taub and N. L. Wendler, *Proc. Chem. Soc.* 214 (1961).
[6] J. E. Cole, W. S. Johnson, P. A. Robins and J. Walker, *J. Chem. Soc.* 244 (1962).
[7] M. Amorosa, L. Caglioti, G. Gainelli, H. Immer, J. Keller, H. Wehrli, M. Lj. Mihailovic, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 2674 (1962).
[8] J. A. Steele, L. A. Cohen and E. Mosettig, *J. Amer. Chem. Soc.* **85**, 1134 (1963).
[9] R. F. Zürcher, *Helv. Chim. Acta* **46**, 2054 (1963).
[10] S. N. Ananchenko, V. N. Leonov, V. I. Zaretskii, N. S. Wulfson and I. V. Torgov, *Tetrahedron* **20**, 1279 (1964).
[11] *NMR at Work* No. 51, Varian Associates Instrument Division, *Chem. and Eng. News* Sept. 22nd, 59 (1958).
[12] R. F. Zürcher, *Chimia* **18**, 349 (1964).

the position of the signal from the angular methyl group in the NMR spectra of 17-furfurylidene derivatives of stereoisomeric $\Delta^{1,3,5(10),9(11)}$-19-nor-D-homoandrostatetraene-17a-ones. The increment of transition to 19-norsteroids has been taken as zero since under similar conditions testosterone and 19-nortestosterone have the $H_{(18)}$-signal position correspondingly at 47·2 and 47·3 c/s and a mixture of the two gives (at maximal resolution) only a single $H_{(18)}$-signal with the peak halfwidth of about 2 c/s (signal of tetramethylsilane had halfwidth of about I c/s).

The increment determination for transition to D-homosteroids presents a more difficult problem. In the only paper on NMR spectra of D-homosteroids published by Trenner *et al.*,[5] this increment was determined simply as the difference between the $H_{(18)}$-signal positions for an ordinary steroid and the corresponding D-homosteroid in which "the only change is that due to D-ring expansion by one CH_2 group".[5] But in fact the difference between these two steroids is more fundamental since the substituents in the ring D of D-homosteroids must in general have increments *differing*

TABLE 1. NMR SPECTRAL DATA OF STEROIDS EXAMINED
(Chemical shifts are measured from internal tetramethylsilane taken as zero)

		Chemical shift of signal from				
		$H_{(18)}$		$H_{(4)}$	$H_{(17)}$ or $H_{(17a)}$	Other protons
Number	Compound	c/s	ppm	ppm	ppm	ppm
I	Estradiol methyl ether	45·6	0·760		3·8	3·78 (CH_3O)
II	Estrone methyl ether	54·0	0·900			3·79 (CH_3O)
III	D Homoestrone methyl ether	68·0	1·133			3·84 (CH_3O)
IV	$\Delta^{2,5(10)}$-3-Methoxy-19-norandrostadiene-17β-ol	45·1	0·752		3·6	3·54 (CH_3O) 5·20 (C=C—H)
V	$\Delta^{5(10)}$-19-Norandrostene-17β-ol-3-one	45·2	0·753	2·70	3·6	2·40 (1,2-CH_2)
VI	$\Delta^{5(10)}$-19-Nor-D-homoandrostene-17aβ-ol-3-one	48·4	0·807	2·71	3·2	2·40 (1,2-CH_2)
VII	19-Nortestosterone	47·3	0·789	5·80	3·6	
VIII	Δ^4-19-Norandrostene-3,17-dione	54·7	0·913	5·81		
IX	$\Delta^{4,9}$-19-Norandrostadiene-17β-ol-3-one	52·5	0·876	5·62	3·6	2·40 (1,2-CH_2)
X	$\Delta^{4,9}$-19-Norandrostadiene-3,17-dione	59·8	0·998	5·60		2·40 (1,2-CH_2)
XI	$\Delta^{4,9}$-19-Nor-D-homoandrostadiene-17aβ-ol-3-one	57·6	0·960	5·62	3·2	2·43 (1,2-CH_2)
XII	$\Delta^{4,9}$-19-Nor-D-homoandrostadiene-3,17a-dione.	74·0	1·232	5·64		2·45 (1,2-CH_2)

TABLE 2. THE INCREMENTS OF GROUPINGS (FOR 18-METHYL GROUP) (unperturbed position of 18-methyl group signal in 5α, 14α-D-homoandrostane calculated as 44·5 c/s)

Grouping	Increment c/s	Increment ppm
19-Nor	0	0·00
D-Homo	+3	+0·05
3-Methoxy-$\Delta^{1,3,5(10)}$	+2	+0·03
3-Methoxy-$\Delta^{3,5(10)}$ "$\Delta^{5(10)}$"	+2	+0·03
3-Oxo-$\Delta^{5(10)}$	+2	+0·03
3-Oxo-$\Delta^{4,9}$	+9·5	+0·16
17a-Oxo (in D-homo series)	+21	+0·35
17aβ-Hydroxyl (in D-homo series)	+3	+0·05

All increments for 14α-steroids. Plus sign represents an downfield shift.

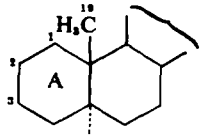
from the corresponding ones in ordinary steroids while the determination cited implicitly suggests *equality* of substituent increments in steroids under discussion. Since Trenner *et al.* used 17- and 17a-oxosteroids for D-homo increment determination it becomes clear why the increment of the 17a-carbonyl group quoted by the authors (+10·8 c/s) almost coincides with the increment of 17-carbonyl group in steroids having a five-membered ring D (+10·0 c/s[9]). However taking into consideration the rule of equality of increments for the same functions in equivalent positions,[9,13] a true

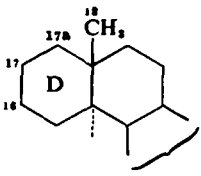
TABLE 3. THE COMPARISON OF CALCULATED AND MEASURED CHEMICAL SHIFT VALUES

Compound number	Calculated chemical shift of 18-methyl protons (c/s)	Difference from measured value (c/s)
I	45·5	−0·1
II	53·5	−0·5
III	67·5	−0·5
IV	45·5	+0·4
V	45·5	+0·3
VI	49·5	+1·1
VII	48·0	+0·7
VIII	56·0	+1·3
IX	53·0	+0·5
X	61·0	+1·2
XI	57·0	−0·6
XII	75·0	+1·0

analogy is expected in the behaviour of the corresponding substituents in the ring A of 5α-steroids, in the ring C of 14α-steriods and in ring D of D-homosteroids. For example, the increments of 1-, 12- and 17a-carbonyl groups should be almost identical in value and the same should be true for 2-, 11- and 17-carbonyl groups.

[13] E. R. Malinowski, M. S. Manhas, G. H. Müller and A. K. Bose, *Tetrahedron Letters* 1161 (1963).





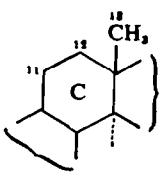


TABLE 4. THE COMPARISON OF INCREMENTS OF EQUIVALENT POSITIONED SUBSTITUENTS

Substituent	Carbonyl		Hydroxyl				
Position in ring A	1	2	1α	1β	2β	3α	3β
Substituent increments (for 19-methyl group), Zürcher's values[9]	+22·5	−1·5	+1·0	+3·0	+15	0	+2·0
Equivalent position in ring D of D-homo-steroid	17a	17	17aα	17aβ	17β	16α	16β
Substituent increments (for 18-methyl group), Trenner's values[5]	+10·8	0·0	−3·0	−3·0	+3·6	+2·4	+3·0

In fact the data obtained by Trenner *et al.*[5] are in contradiction with this rule as can be seen by a comparison (Table 4) with the data published by Zürcher[9] and therefore, the data obtained by Trenner *et al.*[5] has not been used in this work.

We believe that the D-homo increment should be considered as one of transition from an *unsubstituted* steroid (at least in the ring D) to an *unsubstituted* D-homosteroid. Unfortunately, it is impossible in this case to calculate exactly the D-homo increment based on our or published data since no increment of the substituents in the ring D of D-homosteroids is known and data on D-homosteroids unsubstituted in the ring D are not available. However, the problem could be solved if a definite value is assigned to one of the increments. For this purpose, +3 c/s has been chosen as the increment of an 17aβ-hydroxyl group, which is approximately equal to the increments of 1β- and 12β-hydroxyl groups in accordance with the rule cited above.[9,13] The value of D-homo increment presented in Table 2 has been calculated on the basis of this suggestion. It should be noted that certain groups in the ring A of a steroid (3-, Δ^4-3-, $\Delta^{1,4}$-3- and $\Delta^{4,9}$-3-oxo, Δ^2, Δ^4, $\Delta^{5(10)}$ and so on) exercise a considerable effect on the position of the signal from the distant 18-methyl group.[9] On expansion of the ring D to a six-membered one the value of this effect may change in such a way that, strictly speaking, the increments of *all* substituents should perhaps be changed. However we deem it more suitable to take the unchanged increments of the substituents in the rings A, B and C,[9] and to restrict the application of our D-homo increment (and probably increments of the 17a-carbonyl and 17aβ-hydroxyl groups) to the steroids investigated viz. the $\Delta^{5(10)}$- and $\Delta^{4,9}$-3-oxosteroids. This suggestion is reflected in item 2.

Regarding the general pattern of all $\Delta^{5(10)}$-3-oxo- and $\Delta^{4,9}$-3-oxosteroids, the presence of the intensive broadened peak near 2·40 ppm (integral intensity 4 protons) is the most characteristic feature. In addition, there is a similar peak near 2·70 ppm (integral intensity 2 protons) in the spectra of $\Delta^{5(10)}$-3-oxosteroids only (Figs. 1 and 2).

These peaks can only be interpreted as signals from the 4 protons at $C_{(1)}$ and $C_{(2)}$ (for compounds of types A and B) and from 2 protons at $C_{(4)}$ (for type A) respectively.

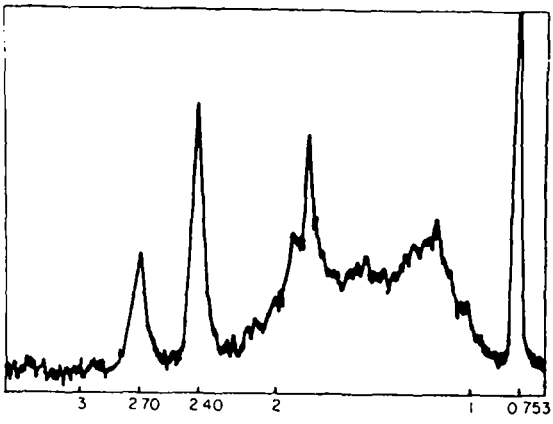


FIG. 1. Part of NMR spectrum of $\Delta^{5(10)}$-19-norandrostene-17β-ol-3-one (V).

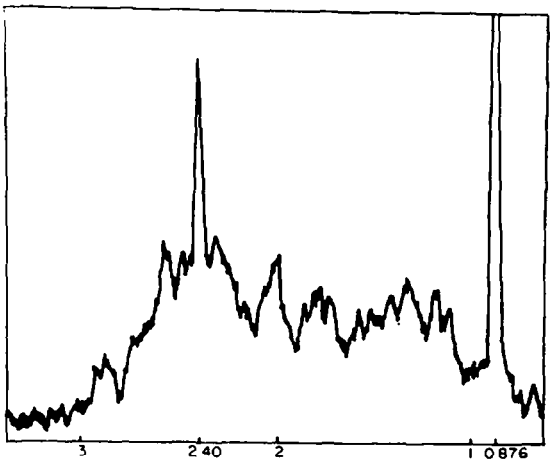
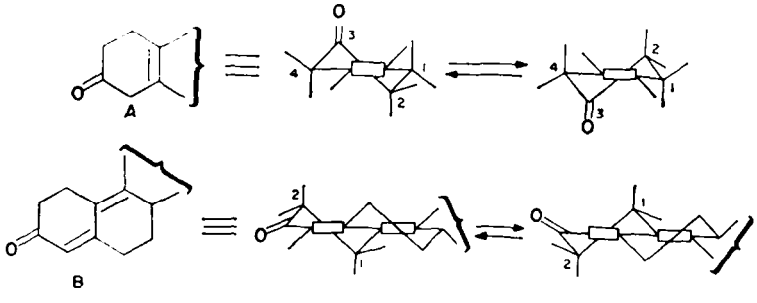


FIG. 2. Part of NMR spectrum of $\Delta^{4,9}$-19-norandrostadiene-17β-ol-3-one (IX).

The relative narrowness of the corresponding signals appears to be due to the proximity of the expected chemical shifts of signals from protons at $C_{(1)}$ and $C_{(2)}$[14] as well

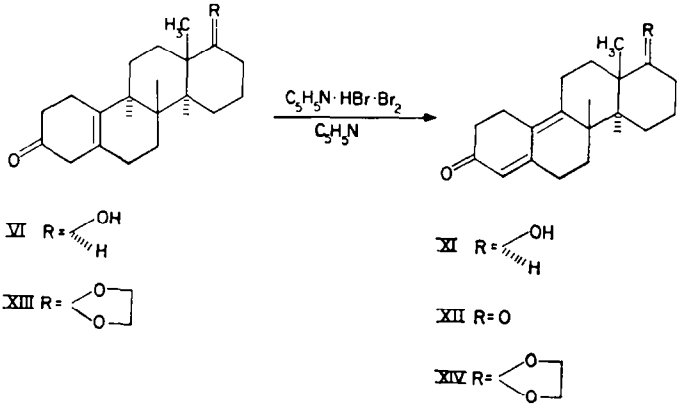


[14] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon Press (1959).

as the easy conformational conversion of ring A in these steroids[15] which results in the averaging of signals from axial and equatorial protons.

EXPERIMENTAL

The compounds I, II, IV, V and VII–X were synthesized by known methods.[16–19] Their constants were in satisfactory agreement with those described. Compounds III and VI (all D-homosteroids were racemates) were kindly presented by Dr. S. N. Anachenko from her collection. Compounds XI and XII were obtained in accordance with the known bromination–dehydrobromination procedure[18,19] starting from XIII[20] and VI[21] which has been synthesized in our laboratory. The intermediate XIV was hydrolysed to diketone XII without isolation.



VI R = OH, H

XIII R = O, O

XI R = OH, H

XII R = O

XIV R = O, O

All the NMR spectra were measured in 98·5% $CDCl_3$ on a JNM-C-60 spectrometer at 60 mc using tetramethylsilane as internal reference. The concentration of solutions was 0·1–0·5 mol/l. depending on the solubility and availability of the steroid and was not determined exactly as within this range the position of the signals from angular methyl groups is practically independent of the concentration.[22] The error in the measurement of the signal position was about 1 c/s.*

All solutions were dried over $MgSO_4$ and evaporated *in vacuo*. The UV spectra were obtained on SF-4 spectrophotometer in EtOH solutions. All the compounds were homogeneous according to the TLC data.[23] M.ps (uncorr.) were determined in capillaries.

$\Delta^{4,9}$-19-*Nor*-D-*homoandrostadiene*-3,17a-*dione* (XII). Pyridine hydrobromide perbromide[24] (180 mg) was added to a suspension of XIII (m.p. 157–161°; 181 mg) in dry pyridine (2 ml). After the mixture has been maintained for 1 hr at 20°, 1 hr at 100° and 30 min at b.p., the precipitation of pyridine hydrobromide ceased. The mixture was cooled, diluted with water, acidified with 2N H_2SO_4

* These measurements were carried out by Dr. V. I. Sheichenko for which we express our deep gratitude.

[15] D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chem. & Ind.* 21 (1954).
[16] A. L. Wilds and N. Nelson, *J. Amer. Chem. Soc.* **75**, 5366 (1953).
[17] B. Pelc, *Coll. Czech. Chem. Comm.* **27**, 2706 (1962).
[18] M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay and R. J. Rapala, *J. Amer. Chem. Soc.* **82**, 2402 (1960).
[19] M. Perelman and E. Farkas (to Eli Lilly and Co.), US patent 3,086,027; *Chem. Abstr.* **59**, 10182 (1963).
[20] S. N. Ananchenko, V. N. Leonov, A. V. Platonova and I. V. Torgov, *Dokl. Akad. Nauk SSSR* **135**, 73 (1960).
[21] S. N. Ananchenko, V. Ye. Limanov, V. N. Leonov, V. M. Rzheznikov and I. V. Torgov, *Tetrahedron* **18**, 1355 (1962).
[22] R. F. Zürcher, *Helv. Chim. Acta* **44**, 1380 (1961).
[23] V. Cerny, J. Joska and L. Labler, *Coll. Czech. Chem. Comm.* **26**, 1658 (1963).
[24] L. F. Fieser, R. P. Linstead, J. A. Elvidge and M. Whalley, *Modern Experimental Methods in Organic Chemistry* p. 90. GNTCL Moscow (1960).

(strong acid reaction) and extracted with ethyl acetate. The extract was washed with sat NaClaq and with $NaHCO_3$aq (twice). Drying and evaporation yielded ketal XIV (190 mg of yellow oil with λ_{max} 224–228 and 306 mμ). This oil was dissolved in a mixture of acetic acid (10 ml), water (2·5 ml) and HClaq (0·20 ml), boiled for 3 min and immediately evaporated to dryness. The residue was dissolved in ether–chloroform (1:1), the solution filtered through a column of alumina (activity II; 10 g), the latter washed with $CHCl_3$ and the filtrate evaporated. The semicrystalline residue was chromatographed on alumina (activity II) layer, 26 cm (start line) × 17 cm (run) × 1 mm (thickness) and developed by ether. The zone which appeared dark violet in UV light (R_f 0·30) was separated and eluated by ether–ethyl acetate mixture. The eluate was evaporated and the crystalline residue (87 mg) suspended in a small amount of ether. After filtration, 67·5 mg (43%) of diketone XII, m.p. 160–162·5° separated. Subsequent recrystallizations from ethyl acetate–hexane and then from methylcyclohexane gave canary-yellow needles, m.p. 163–164·5°, λ_{max} 212–214 and 302 mμ (reported[25] m.p. 165·5–167°, λ_{max} 306 mμ).

$\Delta^{4,9}$-19-*Nor*-D-*homoandrostadiene*-17aβ-*ol*-3-*one* (XI). A mixture of VI (m.p. 120–124°; 21·5 mg), pyridine hydrobromide perbromide (24·5 mg) and dry pyridine (0·50 ml) was boiled for 1 hr and treated as above (except that the size of the layer for chromatography was 10 × 15 × 0·1 cm). Hydroxyketone XI (13·5 mg, 63%) was obtained as a bright yellow oil which could not be crystallized, λ_{max} 221–225 and 306–307 mμ (reported[25] m.p. 137–139·5°, λ_{max} 310 mμ).

Hydroxyketone XI (13·5 mg) was oxidized with 3 drops of Kiliani solution in acetone[26] (2 ml). By means of TLC the diketone XII (m.p. 152–157°, 4 mg) was obtained. This sample was found to be identical with the one described above (m.m.p., R_f and IR spectrum).

[25] G. H. Douglas, J. N. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.* 5072 (1963).

[26] R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 457 (1953).