TWO-DIMENSIONAL NMR SPECTRA OF 17α-(1-AZIRIDINYLMETHYL)-5α-ANDROSTAN-17β-OL

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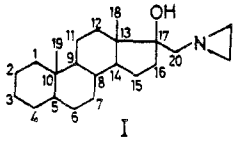
The complex ^1H and ^{13}C NMR spectra of 17α-(1-aziridinylmethyl)-5α-androstan-17β-ol were analyzed using two-dimensional (2M) spectroscopy. The configuration of the substituents at the 17 position was determined using the 2M-spectroscopy of the nuclear Overhauser effect. The direct ^{13}C-^{13}C SSCCs were determined.

When reactive groups are introduced into steroids, the selective inhibition of the enzymes of steroid metabolism or the blocking of the corresponding receptor may be expected. In this connection, we undertook the investigation of steroids modified by three-membered heterocycles.

The structure of 17α-(1-aziridinylmethyl)-5α-androstan-17β-ol (I), obtained by the reaction of the corresponding spirooxirane [1] with aziridine, was studied by the methods of 2M-NMR spectroscopy in the present work. In the usual ^1H NMR spectrum, only the signals of 17-OH and $H_{(20)}$ are successfully assigned (Table 1). It follows from the ^{13}C NMR spectra with complete uncoupling and without uncoupling from the protons that there are 2 primary, 13 secondary, 4 tertiary, and 3 quaternary carbon atoms in the molecule in accord with the proposed structure. The signals of the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, $C_{(8)}$–$C_{(11)}$, $C_{(13)}$–$C_{(15)}$, and $C_{(18)}$–$C_{(22)}$ atoms (Table 2) were assigned on the basis of the comparison with the known CSs of ^{13}C in 5α-androstane and 5α-androstan-17α- and -17β-ols [2] as well as 1-alkylaziridines [3]. The signals of the carbon atoms of the aziridine ring, which are conditionally designated $C_{(21)}$ and $C_{(22)}$, are observed in the same region as are the signals of the atoms of the steroid skeleton; however, they are readily assigned from the values of the $^1J_{CH}$ SSCCs (Table 2) which are higher than those of the remaining methylene groups.



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Compound (I), as well as the majority of the unsubstituted or low-substituted steroids, is affiliated to some of the most complex spin systems; therefore, the complete analysis

TABLE 1. CSs of the Protons of Compound (I)

Proton	δ, ppm	Proton	δ, ppm	Proton	δ, ppm	Proton	δ, ppm
1α	0,86	11α	1,56	5	1,00	16β	1,72
1β	1,64	11β	1,25	6α	1,20	17-OH	3,18
2α	1,48	12α	1,11	6β	1,24	18	0,89
2β	1,41	12β	1,54	7α	0,84	19	0,79
3α	1,25	14	1,08	7β	1,65	20	2,05; 2.65
3β	1,65	15α	1,54	8	1,44	21	1,28, 1,86
4α	1,20	15β	1,29	9	0,59	22	1,28, 1,80
4β	1,24	16α	2,11				

P. Lumumba Peoples' Friendship University, Moscow 117923. Khar'kov Scientific Research Institute of the Endocrinology and Chemistry of Hormones, Khar'kov 310002. Institute of Chemical Physics, Academy of Sciencies of the USSR, Moscow 117977. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1466-1471, November, 1988. Original article submitted January 28, 1987.

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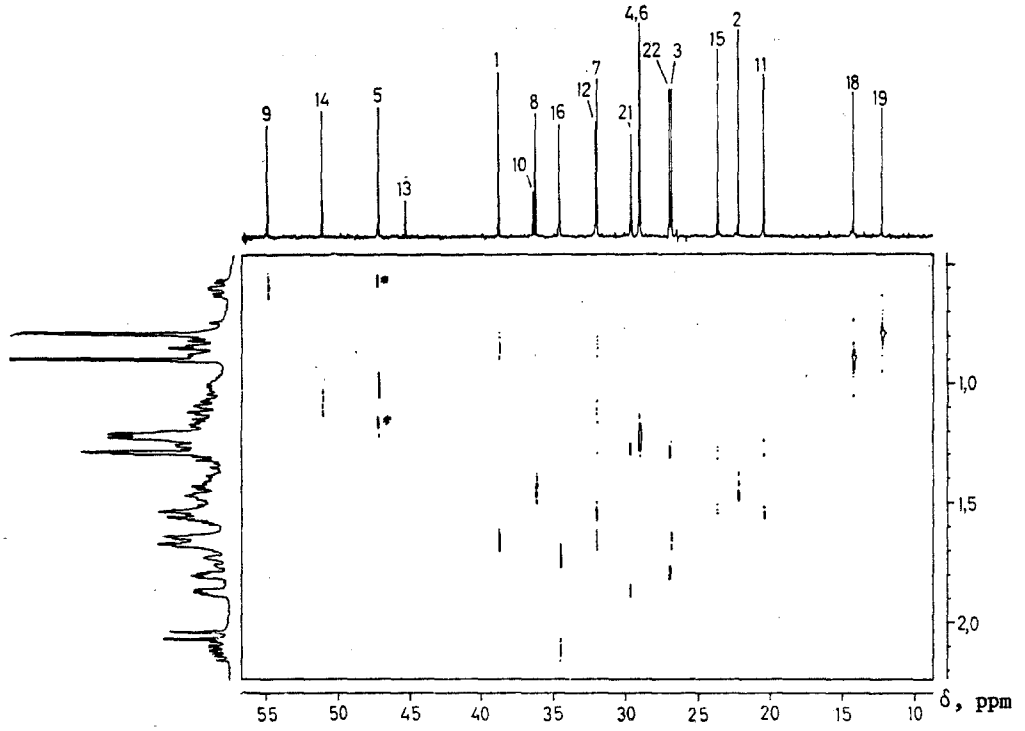

Fig. 1. $^{13}C-^{1}H$ 2M-heteronuclear correlation spectrum of compound (I) (the indicated cross peaks from $C_{(20)}-H_{(20)}$ are noted by the asterisk).

TABLE 2. ^{13}C CSs and $^{1}J_{CH}$ SSCCs for Compound (I)

Atom of C	δ, ppm	$^{1}J_{CH}$, Hz	Atom of C	δ, ppm	$^{1}J_{CH}$, Hz
$C_{(1)}$	38,77		$C_{(12)}$	32,07	
$C_{(2)}$	22,17		$C_{(13)}$	45,33	
$C_{(3)}$	26,81		$C_{(14)}$	51,13	119,6
$C_{(4)}$	29,03		$C_{(15)}$	23,62	
$C_{(5)}$	47,21	119,4	$C_{(16)}$	34,59	
$C_{(6)}$	28,99		$C_{(17)}$	83,00	
$C_{(7)}$	31,96		$C_{(18)}$	14,19	125,5
$C_{(8)}$	36,20	121,6	$C_{(19)}$	12,22	124,3
$C_{(9)}$	54,91	121,1	$C_{(20)}$	67,47	134,9
$C_{(10)}$	36,35		$C_{(21)}$	26,95	164,0 and 174,9
$C_{(11)}$	20,40		$C_{(22)}$	29,60	164,0 and 174,9

of the spectra requires the attention of the 2M-NMR spectroscopy [4]. The most informative modification of the 2M-NMR in the case of the steroids is $^{13}C-^{1}H$ heteronuclear correlation spectroscopy [5]. The cross peaks in such spectra permit the identification of pairs of covalently bound ^{13}C and ^{1}H nuclei. The CSs of the protons connected to the $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, $C_{(8)}$, $C_{(9)}$, $C_{(11)}$, $C_{(14)}$, $C_{(15)}$, and the $C_{(18)}-C_{(22)}$ atoms (Table 1) were determined from the cross peaks in the $^{13}C-^{1}H$ 2M-heteronuclear correlation spectrum of the steroid (I) (Fig. 1). The orientation of these protons was determined on the basis of the data for the unsubstituted androstane [5]. The homonuclear correlation spectra COSY (Fig. 2) were obtained for the assignment of the remaining protons; these spectra permit the separation of the spin systems of the interacting nuclei [6]. Thus, for example, the CSs of α-$H_{(12)}$ and β-$H_{(12)}$ were determined from the known CSs of α-$H_{(11)}$, β-$H_{(11)}$, and the corresponding cross peaks; the CS of $C_{(12)}$ was determined from the $^{13}-^{1}H$ correlation spectrum. Another merit of the 2M-spectra COSY with the intermittent delay τ is the possibility of showing signals of the long-range SSCCs, which have low values and are usually hidden in the width of the unidimensional spectra [6]. We utilized this possibility to study the long-range SSCCs of the steroidal and aziridine protons with $H_{(20)}$. It follows from the spectra with the intermittent delays of 0.13 sec and 0.60 sec with the $H_{(20)}$ proton (δ 2.65 ppm) has a SSCC with the β-$H_{(16)}$ of the D ring. The high value of ^{4}J = 1.4 Hz, which is

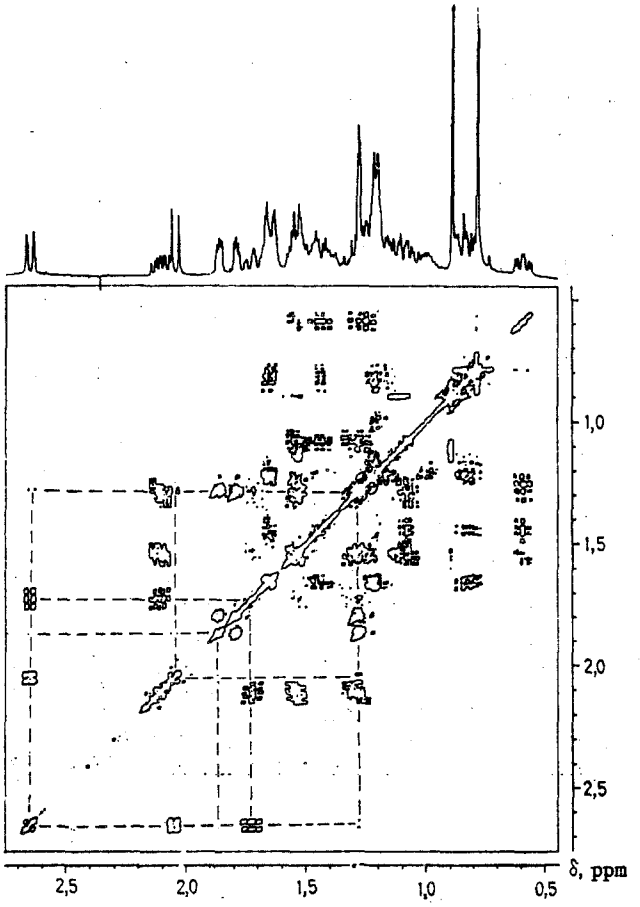

Fig. 2. 2M-spectrum COSY of the steroid (I) with the intermittent delay τ = 0.13 sec. The broken lines indicate the cross peaks expressing the long-range SSCCs with $H_{(20)}$.

TABLE 4. Conditions of the Registration of the Two-Dimensional NMR Spectra

Spectrum	Spectral width, Hz		Time of computation, sec	Relaxation delay, sec	Numerical resolution, Hz		Size of the two dimensional matrix	Intermittent delay, sec	No. of experiments by ω_1
	ω_1	ω_2			ω_1	ω_2			
COSY	±464	928	0,55	4,0	1,81	1,81	512×1024	0,13 0,60	256
NOESY	±464	928	0,55	4,0	1,81	1,81	512×1024	0,60	256
$^{13}C—^{1}H$	±489	5000	0,21	2,0	1,91	4,88	512×2048	0,0035	256
INADEQUATE	±1923	7692	0,13	3,0	7,51	3,76	1024×2048	0,0074	512

found from the ^1H NMR spectrum, can be explained by the W-configuration of these protons. The cross peaks with the coordinates 1.86-2.65, 1.86-2.05, 1.28-2.65, and 1.28-2.05 ppm indicate the presence of the long-range SSCCs of the $H_{(20)}$ protons with the aziridine protons, ^4J = 0.4 Hz. The long-range SSCCs of the methyl protons were also observed; ^4J = 0.8 Hz for $H_{(18)}$ and α-$H_{(12)}$, and ^4J = 0.9 Hz for $H_{(19)}$ and α-$H_{(1)}$.

As was noted above, model compounds were utilized for the assignment of the ^{13}C signals. However, such an approach, as well as the calculation of substituent effects, always contains an element of ambiguity. We therefore utilized the 2M-correlation spectroscopy of $^{13}—^{13}C$ biquantum transitions INADEQUATE [7], which permits the unambiguous identification of pairs of directly bound C—C atoms according to the presence of the direct SSCC $^1J_{CC}$. The $C_{(17)}$ atom, for example, which has only three neighboring carbon atoms in contrast to the quaternary $C_{(10)}$ and $C_{(13)}$ atoms, was readily identified from such a spectrum of the compound (I) (Fig. 3) using a representation of the COSY type [8]. The investigation of the intercepts of the branches in three directions, the initial components of which con-

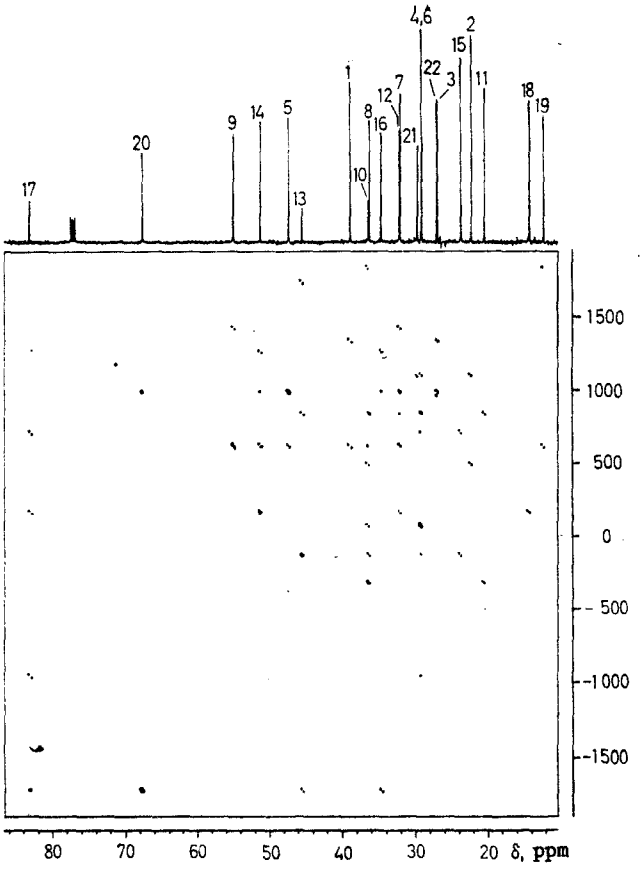

Fig. 3. 2M-spectrum INADEQUATE of compound (I).

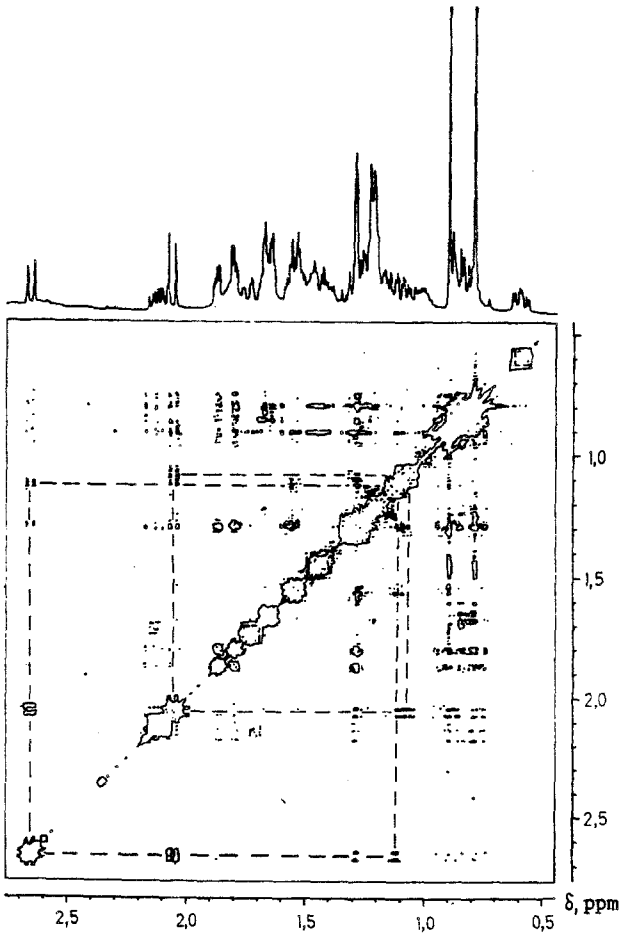

Fig. 4. 2M-spectrum NOESY of the steroid (I). The broken lines indicate the cross peaks of the $H_{(20)}$–α-$H_{(12)}$ and $H_{(20)}$–$H_{(14)}$ proton pairs.

TABLE 3

Atom of C	$^1J_{CC}$, Hz	Atom of C	$^1J_{CC}$, Hz	Atom of C	$^1J_{CC}$, Hz	Atom of C	$^1J_{CC}$, Hz
1,2	33,1	5,10	33,2	9,11	34,7	13,18	36,3
1,10	34,6	6,7	33,3	10,19	36,0	14,15	34,3
2,3	34,0	7,8	34,3	11,12	33,6	15,16	35,2
3,4	33,3	8,9	32,6	12,13	35,1	16,17	38,6
4,5	34,2	8,14	35,9	13,14	34,0	17,20	41,4
5,6	34,2	9,10	34,5	13,17	38,5	21,22	23,7

sist of the $C_{(17)}$–$C_{(13)}$, $C_{(17)}$–$C_{(16)}$, and $C_{(17)}$–$C_{(20)}$ pairs, allows the assignment of the signals due to $C_{(13)}$, $C_{(16)}$, and $C_{(20)}$. Moving in such a way along the skeleton of the molecule, the assignment of the ^{13}C signals is successfully confirmed (Table 2). The SSCC $^1J_{CC}$ (Table 3) was determined from the unidimensional INADEQUATE spectrum [9].

The configuration at the $C_{(17)}$ atom was established with the aid of the 2M-spectrum NOESY (Fig. 4), the main feature of which is the presence of nondiagonal cross peaks indicating the manifestation of the nuclear Overhauser effect between the sterically contiguous protons [10]. In the NOESY spectrum of the steroid (I), there are cross peaks with the coordinates 2.65-1.11 and 2.05-1.11 ppm from the $H_{(20)}$–α-$H_{(12)}$ proton pairs and 2.05-1.08 ppm from the $H_{(20)}$–$H_{(14)}$ pairs; these indicate the α-orientation of the aziridinomethyl substituent at the position 17.

EXPERIMENTAL

The NMR spectra were registered on a Bruker WM-400 spectrometer with the working frequency of 400 MHz for the ^1H nuclei and 100.6 MHz for the ^{13}C nuclei. The 70% solutions of the steroid (I) in $CDCl_3$ were utilized to obtain the ^{13}C–^1H spectra and INADEQUATE; the 10% solutions were investigated in all the remaining cases. The ^1H and ^{13}C CSs were measured in relation to TMS with the accuracy of up to 0.01 ppm; the SSCCs had the accuracy of up to 0.1 Hz. For the measurement of the long-range SSCCs, a Lorentz–Gauss filter was utilized for the narrowing of the lines in the ^1H 1M-NMR spectrum. Standard impulse trains were utilized to obtain the 2M-NMR spectra: COSY [6], NOESY [10], ^{13}C-^1H [5], and INADEQUATE [8]. The conditions of the registration of these spectra are presented in Table 4.

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