Chemistry of Natural Compounds, Vol. 48, No. 3, July, 2012 [Russian original No. 3, May-June, 2012]

SYNTHESES BASED ON NORFLUOROCURARINE. 5. NMR SPECTRA OF MONOMERIC NORFLUOROCURARINE DERIVATIVES

M. G. Levkovich,* P. Kh. Yuldashev, M. M. Mirzaeva, and B. Tashkhodzhaev

UDC 547.944/945

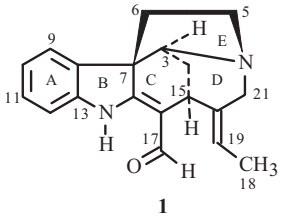
NMR spectra of norfluorocurarine and seven of its derivatives were studied. The NMR spectral parameters were related to stereochemical features using molecular modeling by the semi-empirical AM1 approximation. The resulting steric characteristics of the molecules in solution agreed well with x-ray structure data. The only difference from the x-ray structure data was the ability of several substituents to rotate.

Keywords: indole alkaloids, fluorocurarine, norfluorocurarine, NMR spectroscopy.

NMR spectra of (–)-norfluorocurarine (**1**) (vincanine) in part were reported earlier [1, 2]. Herein a complete description of PMR and ^{13}C NMR spectra of both (–)-norfluorocurarine itself and a large part of its derivatives appearing in our research [3-5] is presented. The steric structures of (–)-norfluorocurarine and its derivatives were studied in parallel by x-ray crystal structure analysis (XSA) for crystalline forms [6] and NMR spectroscopy for solutions. The XSA data and features of the 3D structures were compared using molecular modeling methods. Herein all geometric data of the molecular structures were derived based on molecular modeling results. A characteristic 3D structure for norfluorocurarine was obtained using all these approaches.

A planar indole fragment (rings A and B) and hemispherical fusion of three saturated rings (rings C, D, and E) were characteristic of the 3D structure of norfluorocurarine [3]. The fusion and conformations of the rings were similar to the structure of the related alkaloid strychnine [7]. The C-2=C-16 double bond was situated in the structure and in the related alkaloid strychnine [7] practically in the plane of the aromatic part of the molecule whereas five-membered ring E, which had a twist-conformation transitional between 5α and 6β envelopes (closest to the 5α form), was situated almost perpendicular to the plane of the aromatic system.

Figure 1 shows the key nuclear Overhauser effects (NOE) that defined unambiguously the mutual locations of H atoms that were important for reproducing the steric structure and the structure of the initial geometry for molecular modeling methods. In this respect, aromatic proton H-9, olefinic proton H-19, and methyl protons H-18 could be considered critical. Resonances of these protons describe structures that are convenient for observing differential NOE and; therefore, enable the interactions shown in Fig. 1 to be reliably recorded.



1

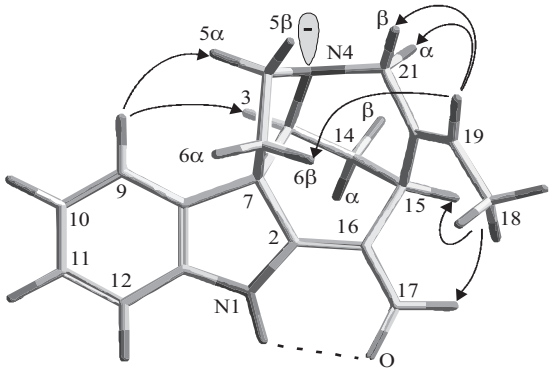


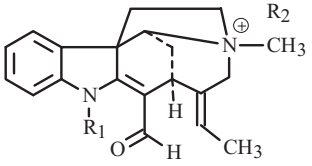
Fig. 1. Chemical and molecular structure of norfluorocurarine (**1**) obtained from NMR spectroscopy data and key nuclear Overhauser effects that defined features of the 3D structure in solution.

S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences, Republic of Uzbekistan, Tashkent, fax (99871) 120 6475. Translated from *Khimiya Prirodnykh Soedinenii*, No. 3, May–June, 2012, pp. 397–403. Original article submitted December 21, 2011.

 0009-3130/12/4803-0440

TABLE 1. PMR Spectrum of Norfluorocurarine (**1**) (CD_3OD, J/Hz, internal standard HMDSO = 0 ppm)

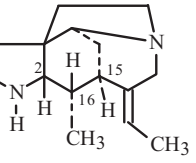
H atom	δ_H	SSCC	H atom	δ_H	SSCC
3	4.641	ddd, 2.9(14α), 2.0 (14β), 1.8 (15)	14α	1.439	ddd, 14.9 (14β), 2.9 (3), 2.8 (15)
5α	3.858	ddd, 14.0 (6β), 12.2 (5β), 6.6 (6α)	14β	2.653	ddd, 14.9 (14α), 4.0 (15), 2.0 (3)
5β	3.637	ddd, 12.2 (5α), 6.7 (6β), 1.2 (6α)	15	4.010	m, $\Delta w(1/2) \approx 10$ Hz
6α	2.064	ddd, 13.6 (6β), 6.6 (5α), 1.2 (5β)	17	9.500	br.s
6β	2.650	ddd, 14.0 (5α), 13.6 (6α), 6.7 (5β)	18	1.627	ddt, 7.0 (17), 2.3 (21β), 1.5 (15)
9	7.488	dd, 7.5 (10), 1.0 (11)	19	5.778	qdd, 7.0 (18), 2.3 (15), 2.2 (21β)
10	6.988	td, 7.5 (9,11), 1.0 (12)	21α	3.717	d, 14.8 (21β)
11	7.220	td, 7.5 (10, 12), 1.0 (9)	21β	4.356	dq dd, 14.8 (21α), 2.3 (18), 2.2 (17), 1.6 (15)
12	7.018	dd, 7.5 (11), 1.0 (10)			



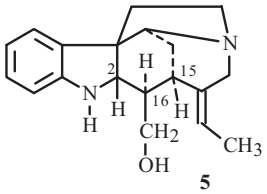
2, 3

2: R_1 = H, R_2 = Br

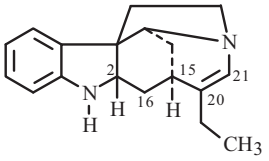
3: R_1 = CH_3, R_2 = Cl



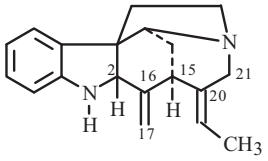
4



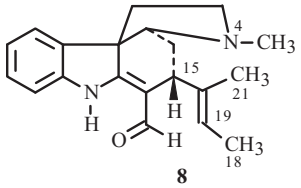
5



6



7



8

NMR spectra of **1** as the hydrochloride were recorded in CD_3OD at room temperature. The internal standard was HMDSO. Owing to specifics of the 3D structure, the NMR spectrum appeared as several spin subsystems weakly coupled to each other. The spectrum of the protons in aromatic ring A was very characteristic of an *o*-substituted benzene structure (Table 1). The alternation of the chemical shifts of the resonances for these protons was characteristic of the alternation of the electron density in substituted benzenes.

Aldehyde proton H-17 resonated as a broad singlet at 9.50 ppm. The reason for this was an NH–CO hydrogen bond, the formation because of this of an almost planar six-membered pseudo-ring, and the approach of aldehyde proton H-17 to methyl H-18. This was also confirmed by a clearly resolved NOE (H-18→H-17) and the narrowing of the H-17 resonance upon substituting the N1–H proton by a methyl in **3**, i.e., upon destroying the pseudo-ring. An isolated group of four protons, methines H-3 and H-15 and methylene pair H-14, which were located in an almost planar W-structure at the fusion of two rings (C and D) that had boat-like conformations, gave characteristic resonances. As a result, protons H-3 and H-15 had a fusion that was unfavorable for significant SSCC with their vicinal partners because of the rather high symmetry in the W-structure and appeared as narrow multiplets. Differential double resonance methods were able to identify in the H-3 resonance three small SSCC of ~2.9, 2.0 and 1.8 Hz to protons H-14α, H-14β, and H-15, respectively. The resonance of H-15 showed analogous SSCC and also small SSCC to olefinic proton H-19, methyl H-18, and methylene proton H-21β. The total of the eight SSCC observed in the H-15 resonance was 17.0 Hz. However, the width of this resonance at half-height was ~10 Hz. The slightly elevated SSCC values given in Table 1 could be a consequence of measuring them somewhat incorrectly by differential double resonance methods from the shape change of their proton-partner resonances. The H-14 protons appeared as two broad doublets with geminal constant J = 14.5 Hz. The broadening occurred because of the aforementioned coupling with methines H-3 and H-15.

The two methylene pairs H-5 and H-6 formed an isolated 4-spin system with well resolved resonances, each of which had one geminal and two vicinal SSCC. The greatest (14.0 Hz) vicinal constant was found for *trans*-orientated protons H-5α and H-6β. The dihedral angle between these axial–axial situated protons was ~156°. The smallest (1.2 Hz) SSCC was observed between equatorial protons H-5β and H-6α dihedral angle ~86°).

TABLE 2. Chemical Shifts of PMR Resonances of **2**–**8** (HMDSO = 0 ppm)

C atom	**2**	**3***	**4**	**5**	**6**	**7****	**8**
2		4.582	3.518	3.253	3.310	3.943	3.027
3	4.533	3.955	3.307	3.402	3.530	3.995	2.742
5α	3.919	4.088	3.039	3.020	3.032	3.110	3.021
5β	3.980	2.010	2.832	2.744	3.249	2.833	2.071
6α	2.105	2.795	1.792	2.445	1.542	1.923	1.627
6β	2.805	7.852	2.065	1.725	2.299	2.115	7.253
9	7.570	7.043	6.925	6.995	7.018	6.946	6.960
10	7.010	7.353	6.602	6.665	6.690	6.672	7.176
11	7.235	7.141	6.913	6.946	6.950	6.974	7.028
12	7.014	1.383	6.534	6.584	6.609	6.559	1.307
14α	1.492	2.694	1.662	1.598	1.684	1.822	1.635
14β	2.738	4.323	1.950	1.838	1.941	1.970	3.815
15	4.028		2.531	2.778	2.000	3.467	
16			2.110	1.637	1.879		
					1.200		
17	9.522	10.041	0.914	3.451		4.899	8.829
				3.445		4.902	
18	1.632	1.589	1.590	1.552	0.954	1.587	1.640
19	5.776	5.673	5.316	5.464	1.920	5.286	5.517
21α	4.093	4.205	3.007	2.994	5.620	2.915	1.595
21β	4.229	4.246	3.511	3.313		3.455	
4N$^+$-Me	3.435	3.475					2.555
1N-Me		3.580					
NH							10.550

Solvent: *DMSO-d_6; **$CDCl_3$; others, CD_3OD.

Methylene pair H-21 was an almost isolated geminal AB-system with J = 14.8 Hz. Although axial proton H-21α resonated as a very narrow pure doublet, the resonance for equatorial proton H-21β was broadened by several small SSCC with protons H-15, H-19, and methyl H-18. Olefinic proton H-19 and methyl H-18 exhibited resonances typical of such groups, i.e., a quartet at 5.78 ppm and a 3H doublet at 1.63 ppm. Both resonances also had several small SSCC with the protons mentioned above.

The preparation of various derivatives of **1** and their XSA were reported [3–5]. Table 2 lists the PMR chemical shifts of **2**–**8**.

Placing a methyl on N-4 in **2** had practically no effect on the 3D structure of the molecule [5]. The mean-square deviation of the N and C atoms of rings C, D, and E from those in **1** was only 0.017 Å according to molecular modeling of these structures using the semi-empirical AM1 method. This was mainly due to distortion of the pyramidal shape of the N atom. The sum of bond angles around the N atom decreased from 330 to 326°. PMR spectra of **1** and **2** in CD_3OD differed only by weak-field shifts of the H-5β (by 0.34 ppm) and H-21α (by 0.38 ppm) resonances and the appearance of a new methyl singlet for MeN-4 at 3.435 ppm. It could also be noted for the H-5 resonances that the resonance for axial proton H-5α in **1** had a larger chemical shift than equatorial H-5β (quite unusual for saturated cyclic systems) whereas in **2** it had a slightly smaller value, the usual position for such structures. Small SSCC could not be measured with the same accuracy as in **1**. Substantial changes relative to **1** were not seen among the easily measured constants.

Adding another methyl (to N-1, **3**) gave PMR spectra with even smaller relative changes. Although the PMR spectrum of **3** given in Table 2 was taken in DMSO; nevertheless, the spectral changes were insignificant. The range of chemical shifts for the aromatic protons increased slightly. The resonance for aldehyde proton H-19 shifted to weak field by ~0.5 ppm; that of H-15, by 0.3 ppm because of the destruction of the H-bond. The easily observed SSCC showed a slight change. The smallest vicinal constant in the four-proton H-5 and H-6 system increased to J = 5.1 Hz. The other SSCC of this spin system were almost unchanged. Apparently these small spectral changes could be ascribed more likely to a solvent effect than to stereochemical features of **3**.

Reduction of **1** by Na in EtOH formed products **4** and **5** [3]. The chemical structure of **4** underwent considerable changes such as hydrogenation of the C-2=C-16 double bond and replacement of the C-17 aldehyde by a methyl.

TABLE 3. Chemical Shifts of ^{13}C NMR Resonances of **1**, **3**–**6**, and **8** (Internal Standard, Solvent Resonance)

C atom	**1**	**3**	**4**	**5**	**6**	**8**
2	167.30	165.64	62.82*	72.27	64.52	113.28*
3	63.89	72.61	66.23*	63.23	60.02	68.20
5	55.92	63.60	54.80**	58.85	52.49	54.70
6	44.57	43.30	39.83	43.60	41.73	44.30
7	57.12	56.28	54.38	54.50	56.11	58.86
8	135.18	134.42	135.33	134.60	122.78	138.95
9	122.20	121.33	120.90	122.79*	123.05	123.37**
10	123.60	121.62	122.32	122.49*	120.61	123.48**
11	130.42	128.88	128.92	128.94	128.79	129.58
12	112.27	108.82	110.26	111.16	111.96	112.27
13	144.44	144.62	152.55	150.71	151.45	144.37
14	29.67	26.40	22.04	29.18**	28.31	36.36
15	29.67	25.57	36.72***	49.91	29.50	32.15
16	113.06	115.80	35.42***	29.78**	36.34	106.33*
17	202.28	183.10	13.35	66.42		189.68
18	14.20	13.46	17.74	13.05	13.43	13.52
19	130.18	126.97	119.61	120.29	27.76	124.74
20	132.65	131.91	139.93	136.09	133.78	135.35
21	55.55	65.14	53.75**	54.50	133.50	19.89
$4N^+$-Me		51.55				41.56
1N-Me		35.91				
Standard	CD_3OD 49.00 ppm	DMSO-d_6 39.54 ppm	CD_3OD 49.00 ppm	CD_3OD 49.00 ppm	CD_3OD 49.00 ppm	CD_3OD 49.00 ppm

Asterisks denote resonances with possible alternate assignment.

All resonances, with the exception of two, were shifted to strong field by 0.3–1.0 ppm; the resonances of H-3 and H-15, to strong field by 1.3 and 1.5 ppm, respectively. Only the resonance of H-6α remained in place. The resonance of H-14α was shifted to strong field by ~0.2 ppm. Such a practically synchronous change of all resonances could be caused only by a general change of the magnetic permeability of the molecule as a whole. This was most likely related to the state of the molecule. The spectrum of compound **4** as the base was recorded in CD_3OD; that of **1**, also in CD_3OD but as the hydrochloride, i.e., as N^+-4. The calculated dipole moment of N^+-4 norfluorocurarine was ~10.2 D whereas that of **4** was only 1.4 D. Naturally, coupling with the medium of such molecules can lead to a general shift of all NMR resonances.

The principal change of the 3D structure was naturally the conversion of the C-2=C-16 double bond to a single bond. Because of this, ring C changed from a twist-boat conformation with a C-2–C-14 axis to a twist-chair conformation with this same symmetry plane. Five-membered ring E changed from 5α–6β twist to 7β envelope.

The aldehyde resonance in **4** disappeared in the PMR spectrum. A methyl doublet (J = 7.2 Hz) appeared at 0.914 ppm. Furthermore, two resonances for methine protons H-2 and H-16 appeared at 3.518 and 2.110 ppm, respectively. The range of displacement of the aliphatic PMR resonances (excluding methyl resonances) narrowed from 3.20 ppm for **1** to 1.85 ppm for **4**. The generation of two new optically active centers at C-2 and C-16 during the preparation of **4** was stereochemically important. The absolute values of optical centers C-3, C-7, and C-15 for **1** were determined [3] as 3*S*, 7*R*, and 15*S*. This also enabled the orientations of the new protons to be established unambiguously as H-2β and H-16β by XSA methods. This corresponded to new optical centers C-2(*S*) and C-16(*S*). This could not be established unambiguously using NMR methods alone. The resonance of H-16, which was key to the stereochemistry, appeared as a quartet of double doublets at 2.110 ppm with J = 7.2, 6.2, and 3.1 Hz. The quartet splitting was from the C-17 methyl (0.914 ppm); the doublets, from methines H-2 (3.518 ppm) and H-15 (2.531 ppm). An almost eclipsed structure (dihedral angle H-2–H-16 = 25°) for the C-2–C-16 bond resulted from modeling using AM1. The dihedral angle between protons H-16–H-15 was close to the gauche-configuration at 71°. This was entirely consistent with the Karplus relationship [8]. However, the reverse confirmation, i.e., establishing the orientation from the SSCC values, would not be convincing. The structure of **4** was also notable because the optical activity changed from 15(*S*) to 15(*R*) because of the reduction of C-16 whereas H-15 retained its orientation. Thus, the complete chemical name of **4** was determined as 2*S*,3*S*,7*R*,15*R*,16*S*-deoxytetrahydronorfluorocurarine [8].

In general the 3D structure of the molecule remained similar to that of **1**. The SSCC changed substantially only for the H-5 and H-6 spin systems. This was related to a conformation change of ring E. The dihedral angle in the N-4–C-5–C-6–C-7 system was about +11°. This produced an almost eclipsed structure in this fragment. This angle in **1** was about –33°. Because of the sign change of the dihedral angle of the C-5–C-6 bond, the *trans*-orientation of the protons switched from 5α, 6β to the opposite, 5β,6α. Although the eclipsed structure made this definition exceedingly arbitrary (dihedral angles between these pairs of protons were 5α–6β 109° and 5β–6α 129°); nevertheless, the change in the mutual orientation of the protons was reflected in their positions in the spectrum. The maximum vicinal constant (H-5α–H-6β) decreased to J = 8.9 Hz. The minimum constant increased to 4.2 Hz. The SSCC between vicinal partners on the same C atom was 7.5 Hz for the α-partners and 6.8 Hz for the β-partners.

Compound **5**, like **4**, was prepared by reduction of starting **1** [3]. However, the orientations of the C-16 substituents in them were inverted. Originally the orientations of the Me in **4** and the CH_2OH in **5** were assumed to be the same. This caused complications with the interpretation of the PMR spectra of **4** as noted above. The strong shifts of resonances for H-16, H-2, and H-15 in **5** relative to **4** were completely explainable by the appearance of an oxygenated C-17 substituent. The shifts of the H-6β, H-21β, and H-19 resonances had to be explained by a different effect. The simplest explanation was the presence in solution of a conformation with the hydroxyl oriented to the side of rings D and E. This was possible only for the β-orientation of the CH_2OH. The hydroxyl turned out in this instance to be only 2.5–3.0 Å from the aforementioned H atoms and was entirely capable of exerting an inductive effect on them.

The H-2 resonance in **5** had a distinct doublet shape with J = 10.0 Hz. This indicated that it was oriented *trans* to H-16 (calculated dihedral angle 153°). The structure of the H-16 resonance could not be directly solved because of extensive overlap with the H-14α resonance. However, the structure of the H-16 resonance as a dddd with J = 10.0, 7.4, 7.0 and ~3.0 Hz could be established based on the resonances of the H-17 pair of methylene protons (3.451, dd, J = 11.5, 7.4 and 3.445, dd, J = 11.5, 7.0) and the shape of the H-15 resonance. The constant of ~3.0 Hz was related to coupling with H-15 methine, the resonance of which, like in previous instances, was a narrow poorly resolved multiplet at 2.778 ppm with several SSCC from 2.0 to 3.0 Hz. Unfortunately, the dihedral angle H-15–H-16 was almost independent of the α- or β-orientation of the H-16 proton and the SSCC (15–16), like for **4**, could not act as a criterion for determining the orientation of the H-16 proton. Compound **5** prepared by us turned out to be identical to the alcohol from the 18-deoxyaldehyde of Wieland–Gumlich [9, 10]. However, the stereochemistry of the 3D structure of this compound was not previously analyzed in detail. The orientation of the H-2 proton also was not determined.

The preparation and XSA of **6** have been published [4]. Dehydrogenation of **1** removed the C-16 formyl substituent and reduced the C-2=C-16 double bond to a single bond. Also, a rather strange migration of the C-19=C-20 double bond to the C-20=C-21 position occurred. Its 20,21-dihydro product was reported under the name (–)-tubifolidine and was also prepared synthetically [11].

Several conformational rearrangements occurred because of the reduction of the double bond and the conversion of all ring C atoms to the tetrahedral geometry. Ring B became practically planar and was a vague 2β envelope. Ring C adopted a slightly distorted 14β half-chair. Ring D was a regular 14β chair. Finally, five-membered ring E became a 3β envelope. The dihedral angle N-4–C-5–C-6–C-7 (planar part of the envelope) was only 1.7°. Thus, the C-5 and C-6 methylenes were completely eclipsed. However, the 3D shape of the whole molecule preserved its characteristic form.

Methylene pair C-19 appeared as a single 2H multiplet that was partially overlapped by resonances of H-14β and H-16β. The structure of the 2H-19 resonance at 1.920 ppm could be described as a quartet of ddd (7.5, 4.0, 1.3, and 0.4 Hz). Both H-19 protons were equivalent because the geminal constant in the resonance of these protons was small. Therefore, free rotation around the C-20–C-19 bond occurred in solution. The constants 4.0 and 1.3 Hz of this resonance were related to the H-21 and H-15 protons; 0.4 Hz, one of the H-16 protons. The resonance of methine H-2 (3.310 ppm) appeared as a well resolved ddd resonance with 10.6 Hz from H-16α (dihedral angle 44°), 6.3 Hz from H-16β (dihedral angle 71°), and 0.4 Hz from H-15. The two H-16 protons resonated at 1.879 (H-16β) and 1.200 (H-16α) with a well resolved SSCC from the aforementioned coupling to the H-2 proton, SSCC from the H-15 proton (2.2 Hz for H-16α and 3.9 Hz for H-16β), and a single through-space constant (J = 2.0 Hz, H-14β–H-16β). The resonance for H-15 was as before complicated and a rather narrow multiplet with width at half-height <10 Hz. Olefinic H-21 of the migrated double bond resonated at 5.620 ppm as a triplet with J = 1.3 Hz. Both constants 1.3 Hz related to coupling with the H-19 methylene pair.

Compound **7** (deoxydihydronorfluorocurarine) underwent insignificant conformational changes relative to starting **1**. The indoline core became nonplanar because of the reduction of the C-2–C-16 bond. Ring B acquired a faint 2α envelope conformation. Ring C was a slightly distorted 3α,16β chair. Rind D became a rather pure 14α, 21α boat. Finally, five-

membered ring E adopted a 7α envelope conformation. The dihedral angle between *trans*-axial protons 5β and 6α was 158° with SSCC 7.9 Hz. The angle between equatorial protons 5α and 6β was 83° with the corresponding SSCC of 4.8 Hz. A new resonance for the H-2 proton appeared as a poorly resolved quartet (J < 1.2 Hz) at 3.943 ppm. The exo-methylene H-19 protons formed a poorly resolved AB-type structure at 4.899 and 4.902 ppm with J = 1.2 Hz. All other resonances retained their shapes that were characteristic of the already discussed structures.

Catalytic hydrogenation of **1** produced **8**. The chemical structure of **8** underwent considerable changes. Ring D opened. The methine proton on C-15 changed orientation [4]. It was assumed in our earlier studies that ring E had opened [11]. However, an XSA [4] and PMR data have now established unambiguously that ring D opened. It is noteworthy that, despite the considerable changes of chemical structure, the conformations of the remaining four rings and their mutual positions remained similar to the starting structure **2**. Rings A and B and the C-2–C-16 bond formed a planar structure. Ring C, as before, was a distorted boat with a C-2–C-14 transverse axis. Five-membered ring E took the twist conformation from a mixture of 5α and 6β envelopes. The orientation of ring E relative to the molecular framework was retained, i.e., it could be concluded that, regardless of the rather complicated chemical structure with the fusion of several rings, the molecular structure of norfluorocurarine (or fluorocurarine) did not experience serious distortions. It almost did not change shape after one of the rings opened. These calculated data agreed well with XSA data [4].

Compound **8** was reported earlier [12]. Acetaldehyde and acetic acid were observed among the products of fluorocurarine oxidation by ozone. The ring-opening product of **8** should also be obtained in order to explain this result according to the EMD hydrogenation scheme. However, this product was not isolated and its structure remained hypothetical.

It was noted [4] that the H-15 proton changed its orientation from the α- to the β-direction. The reason for this transformation cannot yet be explained. However, the very fact that the orientation changed was confirmed unambiguously by an XSA. This led to several characteristic changes in the PMR spectra that complicated the initial interpretation of the PMR spectra [11]. First, the resonance of the H-15 proton itself changed from the usual unresolved narrow multiplet to a broad doublet at 3.815 ppm with J = 10.5 Hz. The appearance of a large vicinal constant was due to the *trans*-orientation (dihedral angle ~174°) of protons H-15 and H-14α (1.307 ppm). This would have been impossible with the previous orientation. The H-15 proton in differential double resonance experiments showed, as before, unresolved small SSCC with the H-14β, H-17, methyl H-18, and new methyl H-21 protons. The H-15 constant with the previous W-partner H-3 disappeared.
Now the H-3 resonance appeared as a very distinct dd at 3.27 ppm with J = 5.1 and 1.3 Hz from coupling only with its vicinal H-14 partners. A differential NOE at the H-15 proton revealed the spatial approach of this proton to aldehyde H-17, olefin H-19, methylene H-6β, and two methyls H-18 and H-21. The NOE at the narrow MeN-4 singlet showed that this group was oriented close to the H-3 proton, both H-5 methylene protons, and the H-14β proton. Resonances for the H-5 and H-6 four-spin system changed shape. The very small vicinal constant (H-5α–H-6β, dihedral angle 91°) became practically equal to zero. The resonance of the H-5α proton was now a very distinct dd with J = 9.5 and 9.0 Hz. The resonance of H-6β was overlapped by resonances for H-14β, H-18, and H-21. It also appeared in differential double resonance as a simple dd with J = 12.0 and 4.5 Hz. All this unambiguously, independently of an XSA, confirmed that ring D opened in **8** and that the H-15 proton had the β-orientation.

Resonances in the ^{13}C NMR spectra were assigned based on data from 2D hetero-correlation NMR spectroscopy. Table 3 presents the chemical shifts of the resonances of these spectra.

The ^{13}C NMR spectrum of **1** in Py solution was published [2]. Resonances were assigned based on increment analysis and coincided practically fully with this work. The only difference was an alternative assignment of resonances for aromatic C-9 and C-10 of 121.7 and 120.7, respectively [2]. The conserved fragments of **1**, **3–6**, and **8** (rings A and E) were apparently rather stable resonances that were similar to the spectrum of starting **1**. Resonances of the variable parts of the molecule (rings C and D) showed large shifts in the spectra. However, they corresponded fully with the changes in the chemical structure.

The detailed study of the PMR spectra enabled all structural modifications of **1–8** to be followed, their chemical structures to be constructed, and the 3D molecular structure in solution to be reproduced independently of XSA studies carried out in parallel. The structures of the compounds in both these studies practically coincided. The most important conclusion about structural features in the liquid phase is that free rotation occurs around the H-20–H-19 bond in **6**. Methylene H-19 protons in solution turned out to be equivalent. Rotation around the H-16–H-17 bond in **5** was hindered. Methylene protons H-17 appeared as independent resonances. An inductive effect of the hydroxyl in **5** on the H-6β, H-21β, and H-19 protons was also observed. This could be explained by the presence in solution of a hydroxyl oriented near the framework of **5**.

EXPERIMENTAL

NMR spectra were recorded in DMSO-d_6 for **3** on a Bruker DRX-500 spectrometer at operating frequency 500 MHz (^{1}H) and 125 MHz (^{13}C); in $CDCl_3$ for **7** and in CD_3OD for all others on a Unity-400+ Varian spectrometer at operating frequency 400 MHz (^{1}H) and 100 MHz (^{13}C). The internal standards for **3** were the solvent resonances (2.50 ppm for ^{1}H and 39.54 ppm for ^{13}C). The HMDSO resonance (0 ppm) for ^{1}H and the CD_3OD resonance (49.00 ppm) for ^{13}C were the standards for all others. Molecular modeling of the 3D molecular structures was performed using the semi-empirical AM1 program with the commonly accepted conditions for geometry optimization in the gas phase.

Fluorocurarine Bromide (2). Fluorocurarine (3.41 g) was dissolved with heating in aqueous MeOH (30 mL, 1:1) and treated with NH_4Br (1.1 g) dissolved in H_2O (10.0 mL). The precipitated fluorocurarine bromide (3.32 g) was recrystallized from H_2O. $C_{20}H_{25}N_2OBr$, mp 277–278°C (dec.).

***N*(α)-Methylfluorocurarine Chloride (3).** Fluorocurarine iodide (8.0 g) was dissolved in aqueous MeOH (250 mL, 4:1) with NaOH (40 mL, 2 N), stirred thoroughly, and treated simultaneously with NaOH (200 mL, 2 N) and dimethylsulfate (70 mL) over 4 h. The acidic reaction mixture was treated with an excess of aqueous sodium picrate. The precipitated picrate (7.27 g) was recrystallized from aqueous acetone (1:1), mp 209–210°C (5.7 g). The *N*(α)-methylfluorocurarine picrate (5.7 g) was dissolved in aqueous acetone (1:1) and passed over a column packed with Amberlite IRA-400 resin (Cl). The aqueous acetone was vacuum distilled to dryness. The solid (4.14 g) was recrystallized from anhydrous MeOH, mp 268–269°C (dec.), $C_{21}H_{26}ON_3Cl$. UV spectrum (λ_{max}, nm, log ε): 242 (4.10), 301 (3.76), 356 (4.35).

ACKNOWLEDGMENT

The work was financed by the Basic Scientific Research Program of KKRNT, RUz, Grant FA-F3-T045 and the Foundation for Support of Basic Research, AS, RUz, Grant FPFI 3910.

REFERENCES

1. M. R. Yagudaev and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 260 (1974).
2. M. R. Yagudaev, *Khim. Prir. Soedin.*, 210 (1983).
3. P. Kh. Yuldashev, B. Tashkhodzhaev, K. K. Turgunov, and M. M. Mirzaeva, *Khim. Prir. Soedin.*, 652 (2010).
4. P. Kh. Yuldashev, B. Tashkhodzhaev, K. K. Turgunov, and M. M. Mirzaeva, *Khim. Prir. Soedin.*, 786 (2010).
5. B. Tashkhodzhaev, K. K. Turgunov, P. Kh. Yuldashev, and M. M. Mirzaeva, *Khim. Prir. Soedin.*, 473 (2010).
6. Cambridge Crystallographic Data Centre (CCDC), deposit No. 818744 (**1**), No. 771515 (**2**), No. 818745 (**3**), No. 775352 (**6**), No. 771516 (**7**), No. 775351 (**8**).
7. M. Messerschmidt, S. Schein, and P. Luger, *Acta Crystallogr., Sect. B: Struct. Sci.*, **61**, 115 (2005).
8. Yu. Yu. Samitov, *Stereospecificity of Nuclear Spin—Spin Coupling Constants and Conformational Analysis* [in Russian], Izd. Kazan. Univ., 1990.
9. K. Bernauer, F. Berlage, W. Von Philipsborn, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **41**, 2293 (1958).
10. W. Von Philipsborn, K. Bernauer, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **42**, 461 (1958).
11. P. Kh. Yuldashev and S. Yu. Yunusov, *Uzb. Khim. Zh.*, No. 4, 61 (1964).
12. K. Bernauer, *Planta Med.*, **9**, 340 (1961).