Chemistry of Heterocyclic Compounds, Vol. 43, No. 3, 2007

SYNTHESIS AND STRUCTURE OF 12-HYDROXYIMINO DERIVATIVES OF 16,16-DIMETHYL-8-AZA-D-HOMOGONA-1,3,5(10),13-TETRAENE-12,17*a*-DIONE

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The reaction of 16,16-dimethyl-8-aza-D-1,3,5(10),13-tetraene-12,17a-dione (3,3-dimethyl-3,4,6,7,11b,12-hexahydro-1H-[2.1-a]1,13(2H)-dione) with hydroxylamine and methoxyamine in ethanol gives the 12-methoxyamino and 12-methoxyamino derivatives. The 12-hydroxyamino derivative was also obtained by the reaction of this 12,17a-dione with hydroxylamine hydrochloride and subsequent cleavage of the hydrochloride salt of the 12-hydroxyamino derivative by the action of base. The 12-methoxyamino derivative was obtained by the methylation of the 12-hydroxyamino derivative using methyl iodide in the presence of sodium methylate. Further evidence for the structures of the derivatives obtained was obtained using COSY, NOESY, HMBC, and HMQC NMR spectroscopy.

Keywords: 8-aza-D-homogona-12,17*a*-diones, 12-hydroxyimino derivatives of 1-aza-D-homogona-12,17*a*-diones, *syn-anti* isomerism, quantum-mechanical analysis, IR, UV, ^{1}H NMR, and ^{13}C NMR spectroscopy, COSY, NOESY, HMBC, HMQC.

Studies of the biological properties of 8-azasteroids, in particular, 8-azagona-12,17-diones [1] and 8-aza-D-homogona-12,17*a*-diones [1-6], have shown that these compounds have immunomodulating properties, affecting the immune systems of higher mammals and humans [2, 3, 6]. Furthermore, Kuz'mitskii et al. [2-4] have found that, depending on their structure, these compounds may act as either activators or suppressors of the immune response. This has led us to try to explain the role of structural factors in the direction and level of the observed immunological activity. We have found that oxyimino derivatives of 8-aza-D-homogona-12,17*a*-diones also display immunological activity [7].

In this communication, we present syntheses for 12-hydroxy (**2**) and 12-methoxy derivatives (**3**) of 16,16-dimethyl-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17*a*-dione (**1**) and the results of IR, UV, and NMR studies to elucidate the steric structure and molecular dynamics of these compounds.

The reaction of 8-aza-D-12,17*a*-dione **1** with hydroxylamine and methoxylamine in ethanol gave 12-oximino derivatives of 8-aza-D-homogonane **2** and **3**. Alternatively, 12-oximino derivative **2** was obtained by the reaction of **1** with hydroxylamine hydrochloride with subsequent cleavage of the resultant salt **4** by such bases as NaOH or NaOMe. 12-Methoxyimino derivative **3** was also obtained by the methylation of hydroxyimino derivative **2** using methyl iodide in the presence of sodium methylate. Physicochemical data were obtained for all these compounds, which permit reliable assignment of their structures.

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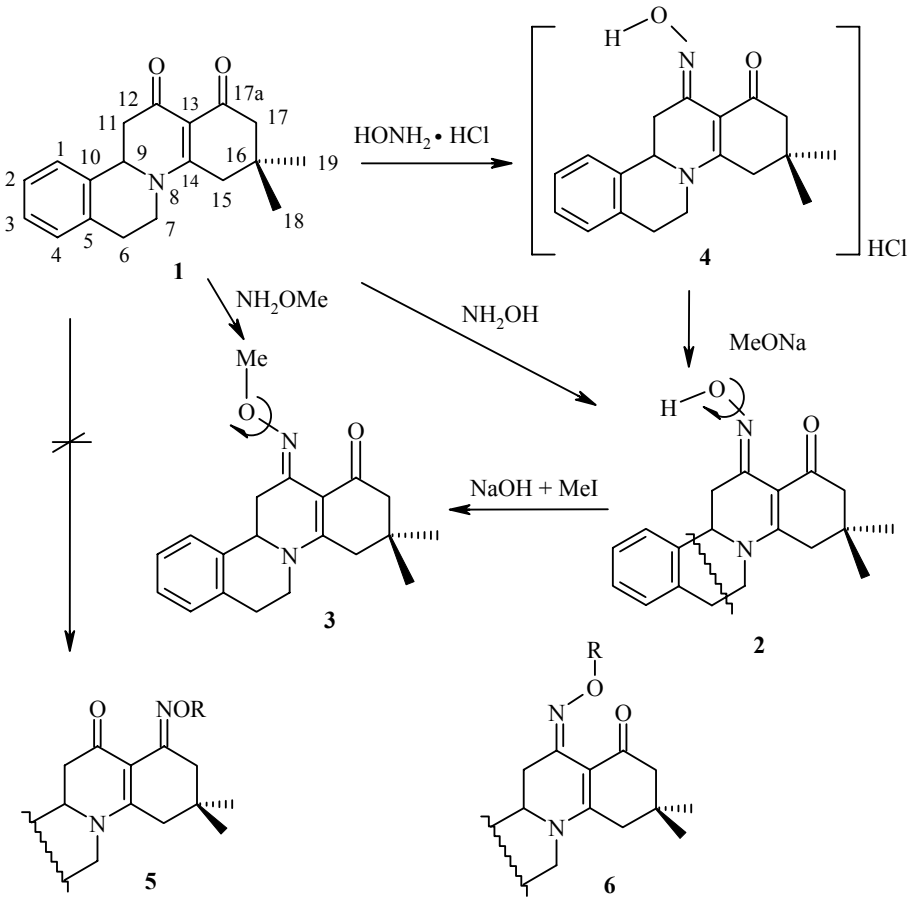


The IR spectra of **2** and **3** shows broad asymmetric bands at ν 1640-1650 cm^{-1} with shoulders at ν ~1610 and ~1590 cm^{-1}. The strong bands at ν 1640-1630 cm^{-1} may be assigned in accord with our previous work [8, 9] to stretching vibrations of $C_{(17a)}$=O bond, while the bands appearing as shoulders may be assigned to C=N bond vibrations. The band of the N-OH group in **2** taken in a KBr pellet is found at ν 3180 cm^{-1}, while this band for a sample in chloroform solution is found ν 3580 cm^{-1}. This discrepancy indicates that the hydroxyl group in the crystalline state participates in hydrogen bonding, while these bonds are destroyed in chloroform solution and vibrations of a free hydroxyl group are seen. This result leads to another important conclusion: the existence of a free hydroxyl group in solution (ν 3580 cm^{-1}) suggests an *anti* or *E*-configuration of the hydroxyimino group.

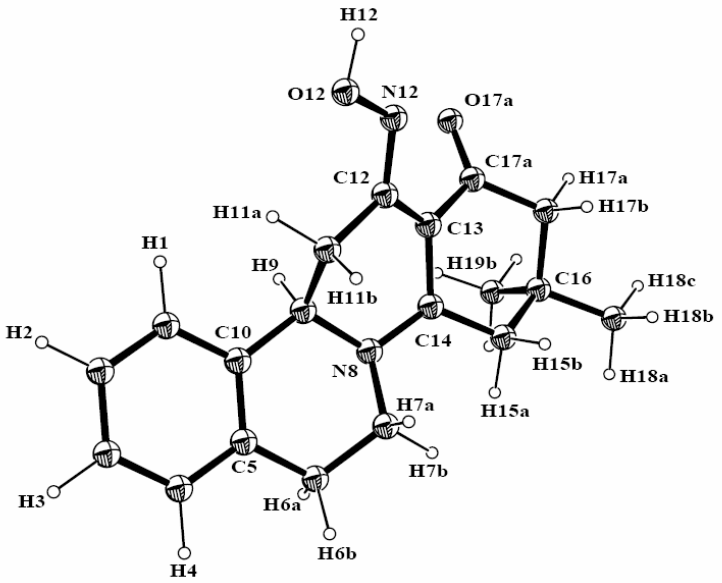
In this communication, we do not discuss the structure of the salt of hydroxyimino derivative **4** since this question has significance apart from the present discussion and will be examined separately.

The electronic absorption spectra of hydroxyimino derivatives **2** and **3**, in contrast to the spectrum of 8-aza-D-homogona-12,17*a*-dione **1**, which has two bands (at λ 267 nm with ε 13,200 and l 310 nm with ε 17500 [10], display a broad band at λ 300-340 nm (ε 17000-20000) and a strong composite band with maximum at λ 199-200 nm, whose long-wavelength tail extends to 240-250 nm. The long-wavelength band, according to our previous work [9], should be assigned to the *trans-s-trans* $N_{(8)}$-$C_{(14)}$=$C_{(13)}$-$C_{(17a)}$=O chromophore, while the short-wavelength band should be assigned to the aromatic chromophore (ring ***A***).

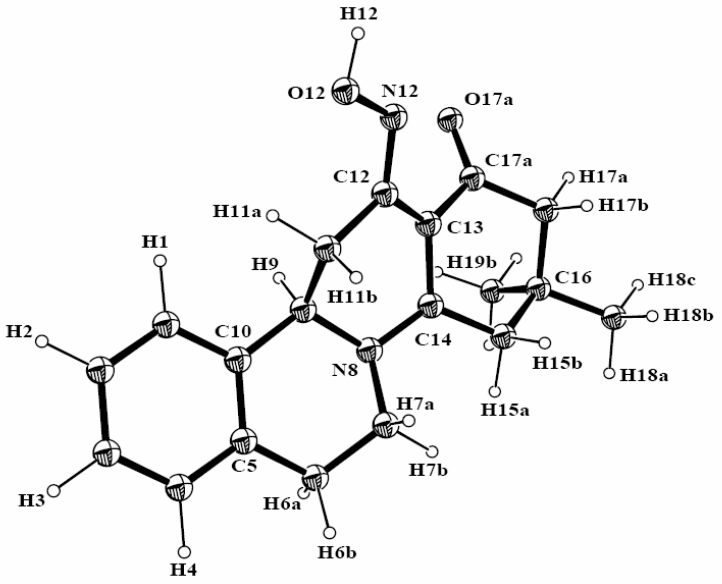
The mass spectra of hydroxyimino derivatives **2** and **3** have molecular ions accompanied by ions with mass [M+1] and [M-1] as well as ions with masses [M-17] and [M-18] for derivative **2** and [M-31] and [M-32] for derivative **3**, which correspond to loss of an OH group and H_2O in the former case and loss of a methoxy group and methanol in the latter case.

The formation of both 12-hydroxyimino derivatives **2** and **3** and 17α-hydroxyimino derivatives **5** may be proposed theoretically for the reaction of 8-aza-D-homogona-12,17*a*-dione **1** with hydroxylamine and methoxyamine. However, our experimental data show that the products obtained are 12-hydroxyimino derivatives **2** and **3**. Furthermore, analysis of the reaction mixtures in an attempt to discover the hypothetical 17*a*-hydroxyimino derivatives **5** gave only negative results. These findings, in the context of our previous work [11, 12] on the synthesis of 17*a*-ethoxyimino derivatives of 8-azasteroids by fusion of 3,4-dihydroisoquinolines to 2-acetyl--1-ethoxyimino-5,5-dimethyl -1,3-cyclohexanedione hold importance for understanding the reactivity of derivatives **1** and the properties of derivatives **2**, **3**, and **5**. On the other hand, we can propose either *syn* (**6**) or *anti* configuration (**2**, **3**) of the hydroxyimino group for 12-hydroxyimino derivatives **2** and **3** although the *syn* configuration **6** is less favorable as a consequence of steric and coulombic interactions with the oxygen atom of the adjacent 17*a*-carbonyl group and, hence, has very low occupancy or may be entirely absent.

2a



2b



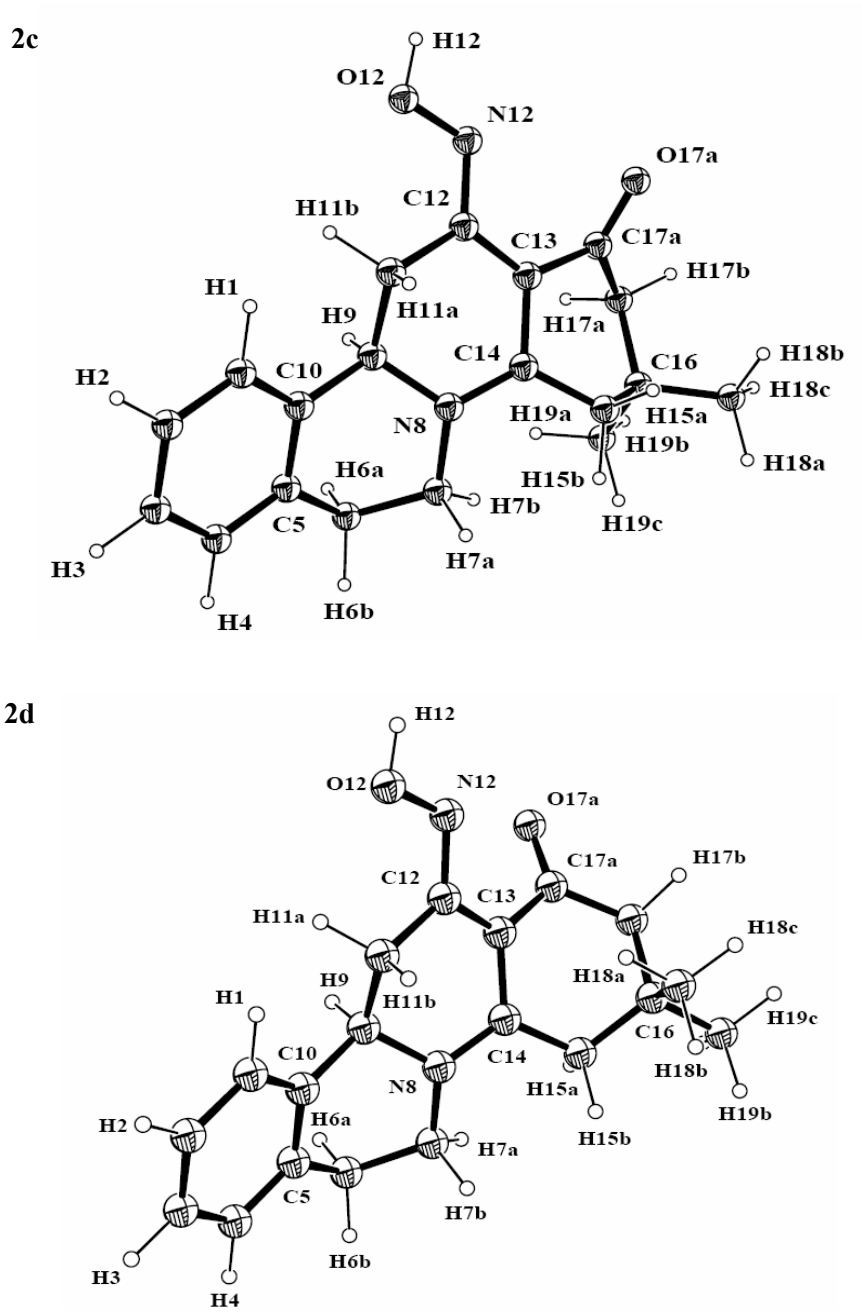


Fig. 1. Stereo projection of the four most favored conformers of oxime **2** from an AM1 semiempirical quantum-mechanical calculation.

Semiempirical AM1 and PM3 (Polak-Ribire algorithm) quantum-mechanical calculations of the molecular structure of 12-hydroxyimino derivative **2** show that this molecule exists as four conformers **2a-d** differing in the conformation of rings ***B*** and ***C*** and the conformation of the unshared electron pair of $N_{(8)}$ relative to the proton at $C_{(9)}$ determining the fusion of rings ***B*** and ***C***, which will arbitrarily be termed the α-configuration.

The four energetically most favored conformers are shown in Fig. 1 as stereoprojections **2a-2d**, while their quantum-chemical parameters are given in Table 1.

Figure 1 shows that the conformer pairs **2a-2c** and **2b-2d** differ in the structure of ring ***D***. Envelope conformation is found for ring ***D***. The vent of ring ***D*** is $C_{(16)}$, which has α-configuration (extrudes behind the mean-square molecular plane) in conformers **2a** and **2c** and β-configuration (extrudes in front of the mean-square molecular plane) in conformers **2b** and **2d**. The **2a-2b** and **2c-2d** conformer pairs differ in the conformation of ring ***B*** and the fusion of rings ***B*** and ***C***: *cis* fusion for conformers **2a** and **2b** and *trans* fusion for conformers **2c** and **2d**. Ring ***B*** in the **2a-2b** conformer pair has *envelope* conformation in conformers **2a** and **2b**; $C_{(7)}$ is the vent atom and has β-configuration. However, ring ***B*** in the **2c-2d** conformer pair has chair or boat conformation, whose stern atoms, $C_{(6)}$ and $C_{(9)}$ have α-configuration.

According to the data obtained in the AM1 calculation given in Table 1, conformers **2a** and **2b** are energetically favored relative to conformers **2c** and **2d**. Conformer **2b** is favored over conformer **2a** in the **2a-2b** conformer pair and, hence, is probably more populated. This result is in good accord with the X-ray structural data obtained for related 12,17*a*-diketo derivatives [13, 14], which indicate that 8-aza-D-homogona-12,17*a*-dione molecules in all cases studied have *cis* fusion of rings ***B*** and ***C*** and α-configuration of $C_{(16)}$.

Thus, our quantum-mechanical calculation indicates preference for conformers **2a** and **2b**, which differ in the configuration of $C_{(16)}$ bearing a *gem*-dimethyl group.

Conformers with *cis* fusion of rings ***B*** and ***C*** are also favored in the PM3 calculations (Table 1). In this case, both methods indicate preference for the conformer with 16α-configuration.

The proton arrangement $C_{(9)}H\text{-}C_{(11)}H_2$ and $C_{(6)}H_2\text{-}C_{(7)}H_2$ for conformers **2a** and **2b** are identical (Fig. 2) and, as a result, a monotypic set of resonance signals corresponding to an ABX spin system for the $C_{(9)}H\text{-}C_{(11)}H_2$ protons and A_2B_2 system for the vicinal $C_{(6)}H_2\text{-}C_{(7)}H_2$ protons should be observed in the NMR spectra of these conformers.

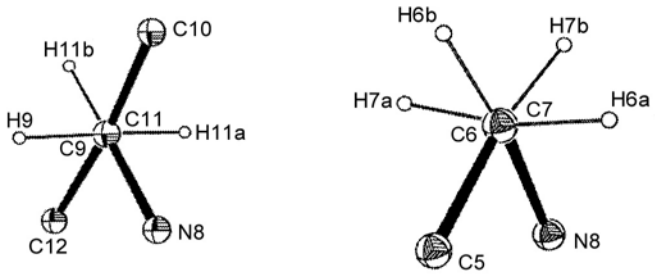
The ^1H and ^{13}C NMR spectra of hydroxyimino derivative **2** in $CDCl_3$ show a single set of resonance absorption signals corresponding to all the structural fragments of the molecule, which is in accord with the quantum-mechanical modeling. The spectra of **2** were taken in $CDCl_3$ and in 2:1 DMSO-$CDCl_3$, which permitted us to separate the overlapping signals of $C_{(11)}Ha$ and $C_{(17)}H_2$ in the ^1H NMR spectrum and $C_{(6)}$, $C_{(19)}$ and $C_{(2)}$, $C_{(3)}$ in the ^{13}C NMR spectrum in order to study internuclear interactions (Tables 2 and 3). Thus, the low-field region (7.10-7.40 ppm) in the ^1H NMR spectrum has a characteristic set of four one-proton signals (two doublets and two triplets) coupled by spin-spin interactions. The high-field region (1.00-2.60 ppm) has

TABLE 1. Bonding Energies and Heats of Formation* of Conformers **2a-d** of Hydroxyimino Derivatives **2** From AM1 and PM3 Semiempirical Calculations

Compound	Conformer configuration	E_b, kcal/mol	T_{for}, kcal/mol
		AM-1**	
2a	9α–8α, 7β, 15α	-4719.6155998	18.6564002
2b	9α–8α, 7β, 15β	-4719.5826692	18.6893308
2c	9α–8β, 6α, 15α	-4717.3305899	20.9414101
2d	9α–8β, 6α, 15β	-4718.6675146	19.6014854
		PM3**	
2a	9α–8α, 7β, 15α	-4728.7718717	9.5001283
2b	9α–8α, 7β, 15β	-4727.0301482	11.2418518
2c	9α–8β, 6α, 15α	-4725.2533976	13.0186024
2d	9α–8β, 6α, 15β	-4726.0513028	12.2206975

* E_b is the bonding energy, T_{for} is the heat of formation.

** Gradient > 0.0001 kcal/mol/Å



a **b**

a $H_{(11b)}–C_{(11)}–H_{(11a)}$ 107.61°; $H_{(9)}–C_{(9)}–C_{(11)}–H_{(11b)}$ 63.70°;
$H_{(9)}–C_{(9)}–C_{(11)}–H_{(11a)}$ 178.0°;
b $H_{(6a)}–C_{(6)}–H_{(6b)}$ 107.55°; $H_{(7a)}–C_{(7)}–H_{(7b)}$ 107.68°;
$H_{(6a)}–C_{(6)}–C_{(7)}–H_{(7a)}$ 165.50°; $H_{(6a)}–C_{(6)}–C_{(7)}–H_{(7b)}$ 48.90°;
$H_{(6b)}–C_{(6)}–C_{(7)}–H_{(7a)}$ 48.40°; $H_{(6b)}–C_{(6)}–C_{(7)}–H_{(7b)}$ 68.20°

Fig. 2. Newman projections along $C_{(9)}$-$C_{(11)}$ (***a***) and $C_{(6)}$-$C_{(7)}$ bonds displaying the arrangement of the protons in these fragments of hydroxyimino derivative **2** for conformer **2a**.

signals for $C_{(16)}$ bearing a *gem*-dimethyl group as two three-proton singlets and AB system signals for strongly-coupled $C_{(15)}$ and $C_{(17)}$ methylene groups. The region 2.70-4.60 ppm has a set of signals corresponding to the $C_{(9)}H$-$C_{(11)}H_2$ and $C_{(6)}H_2$-$C_{(7)}H_2$ fragments. An unusually large downfield shift is found for the signal of the $C_{(11)}H_B$ proton in the $C_{(5)}H$-$C_{(11)}H_2$ ABX spin system ($H_{(11b)}$ in Fig. 2a), which has β-configuration, in comparison with the signal of the analogous proton of starting 8-aza-D-homogona-12,17*a*-dione **1** (δ 2.83 ppm). This finding may be related to the specific anisotropic effect of the oximino group with *anti* configuration. The anisotropic effect of the *anti* hydroxyl is seen even more clearly in the ^{13}C NMR spectrum in the chemical shift of $C_{(11)}$ with δ ~15 ppm in comparison with the effect of the starting diketo derivative (δ $C_{(11)}$ 45.20 ppm). The existence of an isomer with *syn* configuration is, as discussed above, unlikely due to 1) a steric factor and 2) coulombic interactions of the identically-charged oxygen at of the $C_{(17a)}$ carbonyl group and the nitrogen and oxygen atoms of the $C_{(12)}$ oximino group. The AM1 quantum-mechanical analysis of the hypothetical *syn* isomer **6** supported this concept and showed: E_b 4718.4289729; T_{for} 19.8430231 (grad. > 0.0001).

The assignments of the signals of the hydrogen atoms $C_{(5)}H$*a* and $C_{(7)}H$*e* are obvious. $H_{(9a)}$, which serves as the X-part of the ABX spin system for $C_{(5)}HC_{(11)}H_2$, has two coupling constants with the protons at $C_{(11)}$, corresponding, according to the Karplus rule [16], to relative *trans* and *gauche* arrangement (Fig. 2*a*). This permits a clear assignment of configuration for the protons at $C_{(11)}$. Equatorial configuration for $C_{(7)}$β*H*e is assigned to the downfield proton at $C_{(7)}$ by quantum-mechanical modeling.

The carbon atom signals in the ^{13}C NMR spectra given in Tables 2 and 3 were made were assigned by analyzing the HMQC and HMBC correlation spectra. The assignments of the quaternary carbon atoms are based on the following observations in the HMBC spectrum: $C_{(5)}$ has cross peaks with all the aromatic ring protons, while $C_{(5)}H$*a* also has cross peaks with $C_{(7)}$ and $C_{(6)}$. In turn, $C_{(10)}$ does not have cross peaks with the protons at $C_{(1)}$ and $C_{(7)}$ but signals are observed with protons at $C_{(11)}$. $C_{(13)}$ has cross peaks with $C_{(11)}$β*H*a, $C_{(17a)}$α*H*, $C_{(17)}$β*H*, and a strong signal with $C_{(11)}$α*H*e, which additionally indicates an equatorial position of this proton. $C_{(14)}$ has cross peak with protons at $C_{(15)}$ and $C_{(7)}$ and the signal of $C_{(7)}$β*H*e is stronger, as expected considering its equatorial position (angle close to 0). It is interesting to note the cross peak of $C_{(17a)}$ with $C_{(19)}H_3$. Although its intensity is low, we may note that there is an interaction through four bonds (*w* constant), which indicates an equatorial position of the $C_{(19)}$ methyl group and, thus, assigns axial configuration to the $C_{(18)}$ methyl group.

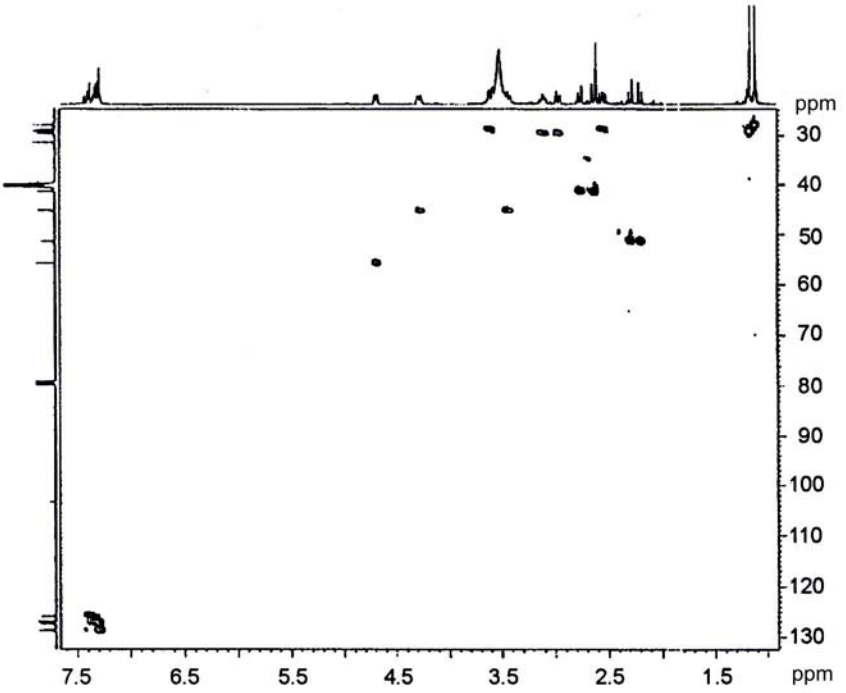


Fig. 3. HMQC spectrum of oxime **2** in DMSO-d_6–$CDCl_3$.

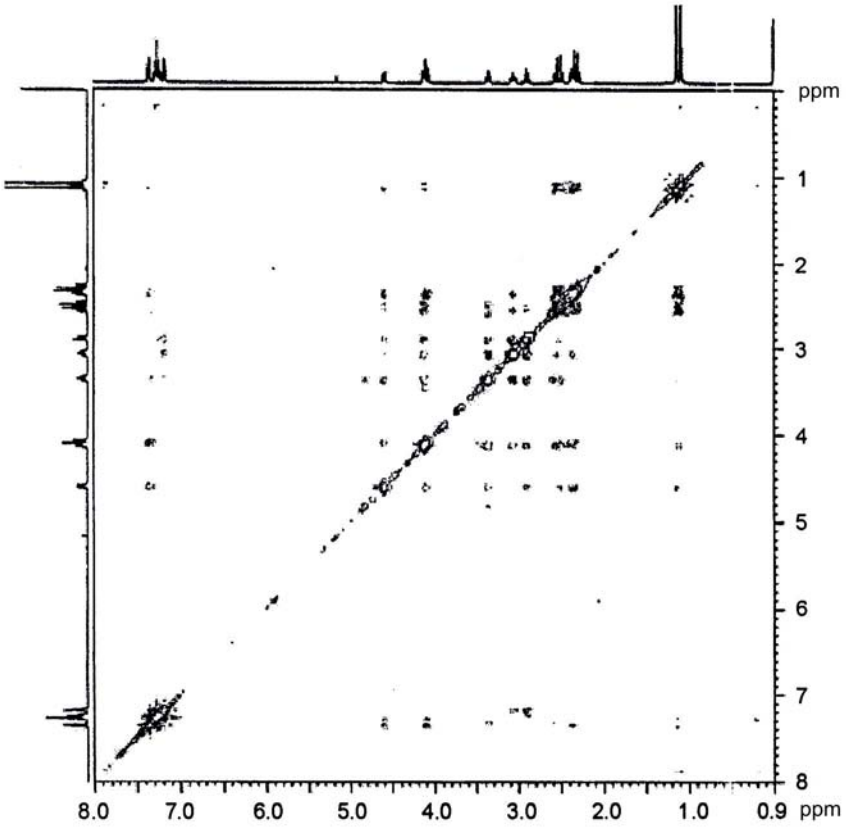


Fig. 4. NOESY spectrum of oxime **2** in $CDCl_3$.

Therefore, analysis of the 1D proton spectrum, COSY spectra, and NOESY spectra permitted us to obtain unequivocal assignments of the signals of all the protons and establish their position relative to the molecular plane. $C_{(1)}H$ is readily determined from the interactions with $C_{(9)}\alpha H\textit{a}$ and $C_{(11)}\alpha H\textit{e}$, while $C_{(4)}H$ is determined from the interactions with both protons at $C_{(6)}$ in the COSY and NOESY spectra. $C_{(2)}H$ in the COSY spectrum taken in $CDCl_3$ has a weak cross peak with $C_{(9)}\alpha H\textit{a}$, while $C_{(3)}H$ has a weak cross peak with $C_{(6)}\beta H\textit{a}$. These correlations could be found in a mixture of solvents due to signal overlap only for the interaction

TABLE 2. ^{1}H and 13C NMR Spectra and Internuclear Interactions of Oxime **2** in $CDCl_3$

Atom No.	Chemical shifts, δ, ppm (*J*,Hz)*			
	C	αH*a/e*	βH*a/e*	Observed effects
OH	—	~12.75 (br)	—	—
1	126.35	7.36 (d, *J* = 7.7)	—	COSY 9α, NOESY 9α (*s*), 11α (*s*), 7α (*w*), HMBC 9H
2	127.42	7.25 (t, *J* = 7.2)	—	COSY 1, 9α (*w*)
3	127.42	7.28 (t, *J* = 7.4)	—	COSY 4, 6β (*w*)
4	128.36	7.18 (d, *J* = 7.4)	—	COSY 6, NOESY 6
5	133.63	—	—	HMBC 7αβ
6**	29.76**	*e* 2.89 (dt, *J* = 15.7, *J* = 3.2)	*a* 3.06 (ddd, *J* = 15.6, *J* = 11.5, *J* = 4.2)	α-NOESY 9α, 7αβ, β-NOESY 11β (*w*), 15β (*vw*)
7	44.74	*a* 3.36 (m)	*e* 4.12 (dt, *J* = 12.4, *J* = 3.7)	α-NOESY 9α, 1 (*w*), 6α (*s*), 6β (*w*), 15α (*w*); β-NOESY 6α (*w*), 6β (*w*), 15α (*s*), 15β (*s*)
9	55.91	*a* 4.59 (dd, *J* = 13, *J* = 3.4)	—	
10	135.10	—	—	HMBC 11α, 11β
11	29.27	*e* 4.09 (dd, *J* = 16.5, *J* = 4.0)	*a* 2.36 (dd, *J* = 12.8, *J* = 16.3)	α-NOESY 9α (*s*), β-NOESY 9α (*w*)
12	145.19	—	—	HMBC 11α (*s*), 11β (*w*), no 9α-angle 90°
13	102.16	—	—	HMBC 11α (*s*), 11β (*w*), 17αβ
14	161.29	—	—	HMBC 7β (*s*) 7α (*w*), 15 αβ
15	42.05	*a* 2.48 (d, *J* = 16.6)	*e* 2.55 (d, *J* = 16.6)	α-NOESY 7α (*s*), 7β (*s*), 9α (*w*), 17α (*s*), 18, 19 β-NOESY 7β (*s*), 7α (*w*), 17β, 18, 19
16	31.76	—	—	
17	50.32	*a* 2.35 (d, *J* = 16.0)	*e* 2.28 (d, *J* = 16.0)	α-NOESY 9α, 15α, β-COSY long-range *w*-constant 15β, NOESY 15β
17*a*	193.72	—	—	HMBC 17, 19
18β	27.69	—	*a* 1.08	COSY long-range *w*-constant 15α, 17α
19α**	29.74**	*e* 1.13	—	NOESY 9α (*w*), HMBC 17*a*

* *a*–axial, *e*-equatorial.

** The reverse assignment of these carbon atom signals may be possible.

of $C_{(3)}H$ with $C_{(6)}\beta H$*a*. The configuration of the protons in ring ***B*** was supported by the NOE of $C_{(7)}\alpha H$*a* with $C_{(9)}\alpha H$*a* and of $C_{(6)}\beta H$*a* with $C_{(11)}\beta H$*a*. The finding of strong cross peaks of $C_{(7)}\beta H$*e* (*e*-equatorial position of $C_{(7)}\beta H$) with the protons at $C_{(15)}$ both supports the assignments made for ring ***B*** and unequivocally proves the chemical shift of the AB spin system of the protons at $C_{(15)}$.

The greatest difficulty arises in the assignment of the protons in ring ***D*** since this system is rather isolated from the other protons in the molecule. The stereochemical assignments were carried out as follows. The protons at $C_{(19)}$ show a weak NOE effect with $C_{(9)}\alpha H$*a* in the solvent mixture, which may be a consequence of an axial position for this methyl group. Hence, taking account of the cross peaks in the NOESY spectrum (solvent mixture) of $C_{(19)}$*a* with $C_{(17)}\alpha H$*a* and $C_{(15)}\alpha H$*a* and of $C\beta_{(18)}$*e* with $C_{(15)}\beta H$*e*, we establish the stereochemistry of the protons in ring ***D***. Additional proof for this assignment is found in the long-range interactions (*w*-constant through four bonds) in the COSY spectrum. Thus, cross peaks are observed between $C_{(15)}\beta H$*e* and $C_{(17)}\beta H$*e*. This is possible when these atoms are located one side of the molecular plane and are in equatorial position. However, cross peaks are found in the spectrum between $C\beta_{(18)}H_3$, $C_{(15)}\alpha H$*a*, and $C_{(17)}\alpha H$*a*. In this case, the 18-methyl group must be axial and the 19-methyl group must be equatorial. The latter position is in contradiction to the above interaction with $C_{(9)}\alpha H$*a*. Such a conformation also is not in accord with

TABLE 3. ^{1}H and 13C NMR Spectra and Internuclear Interactions of Oxime **2** in DMSO-d_6–$CDCl_3$

Atom No.	Chemical shifts, δ, ppm (*J*, Hz)			
	C	αH*a*/*e*	βH*a*/*e*	Observed effects
1	125.64	7.38 (d, *J* = 7.4)	—	COSY 9, NOESY 9, 11α, 11β
2	127.09	7.28 (m)	—	
3	126.81	7.33 (m)	—	COSY 6β
4	128.53	7.29 (m)	—	COSY 6, NOESY 6α
5	134.68	—	—	
6	29.33	*e* 2.96 (dt, *J* = 16.0, *J* = 3.5)	*a* 3.10 (ddd, *J* = 15.7, *J* = 11.7, *J* = 4.2)	COSY 4, α-NOESY 7α, β-NOESY 7β
7	44.94	*a* 3.44 (ddd, *J* = 13.4, *J* = 11.1, *J* = 2.8)	*e* 4.28 (dt, *J* = 13, *J* = 3.9)	α-NOESY 9α, β-NOESY 15α, 15β
9	55.54	*a* 4.69 (dd, *J* = 3.8, *J* = 11.2)	—	
10	136.02	—	—	
11	28.59	*e* 3.60 (dd, *J* = 4.3, *J* = 15.9)	*a* 2.54 (dd, *J* = 11.5, *J* = 15.7)	α-NOESY 9α (*s*), β-NOESY 9α (*w*)
12	148.39	—	—	
13	103.12	—	—	
14	162.82	—	—	
15	41.09	*a* 2.62 (d, *J* = 17)	*e* 2.76 (d, *J* = 17)	α-NOESY 17α, 19, β-NOESY 17β, 18
16	31.31	—	—	
17	51.15	*a* 2.29 (d, *J* = 17)	*e* 2.19 (d, *J* = 17)	α-NOESY 15α, 19, β-COSY long-range *w*-constant 15β, NOE 18
17*a*	191.28	—	—	
18β	27.72	—	*a* 1.11	COSY long-range *w*-constant 15α, 17α
19α	28.98	*e* 1.17	—	

conformation obtained in the AM1, PM3, and MM2 calculations. An explanation of this anomaly may lie in the circumstance that the molecular structure is not absolutely rigid and conformational transformations of ring ***D*** are possible with some occupancy of conformer **2b**. As a result, the protons at $C_{(15)}$ and $C_{(17)}$ may occupy both pseudoaxial and pseudoequatorial positions, which is indicated by the NOE effects of different intensity of the protons at $C_{(15)}$ with the protons at $C_{(7)}$.

Some conformational flexibility also probably exists in ring ***B*** since an NOE effect is found for $C_{(6)}$αH*e* with 9αH*a* and, correspondingly, for $C_{(7)}$αH*a* with the protons at $C_{(15)}$ (much weaker than for $C_{(7)}$βH*e*).

An attempt to determine the configuration of the oximino group in derivative **2** using COSY and NOESY proved unsuccessful, probably due to rotation about the N–O bond. Hence, we analyzed the methyl ether 3 of the hydroxyimino derivative. However, the NOESY spectrum in this case also failed to detect actual cross peaks of the oxime methyl group with protons of the tetracyclic molecular skeleton. This failure is also probably a consequence of rotation around the N–O bond.

TABLE 4. ^{1}H and ^{13}C NMR Spectra and Internuclear Interactions of Methoxyimino Derivative **3** in $CDCl_3$

Atom No.	Chemical shifts, δ, ppm (*J*,Hz)			
	C	αH*a/e*	βH*a/e*	Observed effects
NOMe	61.64	3.98 (s)	—	
1	125.96	7.29 (m)	—	COSY 9αH, NOESY 9αH, 11H
2	127.22	7.23 (t, *J* = 7.2)	—	COSY 1H, 3H, 9αH
3	127.13	7.27 (m)	—	COSY 4H, 6βH (*w*)
4	128.42	7.17 (d, *J* = 7.4)	—	COSY 6H, NOESY 6H
5	133.91	—	—	HMBC 9H, 7H, 6H
6	29.83	*e* 2.87 (dt, *J* = 15.9, *J* = 3.1)	*a* 3.04 (m)	COSY 4H, α-NOESY 7H, 9αH (*w*), β-NOESY 7βH, 11βH (*w*)
7	44.58	*a* 3.31 (m)	*e* 4.08 (dt, *J* = 12.8, *J* = 4.0)	α-NOESY 6αH, 9αH, β-NOESY 6H, 15H
9	56.03	4.52 (dd, *J* = 3.2, *J* = 12.5)		
10	135.59	—	—	HMBC 9H, 11H, 6H
11	30.20	3.78 (dd, *J* = 15.9, *J* = 4.0)	2.32 (dd, *J* = 12.7, *J* = 15.9)	α-NOESY 9αH, HMBC 17a (*w*-constant)
12	149.50	—	—	HMBC 9H, 11H, 17H, Ome
13	104.32	—	—	HMBC 11αH, 15H, 17H
14	161.54	—	—	HMBC 7H, 9H, 19αH (*w*-constant)
15	42.04	2.45 (d, *J* = 16.7)	2.50 (d, *J* = 16.7)	α-NOESY 18α, β-NOESY 19β
16	31.67	—	—	
17	51.14	2.32 (d, *J* = 16.0)	2.27 (d, *J* = 16.0)	β-COSY 15βH (*w*-constant)
17*a*	191.70	—	—	HMBC 15H, 17H, 11αH и 19αH (*w*-constant)
18β	27.81	—	1.08 (s)	COSY 17αH and 15αH (*w*-constant), NOESY 17βH, 15βH
19α	29.57	1.12 (s)	—	HMBC 17*a* (*w*-constant), NOESY 15αH, 17αH, 9αH (*vw*)

On the whole, the spectra of the ether, as expected, are extremely similar to the spectra of the oxime itself. Nevertheless, the following differences were detected in the spectra (Table 4). The introduction of the methyl group had a slight effect on the chemical shifts of a series of protons and carbon atoms. Thus, the signals for $C_{(11)}$αH and $C_{(1)}$H were shifted upfield by 0.31 and 0.08 ppm, respectively, while the intensity of the outer lines in the AB system of the protons at $C_{(15)}$ (the chemical shift–coupling constant ratio was 1.5). The ^{13}C NMR spectrum shows shifts for $C_{(12)}$ and $C_{(13)}$ downfield by 14.5 and 2.1 ppm, respectively, and for $C_{(17a)}$ upfield by 2 ppm.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer. The UV spectra were taken on a Specord M-400 spectrophotometer in ethanol. The ^{1}H and ^{13}C NMR spectra as well as the COSY, NOESY, HMBC, and HMQC spectra were taken on a Bruker Avance spectrometer at 500 and 126 MHz, respectively. The ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ and $CDCl_3$–DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Varian MAT-311 mass spectrometer with direct inlet and 70 eV ionizing electron energy. The melting points were determined on a Böetius heating block. The reaction was monitored by thin-layer chromatography on Silufol UV–254 plates with 9.5:0.5 or 9:1 chloroform-methanol as the eluent. The sample of 16,16-dimethyl-8-aza-D-homogona-1,3,5(10),13-tetraene-12,17*a*-dione **1** was obtained by fusing 3,4-dihyroisoquinoline by means of 2-acetyldimedone [10].

12-Hydroxyimino-16,16-dimethyl-8-aza-D-homogona-1,3,5(10),13-tetraen-17*a*-one (2). A sample of a solution, obtained by mixing 0.56 g (8 mmol) hydroxylamine hydrochloride and 0.66 g (8 mmol) fused sodium acetate in 15 ml ethanol and filtering off the NaCl precipitate, to a solution of 2.22 g (7.5 mmol) 8-aza-D-homogona-12,17*a*-dione **1** in 25 ml ethanol. The mixture obtained was left at 20°C, following the reaction by thin-layer chromatography on Silufol UV-254 plates with 9.5:0.5 chloroform-methanol as eluent and detection in UV light or exposure to iodine vapor with subsequent heating at 200-250°C. Then, the reaction mixture was evaporated to half volume and ether was added until slight turbidity formed. The mixture was left to crystallize at 5°C. Filtration gave 2.2 g hydroxyimino derivative **2** as transparent, light cream-colored prisms. The yield of **2** was 95.2%, mp 230°C (dec.) (from ethanol-ether). IR spectrum (KBr pellet), ν, cm^{-1}: 3210, 3100-2830, 1635, 1590 sh, 1523, 1495, 1470, 1460-1430, 1360, 1325, 1285, 1225, 1180, 1150, 1120, 1085, 1030, 970, 915, 890, 770, 745; (vaseline mull): 3180, 1635, 1523, 1475-1435, 1380, 1365, 1320, 1285, 1120, 970, 915, 770, 745; (solution in $CDCl_3$): 3585. UV spectrum in EtOH (*c* 2.31·10^{-4} mole/l), λ_{max}, nm (ε): 200 (19280), 210 (16250), 247 (5635), 317 sh (14950), 338 (16900); λ_{min}, nm (ε): 208.3 (16030), 239.7 (5635, 270.3 (3900). Found, %: C 73.48; H 7.03; N 9.15 $[M]^+$ 310. $C_{19}H_{22}N_2O_2$. Calculated, %: C 73.52; H 7.14; N 9.03; M 310.39.

Compound 2 was alternatively obtained by heating an equimolar mixture of 3.5 mmol 8-aza-D-homogona-12,17*a*-dione **1** and hydroxylamine hydrochloride in ethanol for 1 h with subsequent work-up as in the above procedure. The yield of **2** was 0.99 g (91.5%) oximino derivative **2** as transparent prisms, mp 231-232°C (dec., from $CHCl_3$).

12-Methoximino-16,16-dimethyl-8-aza-D-homogona-1,3,5(10),13-tetraen-17*a*-one (3). A solution of 0.55 ml (10 mmol) methoxyamine in 10 ml ethanol was added to a solution of 1.48 g (5 mmol) **1** in 20 ml ethanol and left at 20°C, following the reaction course by thin-layer chromatography (see above). After 36 h, the reaction mixture was evaporated to dryness at reduced pressure. The residue was dissolved in chloroform. Ether and hexane were added until slight turbidity was noted and the mixture was left at 5°C to crystallize. Tetraenone **3** was obtained as white prisms. The yield of **3** was 1.4 g (87.2%), mp 164-167°C (dec., from ether-hexane). IR spectrum (KBr pellet), ν, cm^{-1}: 3050-2830, 1642, 1610 sh, 1575, 1520, 1495, 1450, 1380, 1370-1345, 1320, 1290, 1230, 1220, 1150, 1120, 1095, 1050, 835, 760, 750. UV spectrum (in EtOH),

c $4.22 \cdot 10^{-4}$ mol/l), λ_{max}, nm (ε): 199 (19,455), 207 sh (13,525), 231 sh (2610), 304 (19,930); λ_{min}, nm (ε): 250 (950). Found, %: C 74.24; H, 7.40; N, 8.49%, $[M]^+$ 324.%. $C_{20}H_{24}N_2O_2$. Calculated, %: C 74.04; H 7.46; N 8.64; M 324.48.

Compound 3 was alternatively also obtained by the alkylation of **2.** A sample of 0.1 g (2.5 mmol) NaOH in 5 ml ethanol was added to a solution of 0.78 g (2.5 mmol) **2** in 15 ml ethanol in an argon stream. The mixture was stirred for 10-15 min and then a solution of 0.17 ml (2.7 mmol) methyl iodide in 5 ml ethanol was added. The mixture obtained was maintained for 2 h at 20°C, then heated at reflux for 1 h, and evaporated to dryness. The residue was dissolved in 3-5 ml chloroform and filtered through 3 g neutral alumina. Chloroform was used as the eluent in the chromatography. The desired product was separated as in the above experiment to give **3** in 85.1% yield, mp 166-167°C (dec., from chloroform-ether-hexane).

Hydrochloride of 12-Hydroxyimino-16,16-dimethyl- 9-aza-D-homogona-1,3,5,(10),13-tetraen-17*a*-one (4). A solution of 0.065 g (0.94 mmol) hydroxylamine hydrochloride in 5 ml ethanol was added to a solution of 0.25 g (0.8 mmol) **1** in 5 ml ethanol and the mixture obtained was heated at reflux for 1 h. The solution was then evaporated to half volume, diluted with ether until turbidity appeared, and left for 36 h at 5°C. The crystalline precipitate was filtered off, washed on the filter with 1:2 ethanol-ether, and recrystallized from ethanol-ether to give **4** in 93.5% yield, mp 232°C (dec., from ethanol). IR spectrum (KBr pellet), ν, cm^{-1}: 3100-2830, 2640 br, 2385 br, 1663, 1635, 1612, 1593, 1555; (vaseline mull): 2365 br, 1663, 1610, 1593, 1500-1420, 1380, 1325, 1315, 1280, 1230, 1220, 1180, 1120, 1095, 1065-1025, 1000, 970, 950, 930, 870, 835, 760, 740. UV spectrum (in ethanol, *c* $2.35 \cdot 10^{-4}$ mol/l), λ_{max}, nm (ε): 200.4 (17525), 282.9 (11000), 324.5 (16500); λ_{min}, nm (ε): 249.1 (2980), 299.1 (10000). ^{1}H NMR spectrum in $CDCl_3$, δ, ppm (*J*, Hz): 1.13 (3H, s, $C_{(16)}CH_3$), 1.20 (3H, s, $C_{(16)}CH_3$), 2.37 (1H, d, *J* = 15.6, $_{(17)}H_B$), 2.49 (1H, d, *J* = 15.6, $C_{(17)}H_A$), 2.80 (1H, d, *J* = 16.8, $C_{(15)}H_B$), 2.84 (1H, dd, *J* = 16.8, *J* = 15.6, $C_{(11)}H_B$), 3.06 (1H, tt, *J* = 16.2, *J* = 3.6, *J* = 3.6, $C_{(6)}H$*e*), 3.19 (1H, dtd, *J* = 16.2, *J* = 10.8, *J* = 3.6, $C_{(6)}H$*a*), 3.63 (1H, dtd, *J* = 13.2, *J* = 10.8, *J* = 3.6, $C_{(17)}H$*a*), 3.87 (1H, dd, *J* = 16.8, *J* = 4.8, $C_{(11)}H_A$), 4.36 (1H, tt, *J* = 13.2, *J* = 3.6, *J* = 3.6, $C_{(17)}H$*e*), 5.07 (1H, dd, *J* = 15.6, *J* = 4.8, $C_{(9)}H_X$), 7.26-7.41 (4H, m, $C_{(1)}H$, $C_{(2)}H$, $C_{(3)}H$, $C_{(4)}H$). Found, %: C 66.00; H 6.70; Cl 10.57; N 8.07, $[M]^+$ 311. $C_{19}H_{22}N_2O_2 \cdot HCl$. Calculated, %: C 65.79; H 6.68; Cl 10.22; N 8.08, M 346.86.

The authors express their gratitude to Prof. A. A. Akhrem, Academician of the National Academy of Sciences of the Republic of Belarus for taking interest in this study and for helpful discussion of the results.

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