SYNTHESIS OF SOME NEW ANALOGS OF ARGEMONINE OF THE TYPE OF 4,4,8,8-TETRAMETHYL-2,3;6,7-DIBENZO-9-AZABICYCLO [3.3.1] NONANE-1,5-DIOLS

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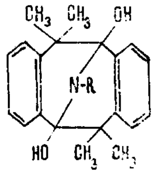
It has been shown previously [1] that 3,3,7,7-tetramethyl-1,2;5,6-dibenzocyclooctane-4,8-dione (I), obtained by the oxidation of 5,5,10,10-tetramethyl-4b,5,9b,10-tetrahydroindeno[2,1-a]indene under certain conditions undergoes a number of interesting transannular transformations. The reaction of (I) with ammonia and methylamine in a neutral medium gives high yields of 4,4,8,8-tetramethyl-2,3;6,7-dibenzo-9-azabicyclo[3.3.1]nonane-1,5-diol and its N-methyl derivative [2], the basic skeleton of which is analogous to that of the molecule of argemonine and related alkaloids [3-6]. The reaction considered has a general nature. The reaction of the diketone (I) with various aliphatic and aliphatic-aromatic primary amines under similar conditions readily and with good yields forms the corresponding dibenzo-9-azabicyclo[3.3.1]nonanediols; however, aniline, unlike other amines under these conditions, does not react with the diketone (I). Table 1 gives the compounds synthesized, their melting points, and the yields obtained.

TABLE 1



Compound	*R*	mp, °C	Yield, %	Formula
II	$-CH_2-CH_3$	130–131,5	85,3	$C_{22}H_{27}O_2N$
III		209–210	93	$C_{22}H_{27}O_2N \cdot HCl$
IV	$-(CH_2)_3-CH_3$	115	37	$C_{24}H_{31}O_2N$
V		215–216	88	$C_{24}H_{31}O_2N \cdot HCl$
VI	$-(CH_2)_2-OH$	211–212	70	$C_{22}H_{27}NO_3$
VII		181–183	83,5	$C_{22}H_{27}NO_3 \cdot HCl$
VIII	$-OH$	165–166	77	$C_{20}H_{23}NO_3$
IX		185–186	91	$C_{20}H_{23}NO_3 \cdot HCl$
X*	H	176	94	$C_{20}H_{23}NO_2 \cdot HCl$
XI*	$-CH_3$	223–224	93,5	$C_{21}H_{25}NO_2 \cdot HCl$
XII	$-CH_2-C_6H_5$	160–160,5	85	$C_{27}H_{29}NO_2$
XIII		182	95	$C_{27}H_{29}NO \cdot HCl$
XIV	$-(CH_2)_2-CH-CH_3$	192	93	$C_{30}H_{35}NO_2 \cdot HCl$
XV	$-(CH_2)_2-\underset{C_6H_4(CH_3)_2}{\overset{C_6H_5}{CH}}-CH_3$	189–190	91	$C_{32}H_{39}NO_2 \cdot HCl$
XVI	$-(CH_2)_2-NH_2$	225	80	$C_{22}H_{28}N_2O_2$
XVII		163–164	92,5	$C_{22}H_{28}N_2O_2 \cdot 2HCl$
;XVIII	$-(CH_2)_6-NH_2$	81–82	50	$C_{26}H_{36}N_2O_2$
XIX		195–197	83	$C_{26}H_{36}N_2O_2 \cdot 2HCl$
XX	$-(CH_2)_2-NHCOCH_3$	202–203	80	$C_{24}H_{30}N_2O_3$

* The bases (X) and (XI) have been described previously [2].

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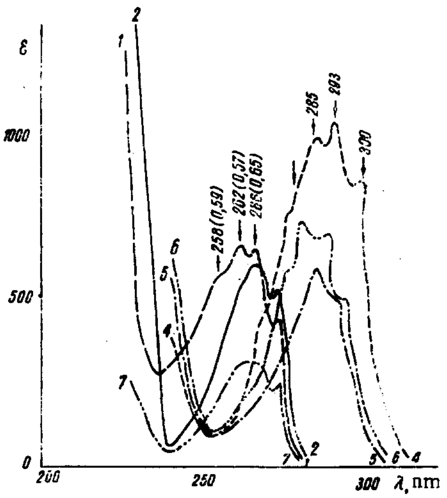
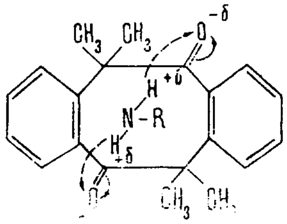


Fig. 1. UV spectra of the compounds: 1) (XIV); 2) (XV); 4) argemonine; 5) O,O-dimethylmunitagine; 6) munitagine; 7) N-methyl derivative of 4,4,8,8-tetramethyl-2,3;6,7-dibenzo-9-azabicyclo-[3.3.1]nonane-1,5-diol.

The formation of these compounds evidently takes place in the following way. The presence of two spatially adjacent polarized carbonyl groups in an eight-membered ring favors the migration of hydrogen atoms from the NH_2 group to the negatively charged oxygen atom, which leads to the formation of a bridge between the nitrogen atoms and a positively charged carbon atom.

The presence of two neighboring gem-dimethyl groups probably additionally prevents the approach of the NH_2 group to each of the carbonyl groups individually. This apparently also explains the fact that the reaction of hydroxylamine with the diketone (I) leads not to a mono- or a dioxime but to the corresponding aza adduct (VIII).



The IR spectra of the aza compounds obtained show absorption bands in the 760-765-cm^{-1} region which are characteristic for a 1,2-disubstituted benzene ring. Absorption bands in the 3500-3600-cm^{-1} region are due to the stretching vibrations of free OH groups (in $CHCl_3$ and CCl_4), and absorption bands at 3370-3380 cm^{-1} show the presence of a hydrogen bond (KBr tablet). Absorption bands in the 2965-cm^{-1} region are characteristic for CH_3 groups. In the spectra of the compounds containing a CH_2 group, absorption bands appear at 2927 cm^{-1}. In the hydrochlorides of (III, V, VII, IX, XI, and XII-XV), in addition to broad absorption bands of OH groups (3200-3600 cm^{-1}), there are bands in the 2400-2800-cm^{-1} region characteristic of salts of tertiary amines, and at 1575 cm^{-1} apparently due to NH groups. The hydrochloride of (X), in agreement with the literature [7], shows the absorption band of an NH_2 group at 2800 cm^{-1}.

In the UV region, the absorption spectra of the N-methyl derivative of 4,4,8,8-tetramethyl-2,3;6,7-dibenzo-9-azabicyclo[3.3.1]nonane-1,5-diol and of compounds (XIV) and (XV) and also those of alkaloids of the argemonine group [5] are similar, but the absorption maxima of the bands in the UV spectra of these alkaloids are shifted in the longer-wave direction. These characteristics agree well with the known fact that the introduction into an aromatic nucleus of functional groups containing unshared electrons or n-electrons is connected with a considerable increase in the absorption of UV radiation and with a shift in the maxima of the absorption bands into the long-wave region of the spectrum [8] (Fig. 1).

It has been shown previously [2, 3] that the PMR spectra of 4,4,8,8-tetramethyl-2,3;6,7-dibenzo-9-azabicyclo[3.3.1]nonane-1,5-diol and its N-methyl derivative have two types of signals of the methyl protons. According to a Dreiding model, the appearance of these two types of signals is a consequence of the particular arrangement of one of the four methyl groups relative to the nitrogen atom and the interaction with it of its long pair of electrons. A similar picture is found in the PMR spectra of compounds (VIII) and (XII). The spectrum of (VIII) has three signals from the four CH_3 groups: at 1.5 ppm ($2CH_3$), 1.47 ppm ($1CH_3$), and 1.40 ppm ($1CH_3$). Two isolated signals appear at 4.65 and 3.35 ppm which are characteristic for two hydroxy groups. A broad band at 5.90 ppm relates to a hydroxy group attached to a nitrogen atom.

The PMR spectra of (VIII) were obtained in deuterochloroform at room temperature and at 40°C. With a rise in the temperature, a pronounced broadening of the signal of the N—OH group took place, and all three signals relating to OH groups shifted in the upfield direction. The spectrum of (XII) also shows two types of signals of methyl protons: at 1.48 ppm ($3CH_3$) and 1.37 ppm ($1CH_3$). At 2.24 and 2.72 ppm there are signals of protons of hydroxy groups and, together with these, two doublet signals appear at 3.38 and 3.97 ppm which are characteristic for the protons of a CH_2 group. The signals of aromatic protons are found in the region of the spectrum from 6.86 to 7.71 ppm.

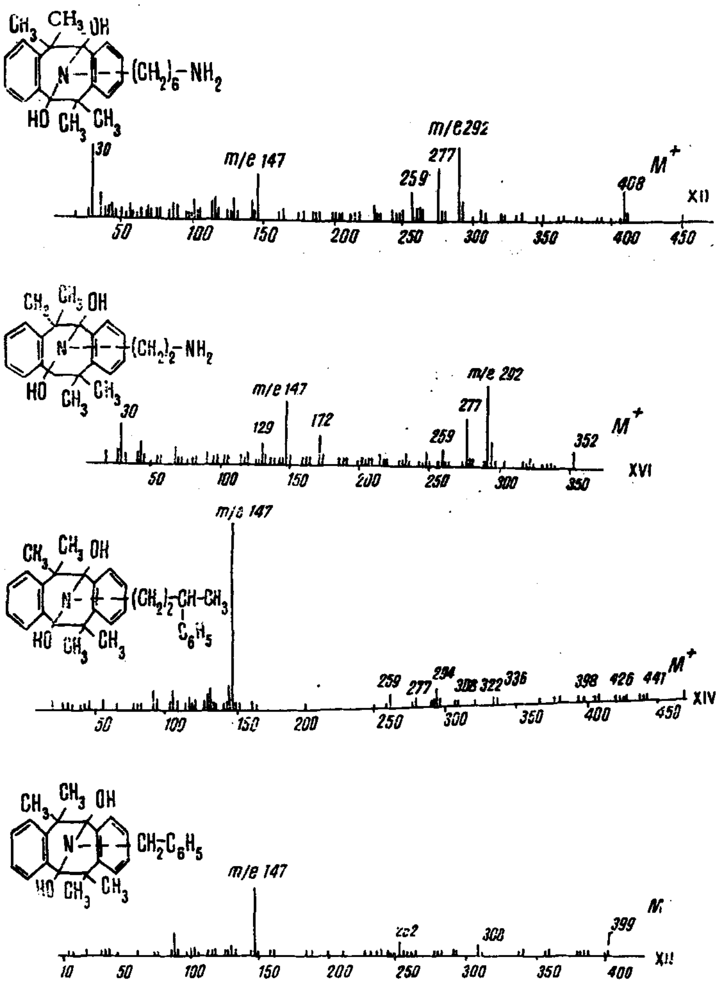
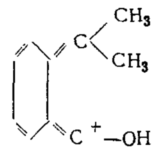
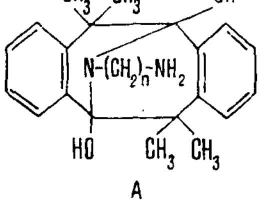


Fig. 2. Mass spectra of substances (XII, XIV, XVI, and XIX).

The mass spectra of (VIII, X, XII, XIV, XVI, XIX, and XX) show the peaks of the molecular ions (M^+) and the peak of an ion with m/e 147 probably having the following structure:

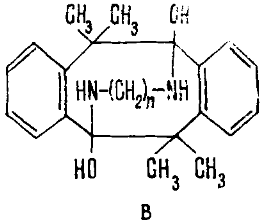


and the peaks of the ions $(M-147)^+$. In the mass spectra of 4,4,8,8-tetramethyl-2,3;6,7-dibenzo-9-azabicyclo-[3.3.1]nonane-1,5-diol and (XII) and (XIV) the peak of the ion with m/e 147 has the maximum intensity in each case. For the adducts of diamines (XVI) and (XIX) the intensities of the peaks of these ions are also high, but the maximum peak is that of the ion with m/e 292 which is formed by the elimination from the molecular ion of molecules of ethylenediamine and of hexamethylenediamine, respectively. The peaks of the ions with m/e 292 in the mass spectra of compounds (XII and XIV) have a low intensity, apparently because of the influence of the voluminous substitutents on the nitrogen atom on the rate of decomposition of M^+ under electron impact (Fig. 2).



A

XVI. n=2 XVIII. n=6



B

XVI. n=2 XVIII. n=6

The existence of the two alternative structures A and B may be put forward for the adducts of the diketone (I) with ethylenediamine (XVI) and hexamethylenediamine (XVIII).

Because of the overlapping of the absorption bands characterizing the OH, NH, and NH_2 groups in the IR and PMR spectra of these compounds and their hydrochlorides, it is not possible to make an unambiguous choice between these two structures. It was possible to resolve this problem through a study of the properties of the monoacetate (XX) obtained by the reaction of the adduct (XVI) with acetic anhydride at room temperature. The IR spectrum of (XX) showed absorption bands at 1665 and 1558 cm^{-1} characteristic of an amide group, at 3458 cm^{-1}, corresponding to the NH group of a secondary amine, and at 3540 cm^{-1}, which is characteristic for an OH group, all this corresponding to structure A. In the mass spectrum of (XX) there is the peak of the molecular ion with m/e 294. The peak of the ion with m/e 292 has the maximum intensity, as is the case in the mass spectra of (XVI) and (XIX).

EXPERIMENTAL

The NMR spectra were taken on a JEOL-4H-100/100 MHz instrument (in $CHCl_3$ with TMS as internal standard), and the mass spectra on an LKB 9000 instrument with an energy of the ionizing electrons of 70 eV and a temperature of the ionization chamber of 230-250°C.

N-Ethyl Derivative of 4,4,8,8-Tetramethyl-2,3;6,7-dibenzo-9-azabicyclo[3.3.1]nonane-1,5-diol (II). A solution of substance (I) (0.5 g) in 15 ml of ethanol was treated with 10 ml of a saturated ethanolic solution of ethylamine. The mixture was heated at 40°C for 1.5 h and was then diluted with water. The white precipitate that deposited was filtered off, washed several times with water to neutrality, and recrystallized from ethanol. The product was dried in a vacuum desiccator over P_2O_5.

Compounds (IV, VI, VIII, XVI, and XVII) were obtained under similar conditions.

Substance (XII). To a solution of 0.5 g of compound (I) in 15 ml of absolute ethanol was added 0.2 g of benzylamine in 5 ml of ethanol. The mixture was heated on the water bath at 65°C under reflux for 1 h. Then the solvent was evaporated off and the residue was washed several times with petroleum ether and was recrystallized from ethanol.

N-(3-Phenylbutyl) Derivative of 4,4,8,8-Tetramethyl-2,3;6,7-dibenzo-9-azabicyclo[3.3.1]nonane-1,5-diol (XIV). A solution of 0.4 g of compound (I) in 10 ml of absolute ethanol was treated with 0.27 g of 3-phenylbutylamine (bp 50°C, n_D^{20} 1.5200 [9]).

The mixture was heated to 50°C for 40 min. The solvent was evaporated off and the residual oily substance was purified by thin-layer chromatography of Al_2O_3 in the benzene–ether (1 : 1) system.

To 0.2 g of the crude product (n_D^{20} 1.5610) was added 10 ml of a saturated solution of HCl in ether. The white crystalline substance that deposited was washed several times with absolute ether and was dried in vacuum over P_2O_5.

Substance XV was obtained under the conditions described in the preceding experiment except that to chromatograph the oily product the benzene–hexane (1 : 10) system was used. The 3-(m-xylyl)butylamine had bp 78°C, n_D^{20} 1.5173 [9].

The hydrochlorides of III, V, VII, IX, X, XI, XIII, XIV, XV, XVII, and XIX were formed under similar conditions.

Compound (XX). A solution of 0.4 g of (XVI) in 4 ml of acetic anhydride was left at room temperature. On the second day, the precipitate that had deposited was filtered off, washed with water, and recrystallized from ethanol.

SUMMARY

It has been shown that the transannular reaction of the readily available 3,3,7,7-tetramethyl-1,2;5,6-dibenzocyclooctane-4,8-dione with various aliphatic and aliphatic-aromatic primary amines forms good yields of the corresponding 4,4,8,8-tetramethyl-2,3;6,7-dibenzo-9-azabicyclo[3.3.1]nonane-1,5-diols. These compounds have the symmetrical dibenzocyclooctane skeleton with the aza grouping characteristic for argemonine and alkaloids related to it.

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