RING—CHAIN TAUTOMERISM OF SUBSTITUTED HYDRAZONES.
X.* SYNTHESIS AND SOME PECULIARITIES OF THE STEREOCHEMISTRY OF 3,4-DIMETHYLPERHYDRO-1,3,4-OXADIAZINES

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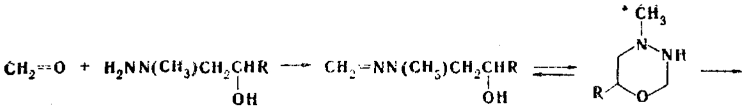
It is shown that the products of condensation of formaldehyde with 2-(N-methylhydrazino)ethanol and 1-(N-methylhydrazino)-2-propanol are reduced by lithium aluminum hydride to the corresponding vicinal N,N'-dimethylhydrazino alcohols. The reaction of the latter with acetaldehyde gave methyl-substituted perhydro-1,3,4-oxadiazines. Their PMR spectra and stereochemistry are discussed.

As we have demonstrated in previous communications of this series, factors associated with the three-dimensional structure of the cyclic form have a substantial effect on the position of the 2-hydroxylalkylhydrazone—perhydro-1,3,4-oxadiazine tautomeric equilibrium. A study of the stereochemical peculiarities of 3-substituted perhydrooxadiazines, which are incapable of reversible isomerization to hydrazones, therefore seems of definite interest. Compounds of this type — substituted 3-methylperhydro-1,3,4-oxadiazines — were previously obtained by alkylation with methyl iodide of the products of condensation of N-aminoephedrine with aliphatic aldehydes [2]. The reaction of carbonyl compounds with vicinal N,N'-disubstituted hydrazino alcohols is apparently a more general method for their preparation. The simplest methods for the synthesis of the latter are probably reduction of the products of the reaction of aldehydes or ketones with N-monosubstituted hydrazino alcohols or opening of alkene oxides with N,N'-disubstituted hydrazines. However, one must bear in mind that the second variant will be convenient only if both nitrogen atoms have identical substituents† or differ so markedly with respect to their nucleophilicity that the reaction with the alkene oxide leads only to one of the structural isomers of hydrazino alcohols.

We used both of these variants to obtain vicinal N,N'-dimethylhydrazino alcohols. Hydrazino alcohols I undergo condensation with formaldehyde to give mixtures of tautomers IIa, b; the cyclic tautomer is the chief product in both cases. The reduction of these tautomeric mixtures with lithium aluminum hydride (LAH) in ether leads to dimethyl-substituted hydrazino alcohols III. Hydrazino alcohol IIIa was also obtained from N,N'dimethylhydrazine and ethylene oxide.

Hydrazino alcohols III react readily with acetaldehyde to give tri- and tetramethylperhydrooxadiazines IVa, b.

The structures of the compounds obtained are confirmed by their physicochemical properties and the PMR spectroscopic data. One should note the considerable depression of the molecular refraction (—0.9) for both perhydrooxadiazines IV. A depression of the molecular refraction was also observed in the case of 3-unsubstituted perhydro-1,3,4-oxadiazines (for example, see [4]).



Ia, b

IIa, b

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*See [1] for communication IX.

†A paper [3] in which the synthesis of 2-(N,N'-dialkylhydrazino)ethanols, which were subsequently converted to the corresponding perhydrooxadiazines by this method, appeared while our paper was being prepared for publication.

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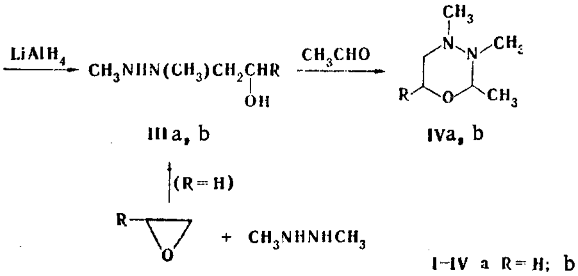


IIIa, b

IVa, b

I–IV a R = H; b R = CH_3

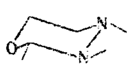
In the PMR spectrum of IVa the protons of the C-methyl group resonate at δ 1.01 ppm; this is characteristic for an equatorially oriented 2-CH_3 group. The methylene protons form an AMXY system, the analysis of the spectrum of which is difficult because of the strongly coupled XY portion (the 6-H protons). Two multiplets of the 5-H protons centered at 2.90 (with a width of 27 Hz) and 2.08 ppm (with a width of 17 Hz) are observed. A comparison of the width of the multiplets makes it possible to assume that the strong-field multiplet corresponds to an equatorial 5-H proton and that the weak-field multiplet corresponds to an axial 5-H proton. This assignment of the signals indicates inversion of the shifts of the 5-H_a and 5-H_e protons in 3-substituted perhydro-1,3,4-oxadiazines IV as compared with the unsubstituted compounds.

The position of the signals of the 2- and 6-CH_3 groups (1.09 and 1.03 ppm) in the PMR spectrum of IVb constitutes evidence for their diequatorial orientation, i.e., perhydrooxadiazine IVb has a cis configuration. The equatorial orientation of the 6-CH_3 group is also confirmed by the fact that the width of the multiplet signal of the 6-H proton (3.72 ppm) is 33 Hz, and the 6-H proton is consequently axially oriented. Because of overlapping of the signals of the protons of the N-methyl and N-methylene groups, analysis of the portion of the spectrum corresponding to the 5- and 6-H protons is impossible. However, the complete absence of signals at 2.7-3.5 ppm indicates a shift of the multiplet that is observed at 2.90 ppm in the case of perhydrooxadiazine IVa to the strong-field region. This shift, which is associated with the introduction of a vicinal equatorial 6-CH_3 group, is characteristic for the signal of precisely an axial 5-H proton rather than an equatorial 5-H proton [4].

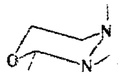
It should be noted that the PMR spectra of the dried reaction mixture obtained from hydrazino alcohol IIIb and acetaldehyde and of the perhydrooxadiazine isolated from this mixture as a result of distillation are virtually identical. This constitutes evidence for the formation of primarily, if not exclusively, cis isomer IVb during the condensation.

A quartet of the 2-H proton is found in the PMR spectra of both IVa and IVb in the same region as in the case of perhydrooxadiazines that are unsubstituted at the $N_{(3)}$ atom and have an equatorial orientation of the unshared electron pair of this nitrogen atom (for example, see [4]). It is known that a considerable difference in the chemical shifts of the 2-H proton, which is shifted ~1.5 ppm to strong field on passing from compounds with an equatorial orientation of this electron pair to compounds with an axial orientation of this pair [6], is observed for saturated derivatives of 1,3-oxazine with a rigidly fixed orientation of the unshared pair of the electrons of the nitrogen atom. In the opinion of Riddell and Lehn [6], the principal contribution to this difference is due to precisely the different orientations of the unshared pair. It would therefore seem that the data that we obtained make it possible to assert that perhydrooxadiazines IVa, b like 3-unsubstituted compounds, have an equatorially oriented unshared pair of electrons attached to the $N_{(3)}$ atom, i.e., the $N_{(3)}$—CH_3 group is axially oriented. Nevertheless, the closeness of the chemical shifts of the 2-H protons for both types of perhydrooxadiazines [with $N_{(3)}$—H and $N_{(3)}$—CH_3 fragments] at best can serve only as an indirect indication of the identical orientation of the unshared pair in these compounds, since, first, the position of the 2-H resonance signal is determined to a considerable extent also by the type and orientation of the other bonds in the molecule and, second, there are no available data for the model perhydrooxadiazines with an axial unshared pair attached to $N_{(3)}$.

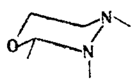
Assuming that of all of the possible conformers of trimethylperhydrooxadiazine IVa, only those that contain no more than one axial alkyl group make a substantial contribution to their equilibrium mixture and taking into account the spectrally proved equatorial orientation of the 2-CH_3 group, one may assume that the principal components of the equilibrium mixture are conformers V-VII (and their enantiomers):



V



VI



VII

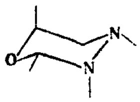
To estimate the relative stabilities of conformers V-VII we performed conformational calculations on the basis of a mechanical model [7] (atom–atom potentials of the "6–12" type [8], the spectroscopic deformation constants of the valence angles, and the monopole–monopole approximation for estimation of the electrostatic interactions were used) with allowance for the gauche effect in the hydrazine fragment [9, 10]. The preliminary results of the calculation show that the percentage of triequatorial conformation V in the equilibrium mixture of conformers should be negligibly small and that 3a,4e conformation VII is considerably (no less than 5 kJ/mole) more stable than 3e,4a conformation VI. The above-mentioned inversion of the chemical shifts of the 5-H_e and 5-H_a protons in 3-substituted perhydrooxadiazines as compared with the unsubstituted compounds is possibly explained precisely by the axial orientation of the 3-CH_3 group (similar deshielding of the 6-H_a proton by a syn-axial 2-CH_3 group has been noted [4]).

During a study of the temperature dependence of the PMR spectra of perhydrooxadiazine IVa, Ferguson and co-workers [3] also did not detect any other conformer than VII. However, the signal at 3.01 ppm [in $CDCl_3$—$CFCl_3$ (1:1)] was evidently erroneously assigned to both 5-H protons in their paper. According to our data, the intensity of the signal in this region corresponds to only one proton. As pointed out above, the signal of the second 5-H proton is found in the strong-field region of the spectrum. The correctness of this assignment is confirmed by the fact that both multiplets are converted to doublets with J_{5a5e} = —11 Hz in the case of decoupling with the 6-H protons.*

In precisely the same way, an error in the interpretation of the low-temperature spectrum of 3,4-dimethylperhydro-1,3,4-oxadiazine is also likely [3]. On the spectrogram presented in [3] it is apparent that the intensity of the multiplet at 3 ppm more likely corresponds to one proton rather than to two protons. The low-intensity signal at 2 ppm must then be related to the second 5-H proton of the same 3a,4e conformer rather than to the resonance of the N-methyl groups of the alternative 3e,4e conformer, as in the assignment of Ferguson and co-workers [3]. There therefore does not seem to be sufficient substantiation for the conclusion that two conformers of the latter compound exist [3].

In the case of the cis and trans isomers of tetramethylperhydrooxadiazine IVb, conformational calculations on the basis of a mechanical model predict the highest populations for the VIII and IX conformations, respectively; the concentration of the cis isomer in the equilibrium mixture with the trans isomer should be no less than 90%.

VIII



IX

EXPERIMENTAL†

The PMR spectra of 20% solutions of the compounds in CCl_4 were recorded with an HA-100D-15 spectrometer at 30-35°C with hexamethyldisiloxane as the internal standard.

4-Methylperhydro-1,3,4-oxadiazine (IIa). A mixture of 49.5 g (0.55 mole) of hydrazino alcohol Ia, 16.5 g (0.55 mole) of paraformaldehyde, and 100 ml of benzene was refluxed in a flask equipped with a Dean–Stark trap. The condensation product was isolated by distillation from the flask to give 25.7 g (41%) of a product with bp 56-59°C (34 mm) and n_D^{20} 1.4450. PMR spectrum, δ: 2.20 (s, 4-CH_3), 2.5 (m, 5-H), 3.7 (m, 6-H), and 4.38 ppm (s, 2-H). Measurements gave d_4^{20} 0.9663 and n_D^{20} 1.4466 after establishment of equilibrium with formaldehyde N-methyl-N-(2-hydroxyethyl)hydrazone. Found: N 27.2%. $C_4H_{10}N_2O$. Calculated: N 27.4%.

4,6-Dimethylperhydro-1,3,4-oxadiazine (IIb). This compound, with bp 61.5-64°C (36 mm), d_4^{20} 0.9685, and n_D^{20} 1.4489, was similarly obtained in 64% yield. PMR spectrum, δ: 0.97

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*Although it has been pointed out that the J_{gem} value in the spectra of saturated nitrogen heterocycles can be used for the determination of the orientation of the unshared pair of electrons of the adjacent nitrogen atom [11], correlations of this type seem doubtful in the light of a later study [12].

†With the participation of B. D. Zaitsev.

(d, 6-CH_3, J = 6.3 Hz); 2.34 (s, 4-CH_3); 1.80, 2.85, and 3.65 (m, 5-H_a, 5-H_e, and 6-H_a, respectively; J_{5a5e} = −11.0, J_{5a6a} = 9.7, and J_{5e6a} = 2.7 Hz); 4.30 and 4.38 ppm (AB system, 2-H, J_{2a2e} = −10.4 Hz). Found: N 23.8%; M 116; MR_D 32.10. $C_5H_{12}N_2O$. Calculated: N 24.1%; M 116; MR_D 32.87. In some experiments higher-boiling fractions enriched in the acyclic tautomer — formaldehyde N-methyl-N-(2-hydroxypropyl)hydrazone — were isolated along with the individual perhydrooxadiazine IVb during distillation of the reaction product. The refractive indexes of these fractions were substantially higher (up to 1.4670), and their PMR spectra indicated the presence of mainly the hydrazone, δ: 1.09 (d, CH_3–C, J = 6 Hz), 2.86 (s, CH_3–N), 3.06 (d, CH_2–N, J = 5 Hz), 4.00 (m, CH), and 6.00 and 6.12 ppm (AB system, CH_2=N, J = 11 Hz).

2-(N,N'-Dimethylhydrazino)ethanol (IIIa). A) A 0.18 g (0.41 mole) sample of ethylene oxide was added with stirring and ice cooling to a solution of 30 g (0.5 mole) of N,N'-dimethylhydrazine in 200 ml of water, and the mixture was maintained at room temperature for 24 h. The water was removed by vacuum distillation, and the residue was distilled with a column to give 25 g (58%) of hydrazino alcohol IIIa with bp 79.5-80°C (23 mm), d_4^{20} 0.9628, and n_D^{20} 1.4529. Found: N 26.7%. $C_4H_{12}N_2O$. Calculated: N 26.9%.

B) A solution of 20 g (0.20 mole) of perhydrooxadiazine IIa in 20 ml of ether was added to 140 ml of a solution of 0.15 mole of LAH in ether at such a rate that the ether boiled continuously, after which the mixture was refluxed with stirring for 27 h and decomposed by the addition of 20 ml of water. The ether solution was separated, and the precipitate was treated with ether in a Soxhlet extractor for 30 h. The combined ether extracts were dried with potassium carbonate and distilled to give 6.15 g (30%) of hydrazino alcohol IIIa with bp 66-68°C (11 mm) and n_D^{20} 1.4519 (bp 80°C (26 mm) [3]).

1-(N,N'-Dimethylhydrazino)-2-propanol (IIIb). This compound, with bp 70-73°C (20 mm), d_4^{20} 0.9173, and n_D^{20} 1.4390, was similarly obtained in 32% yield. Found: N 24.1%; MR_D 34.17. $C_5H_{14}N_2O$. Calculated: N 23.7%; MR_D 34.28.

2,3,4-Trimethylperhydro-1,3,4-oxadiazine (IVa). A 2.75 g (0.06 mole) sample of acetaldehyde was added with stirring and ice cooling in the course of 15 min to 6.15 g (0.06 mole) of hydrazino alcohol IIIa, after which the mixture was maintained at room temperature for 1.5 h. It was then dried with potassium carbonate and distilled to give 3.8 g (49%) of perhydrooxadiazine IVa with bp 43-45°C (9 mm), d_4^{20} 0.9689, and n_D^{20} 1.4527. PMR spectrum, δ: 1.01 (d, 2-CH_3, J = 6 Hz); 2.42 and 2.25 (s, 3- and 4-CH_3); 2.08 (m, 5-H_e); 2.90 (m, 5-H_a); 3.79 (m, 6-H_e and 6-H_a); 4.62 ppm (q, 2-H, J = 6 Hz). Found: N 21.5%; MR_D 36.30. $C_6H_{14}N_2O$. Calculated: N 21.5%; MR_D 37.22. According to the literature data, this compound has bp 81°C (15 mm) [3].

2,3,4,6-Tetramethylperhydro-1,3,4-oxadiazine (IVb). This compound, with bp 62-63°C (20 mm), d_4^{20} 0.9391, and n_D^{20} 1.4459, was similarly obtained in 62% yield. PMR spectrum, δ: 1.09 and 1.03 (d, 2- and 6-CH_3, J = 6 Hz); 2.39 and 2.16 (s, 3- and 4-CH_3); 2.01-2.67 (m, 5-H_e and 5-H_a); 3.72 (m, 6-H); 4.61 ppm (q, 2-H, J = 6 Hz). Found: N 19.6%; MR_D 40.94. $C_7H_{16}N_2O$. Calculated: N 19.4%; MR_D 41.87.

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