RING-CHAIN TAUTOMERISM OF SUBSTITUTED HYDRAZONES

III.* 2-(N-PROPYLHYDRAZINO)- AND 2-(-N-ISOPROPYLHYDRAZINO)-ETHANOL DERIVATIVES

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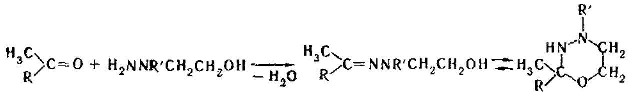
UDC 541.623:547.875

The freshly distilled products of the reaction of acetaldehyde with 2-(N-propylhydrazino)- and 2-(N-isopropylhydrazino)ethanols have substituted perhydro-1,3,4-oxadiazine structures and are isomerized to the corresponding N-alkyl-N-(2-hydroxyethyl)hydrazones via an equilibrium. Mixtures of both tautomeric forms were isolated by the reaction of these hydrazino alcohols with acetone and pinacolone.

It was established in [2] that 2-hydroxyethyl-substituted hydrazines condense with aliphatic carbonyl compounds to form tautomeric mixtures of the corresponding perhydro-1,3,4-oxadiazines and (2-hydroxyethyl)hydrazines. The position of the equilibrium in this system depends markedly on the structure of the starting hydrazine. The concentration of the cyclic tautomer decreases sharply on passing from derivatives of 2-hydrazinoethanol itself (only hydrazones were obtained in all cases) to its N-methyl- and N-ethyl-substituted derivatives. A similar situation was also observed in a number of (2-hydroxypropyl)-hydrazines [1].

In this connection, it seemed of interest to make a further study of the effect of the structure of the alkyl group in 2-(N-alkylhydrazino)ethanols on the position of the N-alkyl-N-(2-hydroxyethyl)hydrazone-perhydro-1,3,4-oxadiazine equilibrium. For this, we synthesized 2-(N-propylhydrazino)- (I) and 2-(N-isopropylhydrazino)ethanols (II) by the reaction of ethylene oxide with the appropriate alkylhydrazines. Hydrazino alcohols I and II were condensed with acetaldehyde and acetone, while II was also condensed with pinacolone, i.e., with those carbonyl compounds whose derivatives had markedly different equilibrium compositions in previously studied cases [1,2].

We found that the behavior of the reaction products was similar in many respects to the behavior of the derivatives of the closest homolog of I and II – 2-(N-ethylhydrazino)ethanol [2].



I, II   IIIB-VIIB   IIIA-VIIA

III $R=H$, $R'=n\text{-}C_3H_7$; IV $R=CH_3$, $R'=n\text{-}C_3H_7$; V $R=H$, $R'=i\text{-}C_3H_7$; VI $R=CH_3$, $R'=i\text{-}C_3H_7$; VII $R=t\text{-}C_4H_9$, $R'=i\text{-}C_3H_7$

The freshly distilled products of the condensation of hydrazino alcohols I and II with acetaldehyde were pure 4-alkyl-2-methylperhydro-1,3,4-oxadiazines (IIIA and VA), judging from their physicochemical properties and spectral characteristics. These compounds were converted to equilibrium mixtures of the cyclic (A) and chain (B) forms 10-12 h after distillation. The appearance of the hydrazone form was indicated by a certain increase in the molecular refraction and the development of a band of the vibrations of a C =N double bond in the IR spectrum (1650-1665 cm^{-1}). Signals of the chain tautomer, which were absent

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*See [1] for communication II.

A. A. Zhdanov Leningrad State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1167-1170, September, 1971. Original article submitted January 21, 1971.

in the spectra of the freshly distilled compounds, are observed in the PMR spectra of the equilibrium preparations. The quartet at weak field ($\tau \sim 3.5$ ppm), which corresponds to the resonance of the proton attached to the azomethine carbon atom, is particularly characteristic in this respect. The equilibrium concentration of the hydrazine, which was evaluated from the increase in the molecular refraction [2] and from the PMR spectra, was 12-13% for IIIB and 10-12% for VB.

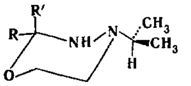
No single tautomer whatsoever could be isolated in any case in the condensation of I and II with ketones. The reaction of 2-(N-isopropylhydrazino)ethanol with pinacolone gave a substance whose physicochemical properties and IR spectrum corresponded to a greater degree to those of hydrazone VIIB than to those of cyclic form VIIa. The PMR spectrum, however, makes it possible to draw a completely definite conclusion regarding the presence of both tautomers: the intense singlet at 8.23 ppm corresponds to the methyl group attached to the C =N double bond in the N-isopropyl-N-(2-hydroxyethyl)hydrazone of pinacolone (VIIB), while the weak singlet at 8.65 ppm corresponds to the methyl group in the 2 position of 2-methyl-4-isopropyl-2-tert-butylperhydro-1,3,4-oxadiazine (VIIA). Just as for other pinacolone derivatives [1,2], the equilibrium position is shifted to favor the hydrazone. (The equilibrium concentration of VIIA is only about 10%.)

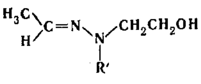
In contrast to the previously studied hydrazino alcohols [1,2], mixtures of tautomers with close to equilibrium compositions were obtained by the condensation of I and II with acetone in both cases immediately after distillation. This is confirmed by the refractometric and spectral characteristics of the freshly distilled preparations. Their IR spectra do not contain the band of the C =N stretching vibrations (1650-1670 cm^{-1}). Signals of both forms are also observed in the PMR spectra: two singlets from the isopropylidene grouping in the 2-position of the cyclic form (about 8.8 ppm). The changes in the density, refractive index, and, consequently, the molecular refraction were insignificant during storage of these preparations. According to the PMR spectra, the equilibrium concentration of the cyclic tautomer is 64% for IVA and 73% for VIA. The composition of a tautomeric mixture of IV could be estimated only approximately, since the signals of the isopropylidene fragment of both forms are partially overlapped by the multiplet of the β-methylene group of the N-propyl group. The impossibility of separating both forms for the ketone derivatives is apparently associated with their high rate of interconversion under the distillation conditions.

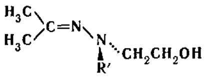
In [2] it was established that the products of the condensation of acetaldehyde and acetone with 2-(N-ethylhydrazino)ethanol contain 9-10% and 42-45% hydrazone, respectively, in equilibrium. Thus, whereas the equilibrium position is practically constant for the acetaldehyde derivatives on passing from 2-(N-ethylhydrazino)- to 2-(N-propylhydrazino)- and 2-(N-isopropylhydrazino)ethanol, it is shifted appreciably to favor the cyclic tautomer for the acetone derivatives in this series.

The introduction of a propyl or isopropyl group into the 4 position of the cyclic form (VIII) apparently does not lead to any substantial destabilization of it. As for the chain tautomer, overlap of the p and π orbitals of the nitrogen atom and of the C =N double bond (IX) can be retained in the disubstituted hydrazones of aldehydes, regardless of the structure of the N-alkyl radical. It is probable that these are the reasons that ethyl, propyl, and isopropyl groups in the aldehyde derivatives have about equivalent effects, and the equilibrium position in the N-alkyl-N-(2-hydroxyethyl)hydrazone-4-alkylperhydro-1,3,4-oxadiazine system is practically constant.

Unfavorable (as compared with aldehyde hydrazones IX), nonbonded interactions between the alkyl group attached to the azomethine carbon atom and the dialkylamino group develop in ketone hydrazones X [3,4]:


VIII


IX


X

These interactions can, first of all, lead to disruption of the p,π conjugation in the > C =N−N < system and, second, to a certain weakening of the intramolecular hydrogen bond between the hydroxyl group and the azomethine nitrogen atom. The role of the unfavorable factors apparently increases with the steric demands of the dialkylamino group, which entails a certain destabilization of the chain tautomer and an increase in the equilibrium concentration of the cyclic form for the ketone derivatives in this series.

The reasons for the increase in the equilibrium concentration of acetone hydrazones IVB and VIB as compared with the analogous acetaldehyde derivatives (IIIB and VB) were previously examined in [2].

EXPERIMENTAL

The PMR spectra were recorded with a YaMR 5535 spectrometer (40 MHz) at ~25° with hexamethyldisiloxane as the internal standard. The IR spectra of thin layers were recorded with a UR-10 spectrophotometer.

2-(N-Propylhydrazino)ethanol (I). Ethylene oxide [59 g (1.32 mole)] was bubbled into an ice-cooled mixture of 101 g (1.36 mole) of propylhydrazine and 10 ml of ethanol with vigorous stirring. The reaction mixture was allowed to stand for 12 h at room temperature and was then distilled with a column with 12 theoretical plates to give 24 g of starting propylhydrazine and 81 g (67% based on converted hydrazine) of alcohol I with bp 113-114° (32 mm), d_4^{20} 0.9557, n_D^{20} 1.4609, n_C^{20} 1.4583, Δ_{FC} 90.2, and ω_{FCD} 19.2. IR spectrum: 1608 cm^{-1} (NH_2 deformation vibrations), 3100-3470 cm^{-1} (OH and NH_2 stretching vibrations). Found %: N 23.3, 23.3; equiv. wt. 115, 119; MR_D 33.92. $C_5H_{14}N_2O$. Calculated %: N 23.6; equiv. wt. 118; MR_D 34.18.

2-(N-Isopropylhydrazino)ethanol (II). This was similarly obtained in 73% yield with bp 108-110° (25 mm), d_4^{20} 0.9587, n_D^{20} 1.4642, n_C^{20} 1.4616, Δ_{FC} 90.2, and ω_{FCD} 19.1. IR spectrum: 1604 cm^{-1} (NH_2 deformation vibrations), 3100-3400 cm^{-1} (OH and NH_2 strtching vibrations). Found %: N 23.3, 23.5; equiv. wt. 119, 119; MR_D 34.02. $C_5H_{14}N_2O$. Calculated %: N 23.6; equiv. wt. 118; MR_D 34.18.

2,2-Dimethyl-4-propylperhydro-1,3,4-oxadiazine (IVA) and Acetone N-Propyl-N-(2-hydroxyethyl)-hydrazone (IVB). Acetone [21 g (0.37 mole)] was added with shaking to 32 g (0.27 mole) of alcohol I. The reaction mixture was heated at 80° for 2.5 h, cooled, and potassium carbonate was added until layers formed. The organic layer was dried with potassium carbonate and vacuum distilled with a column to give 35 g (83%) of a mixture of IVA and IVB with bp 99° (50 mm), d_4^{20} 0.9180, n_D^{20} 1.4471, and MR_D 46.06. The refractive index increased and reached a constant value after 1 h. The physical constants of the equilibrium preparation were as follows: d_4^{20} 0.9180, n_D^{20} 1.4483, n_C^{20} 1.4458, Δ_{FC} 88.9, and ω_{FCD} 19.8. IR spectrum: 1653 cm^{-1} (C =N), 3300-3500 cm^{-1} (NH, OH). Signals from both IVA (8.77 singlet, 2-CH_3) and from IVB [8.12 singlet, 8.17 singlet, $(CH_3)_2C$ =N] could be identified in the PMR spectrum.* Found %: N 18.1, 17.7; mol. wt. 153, 157; MR_D 46.11. $C_8H_{18}N_2O$. Calculated %: N 17.7; mol. wt. 158; MR_D 46.35 (IVA), 47.12 (IVB).

2,2-Dimethyl-4-isopropylperhydro-1,3,4-oxadiazine (VIA) and Acetone N-Isopropyl-N-(2-hydroxyethyl)hydrazone (VIB). These were similarly obtained in 75% yield and had bp 73-74° (18 mm), d_4^{20} 0.9178, n_D^{20} 1.4446, n_C^{20} 1.4423, Δ_{FC} 84.4, and ω_{FCD} 19.0. IR spectrum: 1670 cm^{-1} (C =N), 3250-3500 cm^{-1} (NH, OH). The PMR spectrum contained a signal from both methyl groups in the 2-position of the cyclic form (VIA) (8.79 s) and two singlets (8.12 and 8.75) from the isopropylidene fragment of hydrazone VIB. Found %: N 17.9, 18.1; mol. wt. 157, 161; MR_D 45.86. $C_8H_{18}N_2O$. Calculated %: N 17.7; mol. wt. 158; MR_D 46.35 (VIA), 47.12 (VIB).

2-Methyl-4-propylperhydro-1,3,4-oxadiazine (IIIA). Freshly distilled acetaldehyde [11 g (0.27 mole)] was added with ice cooling and stirring to 29.5 g (0.25 mole) of alcohol I. The reaction mixture was stirred at room temperature for 1 h and at 50° for 1 h, and worked up as described above for the acetone derivatives to give 20 g (59%) of IIIA with bp 68-69° (16 mm), d_4^{20} 0.9306, n_D^{20} 1.4464, n_C^{20} 1.4444, Δ_{FC} 86.5, ω_{FCD} 19.4, and MR_D 41.37. The equilibrium preparation had the following physical constants (after 10-12 h): d_4^{20} 0.9314, n_D^{20} 1.4487, n_C^{20} 1.4462, Δ_{FC} 88.8, and ω_{FCD} 19.7. A weak band from hydrazone IIIB appeared at 1657 cm^{-1} (C =N) in the IR spectrum of the equilibrium preparation. PMR spectrum: 9.18 t (J 6.5 Hz, CH_3 propyl group), 8.90 d (J 5 Hz, 2-CH_3 in IIIA), 5.82 q (J 5 Hz, 2-H in IIIA), 8.27 d (J 4.5 Hz, CH_3C= N), 3.52 q (J 4.5 Hz, CH =N). Found: N 19.0, 19.4; mol. wt. 141, 146; MR_D 41.51. $C_7H_{16}N_{20}$. Calculated: N 19.4%; mol. wt. 144; MR_D 41.70 (IIIA), 42.41 (IIIB).

2-Methyl-4-isopropylperhydro-1,3,4-oxadiazine (VA). This was similarly obtained in 63% yield with bp 85° (48 mm), d_4^{20} 0.9367, n_D^{20} 1.4478, n_C^{20} 1.4454, Δ_{FC} 86.0, and ω_{FCD} 19.2. The equilibrium preparation had the following physical constants: d_4^{20} 0.9372, n_D^{20} 1.4501, n_C^{20} 1.4475, Δ_{FC} 86.0, and ω_{FCD} 19.7. A weak band at 1652 cm^{-1} (C =N in VB) appears in the IR spectrum. PMR spectrum: 9.03 d (J 7 Hz, CH_3 of the isopropyl group), 8.90 d (J 5 Hz, 2-CH_3 in VA), 5.82 q (J 5 Hz, 2-H in VA), 8.27 d (J 4.5 Hz, CH_3C =N), 3.46 q (J 4.5 Hz, CH =N). Found %: N 19.0, 19.1; mol. wt. 141, 143; MR_D 41.36. $C_7H_{16}N_2O$. Calculated %: N 19.4; mol. wt. 144; MR_D 41.70 (VA); 42.41 (VB).

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*Here and elsewhere, the chemical shifts are presented in parts per million on the τ scale. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Pinacolone N-Isopropyl-N-(2-hydroxyethyl)hydrazone (VIIB) and 2-Methyl-4-isopropyl-2-tert-butylperhydro-1,3,4-oxadiazine (VIIA). A mixture of 27.5 g (0.23 mole) of alcohol II, 30 g (0.30 mole) of pinacolone, and 100 ml of benzene was refluxed in a flask equipped with a Dean – Stark trap until azeotropic removal of water ceased. The reaction product was isolated by column fractionation to give 30 g (64%) of a product with bp 114° (16 mm), d_4^{20} 0.8921, n_D^{20} 1.4529, n_C^{20} 1.4503, Δ_{FC} 91.6, and ω_{FCD} 20.2. IR spectrum: 1663 cm^{-1} (strong, $\nu_{C=N}$), 3250-3500 cm^{-1} (strong, ν_{OH} and ν_{NH}). PMR spectrum: 9.00 d[J 7 Hz, $(CH_3)_2C$], 8.91 s [$(CH_3)_3C$], 8.23 s ($CH_3C=N$), 7.2-7.5 m ($CH-N$ and CH_2-N), 6.79 t (J 5 Hz, CH_2-O), 8.65 s (2-CH_3 in VIIA). Found %: N 13.7, 13.8; mol. wt. 198, 202; MR_D 60.69. $C_{11}H_{24}N_2O$. Calculated %: N 14.0; mol. wt. 200; MR_D 61.01 (VIIB); 60.30 (VIIA).

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