PMR SPECTRA AND DYNAMIC STEREOCHEMISTRY OF PERHYDRO-1,3,4-THIADIAZINES

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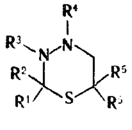
By means of dynamic PMR spectroscopy we have determined the barriers to ring conversion of alkyl-substituted perhydro-1,3,4-thiadiazines I-IV, the first representatives of which were only recently described [1-3].



I-VI

I $R^1=R^2=Me$, $R^3=R^5=H$, $R^4=i\text{-Pr}$; II $R^1=R^2=R^3=R^5=H$, $R^4=i\text{-Pr}$; III $R^1=R^2=Me$, $R^3=R^4=R^5=H$; IV $R^1=R^2=R^5=Me$, $R^3=H$, $R^4=n\text{-Pr}$; V $R^1=R^5=Me$, $R^2=R^3=H$, $R^4=n\text{-Pr}$; VI $R^1=R^2=R^5=H$, $R^3=R^4=Me$

Compounds I and III were previously synthesized [1, 2]. 4-Isopropylperhydro-1,3,4-thiadiazine (II) was obtained by refluxing 2-(1-isopropylhydrazino)ethanethiol with paraformaldehyde in benzene; the product was obtained in 53% yield and had bp 70-71°C (9 mm) and n_D^{20} 1.5123. 2,2,6,6-Tetramethyl derivative IV, with bp 83-86°C (8 mm) and n_D^{20} 1.4828, was prepared in 73% yield from 2-methyl-1-(1-propylhydrazino)-2-propanethiol and acetone as in [1]. The starting hydrazino thiol was synthesized in 67% yield from propylhydrazine and 2,2-dimethylthiirane and had bp 95-96°C (14 mm) and n_D^{20} 1.4766.

The PMR spectra of I-IV (obtained from 1 mole/liter solutions in $CDCl_3$ with a Varian HA-100D-15 spectrometer with hexamethyldisiloxane as the internal standard) at 30°C indicate rapid (on the PMR time scale) conformational transformations that lead to averaging of the signals of geminal $2\text{-}CH_3$ ($\delta \sim 1.5$ ppm for I, III, and IV) and $6\text{-}CH_3$ (1.35 ppm for IV) groups, and the 2-H (4.26 ppm for II) and 5-H (2.31 ppm for IV) methylene protons.

A decrease in the temperature to −60°C leads to a decrease in the rate of ring conversion, and signals of the above-indicated CH_3 groups and protons that correspond to their axial and equatorial orientation are observed in the spectra. Thus in the spectrum of perhydrothiadiazine II the 2- and 3-H protons form an ABX system (2-H_a 4.46, 2-H_e 4.07, 3-H 2.47 ppm, $J_{2a2e} = -12.5$, $J_{2a3a} = 12.5$, $J_{2e3a} \leq 3$ Hz; the latter constant could not be determined accurately because of broadening of the 2-H_e signal as a consequence of long-range coupling, probably with 6-H_e). It follows from the ratio of the vicinal spin–spin coupling constants (SSCC) that II exists in the chair conformation with a primarily axially-oriented proton attached to the nitrogen atom. The signal of the 3-H proton vanishes in the spectrum of a solution in CD_3OD, and the spectrum of the methylene protons attached to $C_{(2)}$ is simplified to an AB quartet.

The fact that tetramethyl derivative IV also probably exists in the chair conformation, despite the syn–axial interaction between the methyl groups in this conformation, was also unexpected. In any case, its spectral characteristics [at −60°C δ 1.65 (s, $2a$-Me), 1.38 (s, 2e-Me), 1.51 (s, $6a$-Me), 1.16 (s, 6e-Me), and 1.91 and 2.80 ppm (d, J = −12.0 Hz, 5-H_e and 5-H_a)] are extremely similar to the parameters of the spectra of I and III and trimethyl derivative V. The latter, with bp 104-105°C (25 mm) and n_D^{20} 1.4854, was prepared in 48% yield by the method used to obtain perhydrothiadiazine IV. PMR spectrum (CCl_4, +30°C), δ: 1.14 (s, 6e-Me), 1.43 (s, $6a$-Me), 1.25 (d, 2e-Me), 4.29 (m, $J_{H,Me} = 6.5$, $J_{2a3a} = 11.8$ Hz), and 1.80 and 2.62 ppm (d, J = −11.9 Hz, 5-H_e and 5-H_a).

The barriers to conversion of I-IV found from the coalescence temperature turned out to be quite high and very close: $\Delta G^{\neq}_{254K} = 12.5$ kcal/mole for I, $\Delta G^{\neq}_{252K} = 12.0$ (11.8 in

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CD_3OD) for II, $\Delta G^{\neq}_{253K}$ = 12.3 for III, and $\Delta G^{\neq}_{257K}$ = 11.9 (±0.5) kcal/mole for IV. The same value of the barrier to conversion (12.7 kcal/mole) was recently found also for 3,4-dimethyl derivative VI [3]. Thus the presence of substituents at both the nitrogen and carbon atoms does not have a substantial effect on the barrier to ring conversion.

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REACTION OF THIIRANES WITH HYDRAZONES

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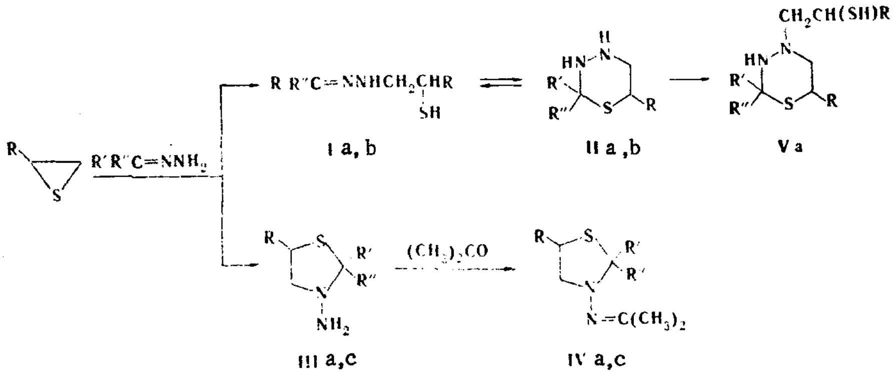
We have found that the reaction of thiiranes with unsubstituted hydrazones (with a fourfold excess of the hydrazone in benzene at 60°C) leads to (2-mercaptoalkyl)hydrazones I, which undergo reversible cyclization to perhydro-1,3-thiadiazines II or to thiazolidine derivatives III.

The synthesis of II from aldehydes or ketones and the corresponding heretofore unknown hydrazino thiols seems more convenient; however attempts to obtain the latter by mercaptoalkylation of hydrazine were unsuccessful because of polymerization of the thiiranes.



I—V a R=H, R′=R″=Me; Ib IIb R=R′=R″=Me; IIIc IVc R=R′=H, R″=*i*-Pr

The formation of I ⇌ II (in 30-40% yields) is complicated by side and secondary processes. Thus distillation of the products of the reaction of acetone hydrazone with thiirane yielded, in addition to perhydrothiadiazine IIa [bp 77-78°C (8 mm) and n_D^{20} 1.5190], 2-hydrazinoethanethiol (8%), with mp 63-64°C (from CCl_4), which is converted to IIa by the action of acetone. The hydrazino thiol is formed simultaneously with acetone azine, evidently as a result of an exchange reaction of hydrazone Ia with the starting hydrazone. The principal reaction product (Ia ⇌ IIa) contained only ~10% of the impurity, to which the singlet at 1.50 ppm (CCl_4) in the PMR spectrum corresponded. The assumption that the impurity has aminothiazolidine structure IIIa that was made on the basis of this is confirmed by the formation of isopropylidene derivative IVa on treatment with acetone; the structure of the latter is in agreement with the mass-spectrometric data and with the presence in the PMR spectrum (CCl_4) of singlet signals of CH_3 groups at 1.42, 1.92, and 1.99 ppm. An adduct involving one molecule of hydrazone and two molecules of thiirane, with bp 124-127°C (11 mm) and n_D^{20} 1.5440, was isolated in 9% yield from the same reaction mixture. The signlet signal of both CH_3 groups observed in the PMR spectrum of the adduct at 30°C (1.50 ppm, $CDCl_3$) is converted below −14°C to two singlets (1.39 and 1.65 ppm), which indicates the relatively high barrier to ring conversion and is more likely in agreement with a six-membered structure (Va) rather than a five-membered structure.

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