1,4,5-Thiadiazepines. I. NMR Investigation of Stereoisomerism and Ring Inversion in Some 2,7-Dihydro-1,4,5-Thiadiazepine Derivatives.

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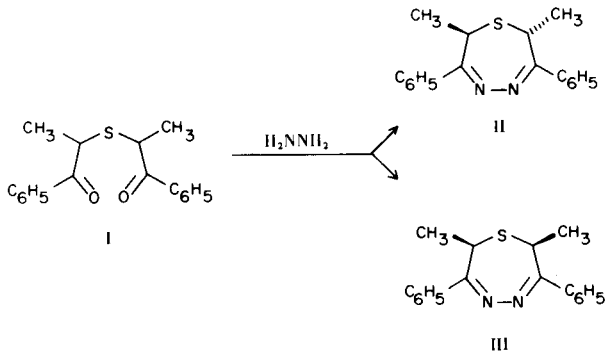
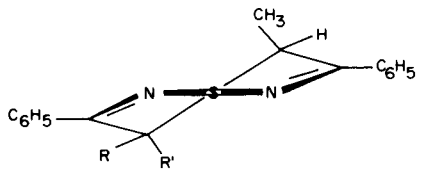
The condensation of 2,2′-thiobispropiophenone (I) with hydrazine in boiling ethanol has been reported in an earlier paper (2) to give 2,7-dihydro-2,7-dimethyl-3,6-diphenyl-1,4,5-thiadiazepine, m.p. 183° (II). The available data were not conclusive evidence for the establishment of the relative configuration, *i.e. cis* or *trans*, of the methyl substituents. Reinvestigation of this reaction has led now to isolation of an isomeric 1,4,5-thiadiazepine derivative, m.p. 123° (III). An examination of the nmr spectra reveals that the methyl groups have a *trans* configuration in the higher-melting isomer and a *cis* configuration in the lower-melting isomer.



Measured in deuteriochloroform, the nmr spectrum of II showed a multiplet at δ 7.36-7.82 (C_6H_5), a quartet at 3.98 (J = 7.3 Hz, CH), and a doublet at 1.30 (J = 7.3 Hz, CH_3) in the ratio of 5:1:3. The nmr spectrum of III showed a multiplet at δ 7.35-8.01 (C_6H_5), a quartet at 4.26 (J = 7.3 Hz, CH), a quartet at 4.03 (J = 7.5 Hz, CH), a doublet at 1.72 (J = 7.5 Hz, CH_3), and a doublet at 1.17 (J = 7.3 Hz, CH_3) in the ratio of 10:1:1:3:3. The chemical shift nonequivalence of the two methine as well as the two methyl groups in III undoubtedly results from occupation of diastereomeric positions on the seven-membered ring. Molecular models indicate that this ring, like the comparable ring of 5,7-dihydrodibenzo[*c,e*]thiepin (3-5), possesses a skew-boat conformation in which equivalent positions are *trans* and nonequivalent positions are *cis* to each other. Compound III is therefore the *cis* or *meso* isomer, and its diastereotopic methine and methyl groups are shown in conformation III′. A model also suggests that the isochronous methyl groups in the *trans* or *dl* isomer (II) experience less steric interference when they are oriented away from the phenyl groups, as shown in conformation II′. The methyl group which appears at a lower field in the spectrum of III has the alternative orientation (R in III′), and is probably affected by the deshielding zone of the adjacent phenyl group.



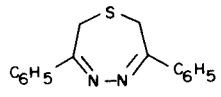
II′, R = H, R′ = CH_3
III′, R = CH_3, R′ = H

The chemical shift nonequivalence observed in III requires ring inversion to be slow on the nmr time scale. Such inversion converts conformation III′ into its enantiomeric form and exchanges the environments of the diastereotopic groups. Under conditions of rapid inversion, the methyl as well as the methine groups will have averaged environments, and therefore become equivalent with respect to the time scale of the measurement. Indeed, the nmr signals of III in nitrobenzene solution (quartets at δ 4.22 and 4.08, doublets at 1.76 and 1.14) broaden as the temperature is raised, and the methyl doublets coalesce to a single broad line at about 148° (11). This coalescence temperature (Tc) is considerably higher than the values reported for other seven-membered ring systems in various solvents (4-10). Using the relationship (4,7,12) $k = \pi(\Delta\nu^2 + 6J_{AB}^2)\,2^{-1/2}$, where $\Delta\nu$ is the chemical shift difference (in Hz) between the anisochronous protons at room temperature (13) and J_{AB} is the coupling constant (J_{AB} = 0 for the methyl groups), the rate of interconversion at the coalescence temperature is found to be 82.6 sec^{-1}. From the transformed Eyring equation (10) $\Delta G^{\ddagger} = 4.57\ Tc\ (10.32 + \log Tc - \log k)$, the free energy barrier to inversion is calculated to be 21.2 ± 0.2 kcal./mole. To our knowledge, this is the largest energy barrier to interconversion between two equivalent confor-

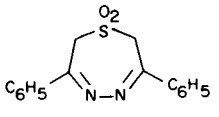
mations ever reported for a monocyclic ring system, and it indicates that the transition state of the inversion, in which all the atoms comprising the ring except sulfur are coplanar, is very strained.

The 2,7-dihydro-1,4,5-thiadiazepine ring possesses considerable rigidity even in the absence of the methyl substituents adjacent to the sulfur atom. The nmr spectrum of 2,7-dihydro-3,6-diphenyl-1,4,5-thiadiazepine (IV) in nitrobenzene solution exhibited an AB quartet centered at δ 3.51 ($\Delta\nu_{AB}$ = 10.8 Hz (13); J_{AB} = 12.8 Hz) due to anisochronous methylene protons. The quartet collapsed to a single broad line at 97°, and this line sharpened as the temperature was raised further. Applying the above equations one obtains k = 73.6 sec^{-1} and $\Delta G^{\ddagger}$ = 18.6 ± 0.2 kcal./mole. The higher barrier to inversion (by *ca.* 2.6 kcal./mole) which is observed for III does not fully reflect the inhibitive effect of the two methyl groups, since these substituents would raise also the ground-state energy of the molecule.

Oxidation of IV to the corresponding sulfone (V) increased the rigidity of the thiadiazepine ring, in agreement with the increase reported for 5,7-dihydrodibenz-[*c*,*e*]thiepine (5). The nmr spectrum of V in nitrobenzene showed an apparent AB pattern centered at δ 4.60 ($\Delta\nu_{AB}$ = 19.9 Hz (13); J_{AB} = 14.3 Hz). The study of temperature dependence was complicated by rapid conversion of V to 3,6-diphenylpyridazine (14) and required frequent replacement of the nmr sample. Coalescence to a broad singlet was observed at about 142°, and similar calculations gave k = 89.5 sec^{-1} and $\Delta G^{\ddagger}$ = 20.8 ± 0.3 kcal./mole.



IV



V

Isomers II and III do not equilibrate under the conditions of their preparation reaction, as demonstrated by their recovery after being subjected separately to a similar treatment.

EXPERIMENTAL

Nmr spectra were recorded on a Varian A-60 spectrometer using a sweep width of 500 or 100 Hz and with TMS as an internal standard. Infrared spectra were measured with a Perkin-Elmer Model 337 spectrophotometer. Melting points are uncorrected.

trans- (II) and *cis*-2,7-Dihydro-2,7-dimethyl-3,6-diphenyl-1,4,5-thiadiazepine (III).

A solution of 15 g. (0.05 mole) of I (15) in 250 ml. of ethanol and 25 ml. of acetic acid was treated with 3.5 g. (0.07 mole) of hydrazine monohydrate, and then heated under reflux for two hours. The solvent was evaporated under reduced pressure, ethanol was added, and the separated solid was collected by filtration and dried, yielding 7.8 g. (53%) of a mixture of the two isomers (63% II and 37% III by nmr). Compound II was purified by repeated recrystallizations from ethanol, and finally by half hour reflux in ethylene glycol to remove traces of III (16). It separated from the latter solvent as colorless needles, m.p. 181-183° (lit. (2) 182-183°). Cooling of the initial filtrate afforded 0.9 g. of III, which was recrystallized from ethanol as colorless prisms, m.p. 122.5-123°. The infrared spectrum of III (in carbon tetrachloride) showed absorption bands at 3064, 2970, 2930, 1491, 1453, 1442, 1376, 1348, 1323, 1313, 1303, 1212, 1011 (vs), 969, 915, 693 (vs), and 557 cm^{-1}. The spectrum of isomer II did not contain the bands at 1348 and 1323 cm^{-1}, but showed greater intensity at 1313 and 1303 cm^{-1}. The mass spectral behavior of the two isomers was very similar, with only minor differences in intensities. Abundant fragments appeared at m/e 163, 149, 131, 130, 117 (base peak), 116, 115, 105, 104, 103, 91, and 77.

Anal. Calcd. for $C_{18}H_{18}N_2S$: C, 73.42; H, 6.16. Found for isomer III: C, 73.22; H, 6.45.

2,7-Dihydro-3,6-diphenyl-1,4,5-thiadiazepine (IV).

This compound was prepared from phenacyl sulfide and hydrazine according to a previously described procedure (2). The infrared spectrum (in Nujol mull) showed major bands at 1554, 1493, 1376, 1324, 1313, 1150, 1016, 918, 778, 741, 698, and 688 cm^{-1}. The mass spectrum showed abundant fragments at m/e 163, 135, 117, 103, 91, and 77 (base peak).

REFERENCES

(1) Present address: Department of Chemistry, Southern Illinois University, Carbondale, Illinois 62901.

(2) C. R. Johnson and I. Sataty, *J. Med. Chem.*, **10**, 501 (1967).

(3) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, **86**, 1710 (1964).

(4) R. J. Kurland, M. B. Rubin and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964).

(5) I. O. Sutherland and M. V. J. Ramsay, *Tetrahedron*, **21**, 3401 (1965).

(6) A. Mannschreck, G. Rissmann, F. Voegtle and D. Wild, *Chem. Ber.*, **100**, 335 (1967).

(7) M. Oki, H. Iwamura and N. Hayakawa, *Bull. Chem. Soc. Japan*, **37**, 1865 (1964).

(8) M. Oki, H. Iwamura and T. Nishida, *ibid.*, **41**, 656 (1968).

(9) H. Friebolin and S. Kabuss, in "Nuclear Magnetic Resonance in Chemistry," B. Pesce, Ed., Academic Press, New York, 1965, p. 125.

(10) P. Linscheid and J. -M. Lehn, *Bull. Soc. Chim. France*, 992 (1967).

(11) Close proximity and extensive broadening of the methine quartets do not permit the determination of their coalescence temperature.

(12) S. Alexander, *J. Chem. Phys.*, **37**, 967 (1962).

(13) The magnitude of $\Delta\nu$ is solvent-dependent. For example, a solution of III in benzene-d_6 gave $\Delta\nu$ = 41.5 Hz, while in acetone-d_6 the value was 33 Hz. The nmr spectrum of IV in acetone-d_6 showed a sharp singlet (δ 3.57) at room temperature.

(14) J. D. Loudon and L. B. Young, *J. Chem. Soc.*, 5496 (1963).

(15) A mixture of *meso* and *dl* diastereomers. See D. Sica, C. Santacroce and R. A. Nicolaus, *Gazz. Chim. Ital.*, **98**, 17 (1968).

(16) Both II and III are converted to 4,5-dimethyl-3,6-diphenylpyridazine in boiling ethylene glycol, but the extrusion of sulfur from the *cis* isomer is appreciably faster. It is not as fast, however, as the extrusion of sulfur from IV to give 3,6-diphenylpyridazine. I. Sataty, to be published.

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