

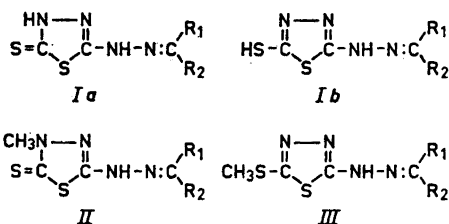
Tautomeric Cyclic Thiones

I. "Mercapto-thiadiazolyl-hydrazones"

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Stollé and Fehrenbach¹ have prepared a compound, which they isolated as hydrochloride and benzylidene derivative and described as 2-mercapto-5-hydrazino-1,3,4-thiadiazole. Sandström^{2,3} has prepared compounds described as acetone and cyclohexanone mercapto-thiadiazolylhydrazones. The mercapto-thiadiazolylhydrazones can exist in the tautomeric forms (Ia) and (Ib). In recent years the tautomerism of cyclic thionamides has been the subject of several investigations, and in most cases (e.g. Refs.^{4,5}) the thione form has been found to preponderate. However, in some bifunctional thiadiazole derivatives^{6,7} the thiol form is found to dominate, and therefore it was considered worthwhile to investigate the tautomeric structure of the so called mercapto-thiadiazolylhydrazones. Because of the strongly chromophoric properties of the thione group, the form (Ia) can be expected to absorb light at longer wavelengths than (Ib).



Since the exchange of the mobile hydrogen atom for a methyl group does not greatly affect the π electron system, a comparison of the spectrum of the parent compound with those of the N- and S-methyl derivatives (II) and (III) might allow a qualitative estimation of the position of the tautomeric equilibrium. Since suitably substituted derivatives were available, the cyclohexanone mercapto-thiadiazolylhydrazone

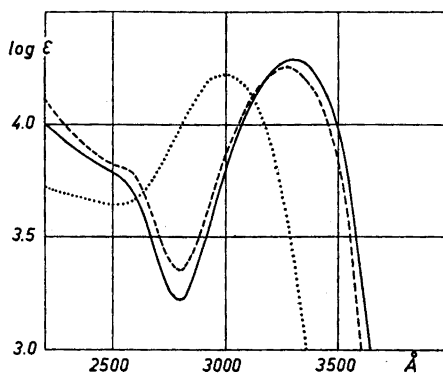


Fig. 1.

- Cyclohexanone 1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (I)
 - - - Cyclohexanone 4-methyl-1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (II)
 Cyclohexanone 5-methylthio-1,3,4-thiadiazol-2-yl-hydrazone (III).

(I, $R_1R_2 = (\text{CH}_3)_2$) was chosen for investigation. The parent compound (I) was prepared according to Ref.³, and when it reacted with diazomethane, a mixture of (II) and (III) was obtained. The S-methyl derivative (III) was prepared in an unambiguous way by reaction between methylthio-thiadiazolylhydrazine² and cyclohexanone. The UV spectra of (I–III) were recorded in absolute ethanol solution (Fig. 1) and the close similarity of the spectra of (I) and (II) shows that (I) is predominantly in the thione form (Ia) in absolute ethanol. It should therefore be called cyclohexanone 1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone. The possibility of an amidine type of tautomerism in (I–III) will be discussed in a forthcoming publication.

Experimental. Cyclohexanone methylthio-thiadiazolylhydrazone (III). Methylthio-thiadiazolylhydrazine² (0.36 g) was dissolved in hot water (10 ml), and cyclohexanone (0.2 g) in ethanol (5 ml) was added. A precipitate of yellow rods was formed, which crystallized from toluene-heptane as pale yellow rods, m.p. 176–176.5°. (Found: C 44.7; H 5.82; N 23.0; S 26.5. $\text{C}_6\text{H}_{14}\text{N}_4\text{S}_2$ (242.35) requires C 44.6; H 5.82; N 23.1; S 26.5).

Cyclohexanone 4-methyl-1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (II). Cyclohexanone 1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (I, $R_1R_2 = (CH_3)_2$, 2.3 g) was added to a solution of diazomethane (0.45 g) in ether (15 ml). A slow evolution of gas ensued, and on the following day the undissolved material (1.4 g) was removed by filtration. It crystallized from a mixture of toluene and heptane as pale yellow rods, m.p. 176–176.5°, not depressed on admixture with the cyclohexanone methylthio-thiadiazolylhydrazone (III) described above.

The ether solution was examined by chromatography on paper, impregnated with dimethyl sulphoxide according to Wickberg⁸. Three spots were located by photographing the paper in UV light, one with R_F ca. 0.33, one with R_F ca. 0.45, corresponding to (III), and one with R_F ca. 1. The solution was evaporated to dryness, and the residue was dissolved in benzene and subjected to chromatography on alumina. Benzene eluted first an orange solid (0.04 g), corresponding to the spot with R_F 1, which was not further investigated. Then a second fraction appeared as a pale yellow solid (0.22 g) with R_F 0.33, which crystallized from benzene-heptane as pale yellow needles, m.p. 182–183°, of cyclohexanone 4-methyl-1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (II). (Found: C 44.6; H 5.65; N 23.0; S 26.4. $C_9H_{14}N_4S_2$ (242.35) requires C 44.6; H 5.82; N 23.1; S 26.5).

Finally ether eluted a third fraction as a pale yellow solid (0.23 g), which crystallized from toluene-heptane as pale yellow rods, m.p. 176–176.5°, not depressed by admixture with (III).

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Resolution of α -*n*-Propylamino-2-methylpropioanilide and the Absolute Configuration of its Stereoisomers

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During recent years, much attention has been drawn to the influence of stereoisomerism on biological activity^{1,2}. It is generally held that local anesthetics, as well as narcotics, act by pure physical-chemical influence on nervous structures, and that chemical binding to specific "receptors" is of minor importance. The differences in anesthetic activity observed earlier in stereoisomers of compounds containing ester linkages and acting as local anesthetics have been interpreted by Schaumann¹ to be due to the contact of the substances with esterases which break down the different stereoisomers of the anesthetic at different rates.

As the surface of the membrane of the nerve cell consists of a protein network, it is of interest to study the effect of stereoisomers of anesthetics containing peptide linkages. Af Ekenstam *et al.*³ studied the toxicity and the anesthetic effect in wheal tests of the isomers of *N*-methylpipercolinoyl-2,6-xylidine but no statistic differences could be established. However, Kudrjashova *et al.*⁴ and Motovilov⁵ report the observation of different anesthetic effects produced by the different stereoisomers of three diethylaminopropioanilides.

The observation of different activity of stereoisomers of compounds acting as local anesthetics may not only be due to differences in "intrinsic anesthetic potency" or in the speed of enzymatic breakdown but may also depend on side effects such as vasomotor activity.

In view of these facts, it is interesting to study the behaviour of the stereoisomers of a local anesthetic in different pharmacological tests.

The present paper describes the resolution of α -*n*-propylamino-2-methylpropioanilide⁶ with the aid of *D*- and *L*-di-*p*-toluoyltartaric acid. By reductive alkylation of *L*-alanine with *n*-propanal and subsequent reaction of the *L*-*n*-propyl-