Cyclo*hexanone 4-methyl-1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (II)*.*Cyclo*hexanone 1,3,4-thiadiazol-5(4)-thion-2-yl-hydrazone (I, R_1R_2= $(CH_2)_5$, 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 *cyclo*hexanone methylthio-thiadiazolylhydrazone (III) described above.

The ether solution was examined by chromatography on paper, impregnated with dimethyl sulphoxide according to Wickberg [8]. 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 cyclo*hexanone 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 Schaumann [1] 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-methylpipecolinoyl-2,6-xylidine but no statistic differences could be established. However, Kudrjashowa *et al.*[4] and Motovilov [5] 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-methylpropioanilide [6] 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-

aminopropionic acid with *o*-tolylphosphazo-*o*-toluidide the absolute configuration of the isomers was shown to be L-(+)- and D-(−)-*α*-*n*-propylamino-2-methylpropioanilide, respectively.

The results of the pharmacological investigations of the isomers will be published elsewhere.

The D- and L-di-*p*-toluoyltartaric acids used were prepared and purified as described by Stoll and Hofmann [7].

(−)-α-n-Propylamino-2-methylpropioanilide hydrochloride — I. To a hot solution of 0.15 mole (62 g) of D-di-*p*-toluoyltartaric acid in 180 ml of 95 % ethanol was added 0.15 mole (33 g) of *α*-*n*-propylamino-2-methylpropioanilide [6] dissolved in 100 ml of hot 95 % ethanol. On cooling, first to room temperature and then in a refrigerator, crystals separated. After three recrystallisations from ethanol a constant rotation was obtained. The tartrate thus obtained was dissolved in water, the base liberated by the addition of 1 N sodium hydroxide, extracted with ether and the ethereal solution dried over sodium sulphate. The hydrochloride was then precipitated by the addition of ethereal hydrogen chloride. On recrystallisation from ethanol colourless crystals were obtained, m.p. 192−194°; $[\alpha]_D = -13.8° \pm 0.1°$ ($c = 1.0$ in glac. acetic acid). Yield 10.2 g (53 %).

(+)-α-n-Propylamino-2-methylpropioanilide hydrochloride — II. The mother liquids from the crystallisations of compound I were combined, the solvent evaporated to dryness and the residue dissolved in water. The base was liberated by the addition of 1 N sodium hydroxide and then taken up in ether. After drying the solution over sodium sulphate and evaporating the ether, 0.084 mole (18.4 g) of *α*-*n*-propylamino-2-methylpropioanilide was obtained. It was dissolved in 100 ml of hot ethanol (95 %) and was added to a hot solution of 0.084 mole (34.8 g) of L-di-*p*-toluoyltartaric acid in 180 ml of 95 % ethanol. On cooling, crystals separated, which were recrystallised and treated as described above for compound I. The hydrochloride had a melting point of 192−194°; $[\alpha]_D = +13.8° \pm 0.1°$ ($c = 1.0$ in glac. acetic acid). Yield 9.5 g (50 %). The mixed melting point of equal quantities of compounds I and II melted at 167−169° in agreement with that of the racemate [6].

L-(+)-α-n-Propylaminopropionic acid — III. L-*α*-Propylaminopropionic acid was obtained by reductive alkylation of L-alanine with *n*-propanal using the method described by Bowman [8] for the preparation of the corresponding N-butyl derivative. M.p. 290° (decomp.) from aqueous acetone; $[\alpha]_D = +6.9°$ ($c = 1.0$ in water). Yield 34 % (Found: N 10.7. Calc. for $C_6H_{13}NO_2$ (131.2): N 10.7).

L-(+)-α-n-Propylamino-2-methylpropioanilide hydrochloride — IV. *o*-Tolylphosphazo-*o*-toluidide was prepared as described by Grimmel *et al.*[9] for the preparation of the corresponding *para* derivative. The product obtained contained 77 % of phosphazo compound and was used in the next step without further purification.

A mixture of 0.007 mole(2.2 g) of the phosphazo compound and 0.014 mole (2.3 g) of the hydrochloride of compound III was heated to 130−140° for 1 h. The reaction mixture was dissolved in water and the pH of the solution was adjusted to 5.9. The mixture was extracted with ether to remove *o*-toluidine. The aqueous layer was then made strongly alkaline with sodium hydroxide and the toluidide was extracted with ether. The ethereal solution was dried over sodium sulphate and the hydrochloride of the toluidide was precipitated by the addition of ethereal hydrogen chloride. On recrystallisation twice from ethanol-isopropyl ether colourless crystals were obtained. M.p. 191−193°; $[\alpha]_D = +13.1°$ ($c = 1.0$ in glac. acetic acid). Yield 0.8 g (22 %).

The mixed melting point of compound IV and II showed no depression whereas that of compound IV and I gave a considerable depression.

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