COMMUNICATIONS TO THE EDITOR

SYNTHESIS AND PHYSIOLOGICAL PROPERTIES OF THE D- AND L-ISOMERS OF α-METHYLPHENETHYLHYDRAZINE (JB-516),[1] A POTENT MONOAMINE OXIDASE (MAO) INHIBITOR

Sir:

The powerful analeptic and MAO inhibitory properties of D,L - α - methylphenethylhydrazine have been described earlier.[2,3,4] This compound has found clinical application in the treatment of the depressed state, angina pectoris,[5] rheumatoid arthritis,[6] and hypertension.[7]

We were interested in preparing the D- and L-isomers of JB-516 to see whether some of its physiologic properties could be either accentuated, reversed or abolished. In this way, we hoped that two new drugs might result having their own therapeutic spectrum and acting more powerfully and selectively than the racemate.

The pure optical isomers were obtained *via* a stereospecific synthesis by treating D- and L- α-methylphenethylamine with chloramine[8] to yield D-α-methylphenethylhydrazine, b.p. 135–138° (10 mm.), $n^{20}D$ 1.5385, $[\alpha]^{25}D$ +4.5° (*c*, 5 in methanol), (*Anal.* Calcd. for $C_9H_{14}N_2$: N, 18.65. Found: N, 18.58) and L-α-methylphenethylhydrazine, b.p. 135–138° (10 mm.), $n^{20}D$ 1.5385, $[\alpha]^{25}D$ −4.5° (*c*, 5 in methanol); *Anal.* Found: N, 18.54. The respective *hydrochlorides* were prepared in isopropyl alcohol by the addition of ethereal hydrochloric acid, then recrystallization from either isopropyl alcohol or acetonitrile: D-isomer, m.p. 152–154°, $[\alpha]^{25}D$ +12.8° (*c*, 5 in water); L-isomer, m.p. 152–154°, $[\alpha]^{25}D$ −12.5° (*c*, 5 in water); *Anal.* Calcd. for $C_9H_{15}ClN_2$: Cl, 18.99; N, 15.00. Found: Cl, 18.95 (D-isomer), 18.96 (L-isomer); N, 14.96 (D- and L-isomers). The mixed m.p. of the two optically active hydrochlorides was 122–123° (m.p. of the racemic mixture 124–125°).

In vitro data show the D-isomer to be approximately fifty per cent. more potent than the D,L-compound and twice as potent as the L-form as an MAO inhibitor in rat liver homogenates.[9] Similar relationships hold true for the respective *in vivo* activities of the two isomers in mice by the reserpine reversal test.[10] As an analeptic agent the L-isomer was only one-tenth as active as the D-α-methylphenethylhydrazine hydrochloride when tested in mice. The pressor properties of the two isomers were compared in dogs. L-α-Methylphenethylhydrazine hydrochloride displayed one-fourth the hypertensive potency of the D-isomer and one-third the activity of the racemate.

Hence, while the MAO inhibitory activities of the two optical isomers and of the racemate of α-methylphenethylhydrazine are comparable, there exist pronounced differences in some of the other pharmacologic properties of the L-isomer on the one hand and the D-isomer and the racemate on the other. The clinical implications of these findings are under investigation.

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THE CONDUCTANCE OF POTASSIUM CHLORIDE IN WATER-GLYCEROL MIXTURES AT 25°

Sir:

Much previous conductance work has centered around the dependence on dielectric constant of the constants of the conductance equation[1]; it has shown that the macroscopic dielectric constant suffices to calculate them.[2] To test the continuum model hydrodynamically, the conductance of potassium chloride was measured in glycerol (η = 9.45) and a series of its mixtures with water (η = 0.00895). For glycerol, D = 42.5; hence this variable was only halved while the viscosity increased by three decades, thus emphasizing hydrodynamic rather than electrostatic properties.

Solutions measured covered the approximate range 0.001 to 0.015 N, never exceeding that corresponding[3] to κa = 0.2; plots of $\Lambda' = \Lambda(\text{obs.}) + Sc^{1/2} - Ec \log c$ against c were linear within 0.02–0.20% for the six systems studied. The slopes determine the Fuoss–Onsager coefficients J, which evaluate the ion size a, average $\mathring{a}$ = 3.8 ± 0.4. The a-values show no trend with composition and average somewhat above 3.07, the value found[4] for water; association is therefore negligible. The (small) Jc term is extremely sensitive to experimental error; conversely, the average reproduces all the data within 0.02–0.2%.

The theoretical significance of the results is shown in Fig. 1, where Δ_R and Δ_H are plotted against $c^{1/2}$ for glycerol and 20.37% glycerol (η = 0.01561). The conductance may be written $\Lambda = (\Lambda_0 - \Lambda_0\Delta_R - \Delta_H)$, where $\Lambda_0\Delta_R = (\alpha c^{1/2} - E_1 c \log c - \sigma_1 c)$, Λ_0 is the decrease due to the relaxation field, and $\Delta_H = (\beta c^{1/2} + E_2 c \log c - \sigma_2 c)$ is the

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