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

The powerful analeptic and MAO inhibitory properties of $D,L - \alpha$ - 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 Lisomers 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 chloramine⁸ 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 C₉H₁₄N₂: 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. $152-154^{\circ}$, $[\alpha]^{25}$ 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 (Dand 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,Lcompound 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 re-serpine 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

(1) Marketed as "Catron" by Lakeside Laboratories.

(2) A. Horita, J. Pharmacol. Exptl. Therap., 122, 176 (1958).

(3) S. Spector, D. Prockop, P. A. Shore and B. B. Brodie, Science, 127, 704 (1958).

(4) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway and A. Horita, THIS JOURNAL, 81, 2805 (1959).

(5) R. Kennamer and M. Prinzmetal, Am. J. Cardiol., 3, 542 (1959). (6) A. L. Scherbel and J. W. Harrison, Ann. N. Y. Acad. Sci., 68,

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No. 4, part 2, 724 (1958). (8) M. O. Forster, J. Chem. Soc., 107, 267 (1915).

(9) A. Horita, private communication.

(10) M. Chessin, E. R. Kramer and C. C. Scott, J. Pharmacol. Expil.

Therap., 119, 453 (1957).

isomers were compared in dogs. L- α -Methylphenethylhydrazine hydrochloride displayed onefourth 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 equation1; 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 $(\eta = 9.45)$ and a series of its mixtures with water $(\eta = 0.00895)$. 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 corresponding⁸ to $\kappa a = 0.2$; 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 $a = 3.8 \pm 0.4$. The a-values show no trend with composition and average somewhat above 3.07, the value found⁴ 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 $\Delta_{\rm R}$ and $\Delta_{\rm H}$ are plotted against $c^{1/2}$ for glycerol and 20.37% glycerol ($\eta = 0.01561$). The conductance may be written $\Lambda = (\Lambda_0 - \Lambda_0 \Delta_{\rm R} - \Delta_{\rm H})$, where $\Lambda_0 \Delta_{\rm R} = (\alpha c^{1/2} - E_1 c)$ $\log c - \sigma_1 c$), Λ_0 is the decrease due to the relaxation field, and $\Delta_{\rm H} = (\beta c^{1/2} + E_2 c \log c - \sigma_2 c)$ is the

(1) R. M. Fuoss, This Journal, 81, 2659 (1959).

(2) See, for example, F. Accascina, A. D'Aprano and R. M. Fuoss, *ibid.*, **81**, 1058 (1958); F. Accascina, S. Petrucci and R. M. Fuoss, ibid., 81, 1301 (1959).

(3) F. Accascina, R. L. Kay and C. A. Kraus, Proc. Nat. Acad. Sci., 45, 804 (1959).

(4) R. M. Fuoss and F. Accascina, "La Conducibilità Elettrolitica," Edizioni dell'Ateneo, Rome, 1959, p. 217.

JOHN H. BIEL

Sir:



Fig. 1.—Relaxation and hydrodynamic terms in conductance for glycerol (top) and water-glycerol (bottom). Arrows show theoretical inflection points of Δ_R curves.

decrease due to purely hydrodynamic effects. The dotted lines correspond to the Onsager limits $\alpha c^{1/2}$ and $\beta c^{1/2}$. The solid curves are calculated using macroscopic dielectric constants and viscosities (and a = 3.8), while the points represent observations. The absolute values of the Δ 's differ enormously for the systems shown, due to the thousand-fold change in viscosity, but qualitatively the two sets of curves are identical (except for the larger relative deviations from the limiting law in glycerol due to its lower dielectric constant). The validity of the continuum model is thus verified. Experimental details will be published shortly.

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SYNTHESES OF CHLOROCYCLOPROPANES FROM METHYLENE CHLORIDE AND OLEFINS

Sir:

The formation of dihalocarbenes in reactions of haloforms with bases has been well substantiated.¹ We now wish to report two novel reactions which strongly suggest the existence of chlorocarbene (I) as a reaction intermediate. When *n*-butyl-lithium is added to methylene chloride in the presence of olefins at -25° , chlorocyclopropanes are formed in fair to good yields depending on the structure of the olefin. Thus 2,3-dimethylbutene-2 gave 67% of 1-chloro-2,2,3,3-tetramethylcyclo-

(1) (a) J. Hine, THIS JOURNAL, **72**, 2438 (1950); (b) W. von E. Doering and A. K. Hoffman, *ibid.*, **76**, 6162 (1954).

propane (II) (b.p. 72° (105 mm.), n²⁰D 1.4458; found: C, 63.22; H, 9.86; Cl, 26.50), transbutene-2 40% of 1-chloro-2,3-trans-dimethylcyclopropane (III) (b.p. 91° (755 mm.), n²⁰D 1.4286; found: C, 57.13; H, 8.87; Cl, 33.84), and cyclohexene 31% of 7-chlorobicyclo[4.1.0]heptane (IV) (b.p. $94-97^{\circ}$ (70 mm.); found: C, 64.28; H, 8.39; Cl, 26.94). The cyclopropane structures assigned to II and III were consistent with their infrared and n.m.r. spectra which provided no evidence of unsaturation. The trans configuration of the methyl groups in III was evident from its n.m.r. spectrum, which showed two partially overlapping doublets between 210 and 220 c.p.s. (relative to external benzene, measured at 40 mc.) to prove the non-equivalence of the methyl groups. II and III were free of isomers within the limit of detection ($\sim 1\%$) by vapor phase chromatography. V.p.c. analysis of IV, however, revealed the presence of two isomers in a 1:2,2 ratio.2 Reduction of the mixture IV using sodium in liquid ammonia to yield 85% of pure bicyclo[4.1.0]heptane demonstrated that the isomers in which the chlorine occupies either an exo or endo position were both formed.

The observed exclusive *cis* addition and increase in yield with increasing nucleophilicity of the olefin³ is consistent with the postulation of chlorocarbene as an intermediate in this reaction. The probable precursor to I, dichloromethyllithium (V), appears to be of low stability since no dichloroacetic acid could be detected after carbonation of the reaction mixture of *n*-butyllithium and methylene chloride at -70° .



Chlorocarbene as a strong electrophilic reagent can be expected to react readily with butyllithium. In line with this expectation, pentene-1, identified as its dibromide, was formed in 82% yield when methylene chloride was added to *n*-butyllithium in ether at -25° . This novel olefin synthesis may be explained by the addition of I to butyllithium yielding 1-chloro-*n*-amyllithium (VI), which undergoes α -elimination and forms the olefin via a hydride shift. An alternative mechanism proceeding through the formation of *n*-amyl chloride, then by β -elimination can be ruled out on the basis that β -elimination from primary halides on reaction with alkyllithium compounds does not proceed readily.⁴

⁽²⁾ The predominant isomer had the longer retention time.

^{(3) (}a) P. S. Skell and A. Y. Garner, THIS JOURNAL, 78, 5430 (1956);
(b) W. von E. Doering and Wm. A. Henderson, *ibid.*, 80, 5274 (1958).

⁽⁴⁾ K. Ziegler and H. Colonius, Ann., 479, 135 (1930).