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Ephedrine Homologs and Isomers: Relationship Between Their Pharmacological Action and Their Chemical Constitution and Stereoisomerism.*

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The recent wide clinical use of ephedrine has led a number of chemists to synthesize its homologs and isomers in the hope that some of them might possess the same physiological action and might eventually be used as substitutes for ephedrine. The present writers have studied and compared from the pharmacological side a series of 24 compounds, including 6 optical isomers of ephedrine. All these compounds may be considered as derivatives of β-phenylethylamine having the general formula $C_6H_5.CHH'.CHR.NR'R''$, where $H' = H$ or OH, and R, R′ and R″ = H or alkyl radicals, respectively. The investigation included the pressor action in animals and in men, the mydriatic action in animals, the astringent property on the human nasal mucous membrane, the action on the isolated intestines and uterus and on the frog's heart, and the toxicity in rabbits. It was found that the primary amines are most, while the tertiary amines are least, active, the secondary amines being intermediate. The pressor action diminishes with the increase in the number of C-atoms in the alkyl groups R, R′ and R″, and in several instances is changed to a depressor action. The introduction of an OH group on the β-C-atom from the amino radical reduces the activity of the substance. The presence of a methyl, or ethyl group at R, when $R' = H$ or CH_3 and $R'' = H$, confers on that compound a more prolonged pressor action. The toxicity is higher in primary amines than in secondary and tertiary amines. It increases with the increase in the number of C-atoms in the alkyl groups R, R′ and R″. The introduction of an OH group on the β-C-atom reduces the toxicity. The depressant action on the frog's heart runs parallel to the toxicity. The majority of these compounds contract the congested nasal mucosa in men. Of the optical isomers of ephedrine, the *l*-form is 3 times as strong as the *d*-form and *d*-pseudoephedrine 7 times as strong as the *l*-pseudoephedrine as determined by their pressor action in pithed cats. Both *l*-ephedrine and *d*-pseudoephedrine occur in nature. The above results may offer a chemical explanation of the typical action of ephedrine, and suggest the synthesis of new compounds which may possess the clinical advantages of both ephedrine and epinephrine.

* Read before Sections C (Chemistry) and N (Medical Sciences) of the American Association for the Advancement of Science on December 27, 1928.