[CONTRIBUTION FROM ABBOTT LABORATORIES]

THE CONFORMATION OF THE EPHEDRINES

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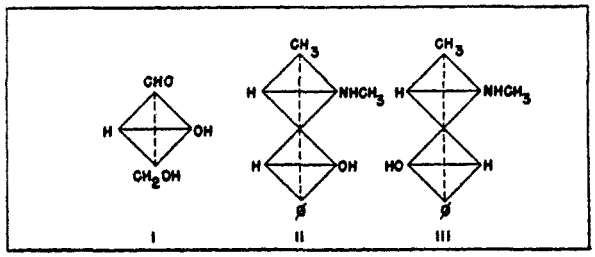
The chemistry of ephedrine and its three optical isomers has attracted widespread interest because of the physiological significance attached to the structure. (−)-Ephedrine was first isolated by Nagai (1) in 1887 and by 1920 all of the optical isomers had been synthesized (2). Shortly thereafter Freudenberg (3, 4) and Leithe (5) established the relative configuration about the two asymmetric centers for (−)-ephedrine, and hence for its optical isomers, since the configurational relationship between compounds of the ephedrine and pseudoephedrine series is well known.[1] The configurations of (−)-ephedrine and (+)-pseudoephedrine may be represented by Figures II and III, respectively, if D-glyceraldehyde is represented as I.



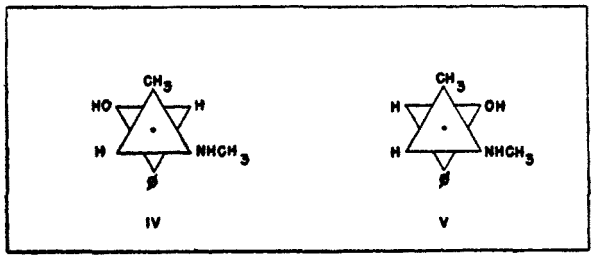
The molecular picture is not complete with the establishment of the relative configuration, however. The *conformation* (11) of the ephedrine molecule is still indeterminate. A consideration of the observed differences in reactivity of ephedrine and pseudoephedrine derivatives has led Fodor and his coworkers (8)

[1] Much confusion has arisen in recent times concerning the configuration about the carbon bearing the methylamino group. Jarowski and Hartung (6) stated that Freudenberg (4) and Leithe (5) arrived at opposite configurations and that the configuration is, therefore, in doubt. Fourneau and Benoit (7) apparently also felt that the configuration had not been established, for they stated that the structures of the diastereoisomers of ephedrine and isoephedrine remain undetermined. More recently, Fodor and coworkers (8) maintained that the configuration at the nitrogen-bearing carbon atom is unsettled, and to indicate this unsettled configuration a double-headed arrow was used in all of the projection formulas relating to the ephedrines. Only Welsh (9) has felt that the configuration has been adequately established.

The authors who believe that the configuration is unsettled may have been misled by an incorrect abstract (10) of Leithe's work, wherein it was stated that "the natural Ephedra bases are not derived from natural *l*-alanine but from the *d*-antipode". Actually, both Freudenberg and Leithe related natural ephedrine to natural L(+)-alanine. Since two independent investigators, by varying technique and by acceptable and logical means, have arrived at identical conclusions, there can be no reasonable doubt concerning the configuration at this asymmetric center.

to the conclusion that there is some restricted rotation about the bond between the carbon bearing the hydroxyl group and the carbon bearing the methylamino group. The evidence pointed to the probability that in the ephedrine molecule the hydroxyl and methylamino groups are relatively distant; in pseudoephedrine, relatively close.

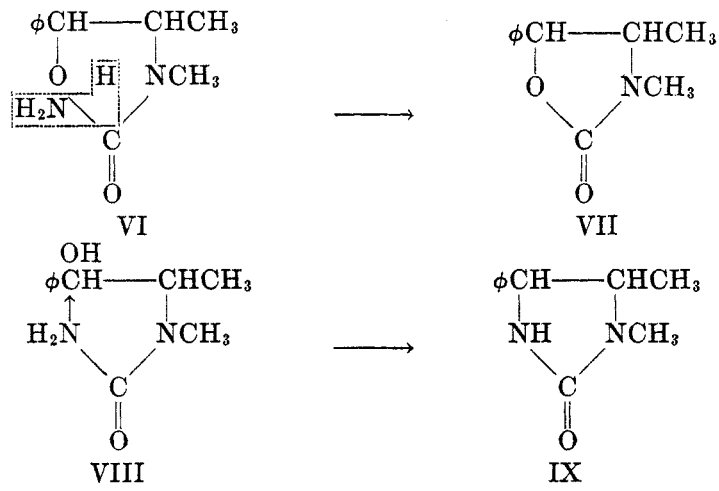
Freudenberg and coworkers (3) had denied that any restricted rotation existed. Recently Welsh (9), interpreting the concept in its strictest sense, also denied its existence on the basis of molecular models. The latter author preferred to explain his data, which was similar to that of Fodor, on the basis of the "differences in the spatial arrangements of the groups in the diastereomers." Welsh concluded that the phenyl and methyl groups in both ephedrine and pseudoephedrine[2] tended to orient themselves *trans* to each other.



The viewpoints of both Fodor and Welsh can be made consistent by assigning the conformations represented by Figures IV and V for (−)-ephedrine and (+)-pseudoephedrine, respectively. These forms preserve the relative configurations established for these molecules.

Experimental evidence of a different type has now been obtained in these laboratories which lends further support to the conformations shown. In the preparation of 2-oxazolidones by the fusion of urea with *beta*-aminoalcohol hydrochlorides, it was found that whereas (+)-pseudoephedrine gave the normal product (VII), *dl*-ephedrine gave an imidazolidone (IX). This difference in behavior can be rationalized by a consideration of the probable mechanism of the urea fusion. At the temperature of the reaction (170–210°) the urea breaks down to cyanic acid, which attacks the basic group to give the intermediate ureido derivative (VI or VIII). Now if the terminal amino group can be brought into close proximity with the hydroxyl group (as in VI), interaction occurs with the formation of the oxazolidone, as shown. Where it is relatively more difficult to bring these groups together (as in VIII), a rearward attack on the carbon atom carrying the hydroxyl group occurs by an S_N2 mechanism, resulting in expulsion of the hydroxyl group. The experimental evidence indicates that (−)-ephedrine corresponds to VIII (and, therefore, to IV), whereas (+)-pseudoephedrine corresponds to VI (and, therefore, to V).

[2] In terms of the usual conventions, Figures III and IV in Welsh's paper represent, respectively, (−)-pseudoephedrine and (+)-ephedrine.



It should not be inferred that the conformations assigned are the only possible geometrical arrangements. Rather, they should be viewed as the most probable arrangements in the resting state of the molecules, or the arrangements which represent the lowest energy states. Although it is probable that similar conformations apply to the norephedrine derivatives (*cf.* Fodor), this could not be demonstrated by the method described above. *dl*-Norephedrine gave the normal oxazolidone. It would appear that the difference in energy levels between the various possible conformations in the *nor*-series is less than in the ephedrine series, and interconversion is accomplished with relatively greater ease. This might be expected in view of the hindering effect of the N-methyl group.

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EXPERIMENTAL[3]

1,5-Dimethyl-4-phenyl-2-imidazolidone (IX). Forty grams of *dl*-ephedrine hydrochloride was mixed with 36 g. of urea and heated for one-half hour at 170–175° followed by one hour at 200–210°. The cooled mixture was treated with water, and the somewhat oily solid which precipitated was washed with 5% hydrochloric acid and water. Recrystallization from alcohol gave 11.8 g., m.p. 140–144°, and 6.6 g., m.p. 139–143° (48%). Further recrystallization brought the melting point to 144.5–145°.

Anal. Calc'd for $C_{11}H_{14}N_2O$: C, 69.5; H, 7.4; N, 14.7.
Found: C, 69.7; H, 7.1; N, 14.6.

Attempts to crystallize the oxazolidone from the filtrate gave only additional small amounts of the imidazolidone. The oily residues were finally distilled at 202–204° (14 mm.). Analysis of the distillate indicated that it contained substantial amounts of the oxazolidone.

Anal. Calc'd for $C_{11}H_{14}N_2O$ (imidazolidone): N, 14.7.
Calc'd for $C_{11}H_{13}NO_2$ (oxazolidone): N, 7.3. Found: N, 10.0.

[3] All melting points are uncorrected.

3,4-Dimethyl-5-phenyl-2-oxazolidone (VII). The procedure described above was followed with 20.2 g. of (+)-pseudoephedrine hydrochloride. The oil which precipitated upon treatment with water was taken up in ether and washed with 5% hydrochloric acid and water. Concentration of the solution gave an oil which solidified readily in Skellysolve B and ether. Fourteen grams (73%) of material melting at 45–49° was obtained. Continued recrystallization from the same solvents brought the melting point to 50–51°.

Anal. Calc'd for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.5.

4-Methyl-5-phenyl-2-oxazolidone. A mixture of 3.6 g. of *dl*-norephedrine hydrochloride and 2.3 g. of urea was treated in the same manner as described. The solid which separated upon the addition of water was extracted with large volumes of ether to remove a small amount of ether-insoluble material. The ether extracts yielded 1.1 g., m.p. 144–146°, and 1.0 g., m.p. 140–143° (62%). An analytically pure sample melted at 146–146.5°. Homeyer (12) records 145–146°.

Anal. Calc'd for $C_{10}H_{11}NO_2$: N, 7.9. Found: N, 7.9.

SUMMARY

It has been found that the fusion of ephedrine with urea gives rise to an imidazolidone, whereas pseudoephedrine yields an oxazolidone. From these data the conformation of the ephedrines is deduced.

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