

Communication to the Editor

Studies on the Infrared Spectra of Ephedrine and Related Compounds

As is well known, normal and ψ -ephedrine, which are diastereoisomers, show different physical and chemical properties. For example, ψ -ephedrine gives a larger pK_a value than ephedrine¹⁾ and 1-chloroephedrine forms a resinous substance by the action of alkali, while the corresponding ψ -ephedrine derivative gives an ethylenimine.²⁾ In order to explain such differences various reasons have been suggested such as restricted rotation about the C₁-C₂ bond,³⁾ spatial approach of the methylamino group to the chlorine atom only in the substituted ψ -1-chloroephedrine⁴⁾ or the existence of hydrogen bond between the methylamino and hydroxyl groups only in ψ -ephedrine⁵⁾. From the consideration of these and other evidences the conformation of ephedrine and ψ -ephedrine has been described in a manner so that the methylamino and hydroxyl groups are *trans* in the normal series and *gauche* in the pseudo series, while the phenyl and methyl groups are *trans* in both diastereoisomers. On the other hand crystal structure analysis of ephedrine hydrochloride⁶⁾ recently revealed a different conformation from the one just given, the methylamino and hydroxyl groups being placed near to each other in the molecule.

In view of this crystal structure it became of significance to reexamine the conformation problem of these ephedrine and related compounds. As already reported⁷⁾ the author observed the infrared spectra in NaCl region of corresponding diastereoisomers of ephedrine, ephedrine hydrochloride, 1-chloroephedrine hydrochloride, N-benzoylephedrine, and O-benzoylephedrine hydrochloride in both optically active and racemic forms, all in solid state. From the observation of these spectra it was suggested that a hydrogen bond exists in crystals of both of the corresponding diastereoisomers, it being only stronger in ψ -ephedrine than in the normal one.⁷⁾

In order to obtain more informations on this problem, the spectra in 3μ region of the diastereoisomeric ephedrine and related substances dissolved in carbon tetrachloride at various concentrations were recently taken with the Perkin-Elmer Model 21 infrared spectrophotometer equipped with LiF prism and cells of 20 and 50 mm. in length. The wave numbers of the absorption bands and their optical densities are listed in Table I. It is rather remarkable that the substances examined showed a more or less common features. The band of the highest wave number observable in this region shows a sharp absorption ($3613\sim 3635\text{ cm}^{-1}$), while the next ($3329\sim 3494\text{ cm}^{-1}$) was fairly broad. The only exception is the case of *erythro*-1,2-diphenyl-2-methylaminoethanol (I) which gave two sharp bands (3617 and 3587 cm^{-1}) instead of the single one. Further, it was found that the wave number difference between the first and second bands was always larger for the pseudo compounds than for the corresponding normal ones. This fact will be of practical value for the discrimination of *threo* and *erythro* compounds showing such pair of bands.

The observed similarity of the spectra mentioned above for the corresponding *threo*

- 1) V. Prelog, O. Haefliger : *Helv. Chim. Acta*, **33**, 2021(1950).
- 2) K. Tanaka : *J. Pharm. Soc. Japan*, **70**, 212(1950).
- 3) W. J. Close : *J. Org. Chem.*, **15**, 1131(1950).
- 4) E. Spät, R. Göring : *Monatsh.*, **41**, 319(1920).
- 5) G. Fodor, V. Bruckner, J. Kiss, G. Ohegi : *J. Org. Chem.*, **14**, 337(1949).
- 6) G. D. Phillips : *Acta Cryst.*, **7**, 159(1954).
- 7) Reported at the Monthly Kinki Local Meeting of the Pharmaceutical Society of Japan, November 21, 1953.

TABLE I. Wave Number (cm^{-1}) of Absorption Bands in $3\ \mu$ Region

Substance $\text{R}_1-\text{CH}-\text{CH}-\text{R}_4$ $\quad \quad \quad $ $\quad \text{OH} \text{NR}_2\text{R}_3$	DL-Erythro (normal)	$\Delta\nu$ cm^{-1}	DL-Threo (pseudo)	$\Delta\nu$ cm^{-1}	concn. mol./L.
$\text{R}_1=\text{R}_4=\text{CH}_3$ $\text{R}_2=\text{R}_3=\text{H}$	3635, 3494*, 3404 (0.225, 0.32, 0.215)	141			0.005
$\text{R}_1=\text{C}_6\text{H}_5$, $\text{R}_3=\text{H}$ $\text{R}_2=\text{R}_4=\text{CH}_3$	3619, 3451*, 3370 (0.204, 0.312, 0.228)	168	3621, 3418*, (0.242, 0.366)	203	0.001 ~0.01
$\text{R}_1=\text{R}_4=\text{C}_6\text{H}_5$ $\text{R}_2=\text{CH}_3$, $\text{R}_3=\text{H}$	3617, 3587, 3466*, 3349 (0.308, 0.314, 0.16, 0.135)	30 151	3621, 3428*, 3360 (0.294, 0.180, 0.160)	193	"
$\text{R}_1=\text{C}_6\text{H}_5$ $\text{R}_2=\text{R}_3=\text{R}_4=\text{CH}_3$	3617, 3460* (0.118, 0.180)	157	3613, 3375* (0.021, 0.335)	238	"
$\text{R}_1=\text{C}_6\text{H}_5$, $\text{R}_2=\text{COC}_6\text{H}_5$ $\text{R}_3=\text{R}_4=\text{CH}_3$	3615, 3340* (0.442, 0.358)	275	3618, 3329* (0.284, 0.362)	289	0.005

* signifies a broad band.

The values in parentheses imply optical densities at a concentration of about 0.005 mol./L.

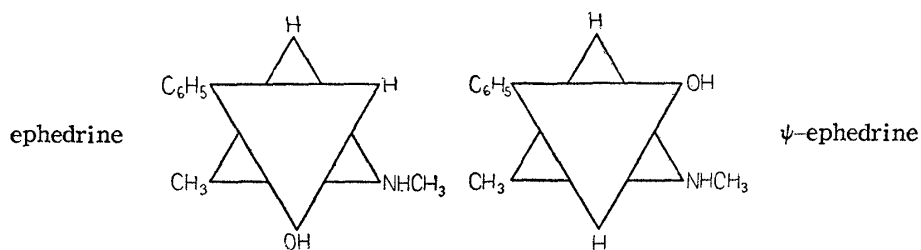


Fig. 1

and *erythro* compounds may make it worth while to assume the possibility of a close relationship in the molecular conformation of the diastereoisomers, at least in the carbon tetrachloride solution. For example, based upon the conformation of ephedrine hydrochloride found by Phillips⁶⁾ in crystalline state, such a close relationship will be realized if it is assumed that the conformations of ephedrine and ψ -ephedrine be given as in Fig. 1. They are different from those hitherto commonly accepted. However, in these two conformations, the spatial relationship of the portions of $\text{C}_6\text{H}_5-\text{C}-\text{C}-\text{CH}_3$ and $\text{CH}_3\text{NH}-\text{C}-\text{C}-\text{OH}$ will become quite similar for both diastereoisomers. Thus it may not be insignificant to check the physical and chemical evidences of such compounds from the view point of the suggested similarity of their conformation. In connection with these the following findings may be added that ephedrine and ψ -ephedrine hydrochlorides precipitate from the carbon tetrachloride solutions about thirty minutes after their preparation.

Finally, following generally accepted elucidation, the sharp bands ($3613\sim 3635\ \text{cm}^{-1}$) may be assigned to the free or almost free OH vibration and the broad bands of the lower wave number ($3329\sim 3494\ \text{cm}^{-1}$) to a more or less bonded OH vibration. Considering the fact that in 2,3-butanediols the shift $\Delta\nu$ due to hydrogen bond formation is of the order of $30\sim 50\ \text{cm}^{-1}$,⁸⁾ $\Delta\nu$ in the present case is generally by far larger and it seems interesting to investigate further how it arises. Since the dependence on concentration of the ratio of optical densities of the two bands mentioned above was not appreciable and also it was reported from the result of the molecular weight determination in benzene solution that the association of the alkamines did not occur in the concentration range such as in the present experiment⁹⁾, it might be said that the hydrogen bond is in a

8) L. P. Kuhn: J. Am. Chem. Soc. **74**, 2492(1952).9) E. D. Bergmann, E. Gil-Av, S. Pinchas: *Ibid.*, **75**, 68(1953).

sense an intramolecular type. It is also worth noticing that in the present case of the carbon tetrachloride solution *threo* compounds always give larger shift $\Delta\nu$ than the corresponding *erythro* ones, though the shift is to some extent dependent on the replacement of the phenyl or methyl group or the hydrogen atom in ephedrine by other groups.

Further experiments are in progress and the full account of this work will be given in the near future.

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