Studies on the Infrared Spectra of Ephedrine and Related Compounds. III. Infrared Spectra of Diastereoisomeric N-Methylephedrines and 1, 2-Diphenyl-2-methylaminoethanols-(1) in 3 micron Region

By Tokunosuke KANZAWA

(Received February 13, 1956)

The spectra of the diastereoisomeric N-methylephedrines and 1, 2-diphenyl-2-methylaminoethanols-(1) in 3 micron region are very like those of ephedrines as shown in the previous paper¹⁾, but their $\Delta\nu$ values, which are differences in wave numbers of the free and the bonded OH absorption band, are somewhat different from those of ephedrines. Thus, the difference in $\Delta\nu$ values between N-methylephedrine isomers ($238-157=81\ \mathrm{cm}^{-1}$) is much larger than that between ephedrines ($203-168=35\ \mathrm{cm}^{-1}$). On the other hand, the two isomers of 1, 2-diphenyl-2-methylaminoethanol-(1) give smaller $\Delta\nu$ values (151 and $193\ \mathrm{cm}^{-1}$) than those of ephedrines, and the erythro isomer exceptionally shows an absorption near $3600\ \mathrm{cm}^{-1}$ consisting of two bands by $30\ \mathrm{cm}^{-1}$ apart from each other, whereas the other compounds examined show only one band. Although these two pairs of compounds are similar in chemical behavior to ephedrines, the appreciable changes in $\Delta\nu$ seem to be related to the change of steric structure caused by substitution of the groups. The object of the present experiments is to obtain information on the molecular structure of these compounds and to discuss their conformations in connection with that of ephedrines as proposed previously²⁾.

Experimental

The spectrophotometer used, its operating conditions and the procedure for the purification of the solvents are the same as described previously²⁾. N-methylephedrines were in optically active forms and 1, 2-diphenyl-2-methylaminoethanols-(1) were racemic modifications. They were supplied by Dr. K. Tanaka and Mr. T. Sugawa in this Laboratory.

---

1) T. Kanzawa, This Bulletin, **29**, 398 (1956).

2) T. Kanzawa, This Bulletin, **29**, 479 (1956).

Experimental Results

A. N-Methylephedrines.—In Fig. 1. the concentration dependence of the absorption for N-methylephedrines is shown. Over a concentration range of 0.001–0.01 mol./l. the spectra of both isomers show no appreciable change in the position and intensity of the absorption bands. On raising the concentration up to a few tenth mol./l. spectral changes are observed for both isomers, although not so marked as in the cases of ephedrines. Thus, for N-methylephedrine the intensity of a sharp band at 3617 cm^{-1} decreases and that of a broad band at 3460 cm^{-1} increases with concentration. For Ψ-N-methylephedrine a band at 3613 cm^{-1} disappears already at 0.045 mol./l. (not shown in Fig. 1b) and the intensity of a broad band at 3375 cm^{-1} decreases. The shift of the broad band towards lower frequency for the concentration change from ~0.005 to ~0.1 mol./l. is about 10 cm^{-1} for both isomers.

Since N-methylephedrines have no NH group, it will be reasonable to assign the higher-frequency band to free OH stretching vibration and the lower-frequency one to bonded OH vibration (OH-N). From a behavior in concentration dependence it may be said that as long as the concentration remains small the hydrogen bond is of an intramolecular type. The possibility of the formation of the ring dimer seems to be difficult to consider from cryoscopic data for alkamines[3]. In the spectra of the dilute solution shown in Fig. 1a and 1b, it will be noticed that, when compared with the corresponding diastereoisomers of ephedrine, N-methylephedrine shows a smaller $\Delta\nu$ value (157 cm^{-1}) and a comparable intensity of the free OH absorption, while Ψ-N-methylephedrine shows a much larger $\Delta\nu$ value (238 cm^{-1}) and a much smaller intensity.

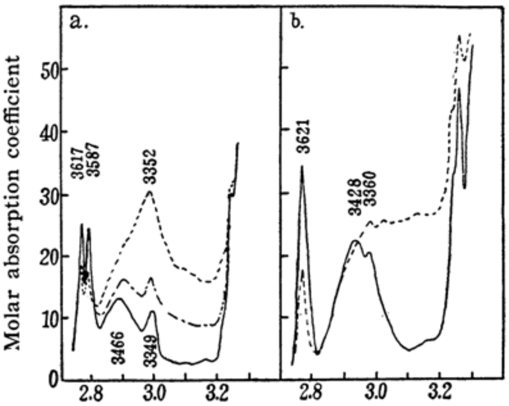


Fig. 1. Concentration dependence. N-Methylephedrine. CCl$_4$ solns.
a) normal. ——— 0.0046 (2 cm.), —·—· 0.097 (0.056 cm.), - - - - 0.19 mol./l. (〃).
b) pseudo. ——— 0.0053 (2 cm.), - - - - 0.45 mol./l. (0.0195 cm.).

The shifts of the bonded OH absorptions with increasing concentration for N-methylephedrines are smaller than those for ephedrines (30 cm^{-1}) and no band appears near 3300 cm^{-1} as seen in the cases of ephedrines, where the band was assumed to be due to OH- - -O intermolecular hydrogen bond. For N-methylephedrine, this absence may be due to the lack of appreciable association at a concentration of 0.19 mol./l. The spectrum at a concentration higher than 0.19 mol./l. could not be taken because of the precipitation of crystallites. For Ψ-N-methylephedrine the spectrum at a concentration of 0.45 mol./l. (Fig. 1b) may show one in a state containing associated molecules, because in the spectrum of liquid state only one broad band appears at 3347 cm^{-1}.

B. 1, 2-Diphenyl-2-methylaminoethanol-(1).—1) Concentration-Dependence.—In Fig. 2a the concentration dependence of the absorption of erythro (normal) 1, 2-diphenyl-2-methylamino-ethanol-(1) is shown. Since this compound has the hydroxyl and methylamino groups like ephedrine, it is expected that spectra similar to that of ephedrine should be obtained. However, as seen in Fig. 2a the spectra are quite different. Thus, the absorption near 3600 cm^{-1} is a doublet composed of two sharp bands (3617 and 3587 cm^{-1}) of about the same intensity, and a broad absorption at 3466 cm^{-1} is weaker than the bands near 3600 cm^{-1} and also a well-defined band appears at 3349 cm^{-1}.

On raising the concentration, the intensities of the two bands near 3600 cm^{-1} decrease in the same degree and at a concentration of 0.063 mol./l. a single absorption appears at 3352 cm^{-1}. Since, as in the cases of ephedrines and N-methylephedrines, the intensities and the positions of the absorption bands remain unchanged in a concentration range 0.001–0. 01 mol./l., the presence of the intramolecular hydrogen bond will be expected in a dilute

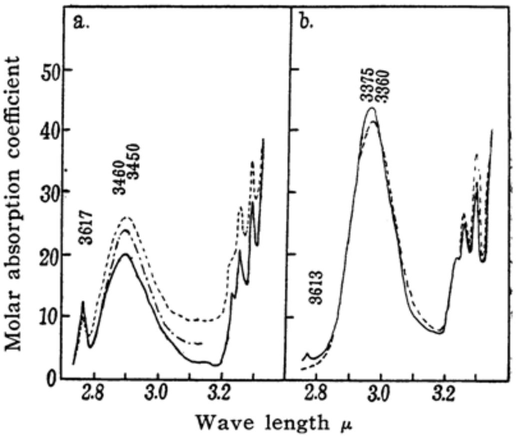


Fig. 2. Concentration dependence. 1,2-Diphenyl-2-methylamino-ethanol-(1). CCl$_4$ solns.
a) erythro (normal).——— 0.0062 (2 cm.), —·—· 0.046 (0.3 cm.), - - - - 0.068 mol./l. (〃).
b) threo (pseudo). ——— 0.0031 (2 cm.), - - - - 0.068 mol./l. (0.3 cm.).

---

[3] E.D. Bergmann, E. Gil-Av. and S. Pincas, *J. Am. Chem. Soc.*, **75**, 68 (1953).

solution. The spectrum at 0.063 mol/l. shows an interaction between molecules and thus the association occurs at a lower concentration than in the cases of ephedrines (0.1–0.2 mol./l.). As for the doublet structure of the bands near 3600 cm^{-1}, it seems that some kind of resonance splitting occurs as will be discussed later.

The band at 3466 cm^{-1}, which becomes stronger and shifts to 3448 cm^{-1} with concentration increase may be due to OH vibration perturbed by an intramolecular OH---N hydrogen bond in the same way as in the cases of ephedrines. The band at 3349 cm^{-1}, which may be assigned to NH vibration, is more intense than the NH absorption for ephedrines. This increase in the intensity of the NH absorption may be attributed to a change of structure from methylethylamine type of ephedrines to methylbenzylamine type*.

An intense peak at 3352 cm^{-1} at a higher concentration may be the superposition of the bonded OH absorption shifted by an intermolecular OH---O hydrogen bond and the NH absorption. It will be noticed that $\Delta\nu$ (151 cm^{-1}) between the higher-frequency component of the free OH vibration and the broad band at 3466 cm^{-1} is smaller than that of ephedrine (168 cm^{-1}) and the intensity ratio of the sharp component to the broad one is much larger than that for ephedrine and N-methylephedrine.

Threo 1, 2-diphenyl-2-methylaminoethanol-(1) (Fig. 2b) shows only one band near 3600 cm^{-1} unlike erythro isomer and a similar absorption in a range 2.7–3.3 μ to that of Ψ-ephedrine and Ψ-N-methylephedrine. The change in the absorption with concentration proceeds in the same manner as the other compounds. Therefore, a band at 3621 cm^{-1} can be assigned to free OH vibration, and a band at 3428 cm^{-1} to bonded OH vibration and further a peak at 3360 cm^{-1} to NH vibration. Here again, the NH absorption is more intense than that of Ψ-ephedrine. At a concentration of 0.068 mol./l. association is appreciable. As in the case of the erythro isomer, at the lower concentration, the free OH absorption is stronger than the bonded one and, at the higher concentration, the bonded OH absorption at 3428 cm^{-1} is covered by a slope of a peak at 3348 cm^{-1}. In this case a continuous absorption over a range 3.0–3.2 μ appears unlike the erythro isomer.

2) Solvent Effect and Interaction with Triethylamine.—The solvent effect and the interaction with triethylamine were studied in order to obtain information on the nature of the doublet band shown by erythro 1, 2-diphenyl-2-methylaminoethanol-(1) (Fig. 3).

In carbon disulfide solution the doublet bands shift towards lower frequency, compared with those in carbon tetrachloride solution, and the lower frequency component (3571 cm^{-1}) is much more intense than the higher-frequency one (3592 cm^{-1}). At a lower concentration, the bonded OH absorption (3442 cm^{-1}) and NH absorption (3338 cm^{-1}) are well-defined. At a higher concentration, association seems to occur and the NH absorption still remains. The tendency of association of the erythro compound in carbon disulfide solution is weaker than that of ephedrine.

In chloroform solution the shift of the doublet is to about the same degree as in carbon disulfide solution and the intensities of the components are about the same. The NH absorption at 3344 cm^{-1} is stronger than the bonded OH absorption. A weak absorption seems to appear in the region with longer wave length than NH absorption, but no appreciable association occurs.

In benzene solution the free OH absorption is not a doublet, but a single band at 3571 cm^{-1}. The bonded OH absorption is weak and the NH absorption is well-defined.

In Fig. 3b the interaction of the erythro compound with triethylamine in carbon tetrachloride solution is shown. By addition of triethylamine, the higher-frequency component of the doublet becomes weaker than the lower-frequency one and a continuous absorption appears in 3.1–3.3 μ region. At a concentration of 0.5 mol./l. of triethylamine the bonded OH absorption still remains and the NH absorption at 3345 cm^{-1} shifts to 3339 cm^{-1} and new bands appear at 3185 and 3143 cm^{-1}. These spectral bahaviors may be explained as in the cases of ephedrines[2]. By the interaction of free molecules with triethylamine an intermolecular OH---N hydrogen bond is formed and gives rise to an absorption at 3143 cm^{-1}. At the same time NHCH$_3$ group bridged by an intramolecular OH---N bond may interact with triethylamine and causes an absorption (NH---N) at 3185 cm^{-1}. It is seen that the intramolecularly bonded OH absorption and the NH absorption still remains at higher concentrations of triethylamine.

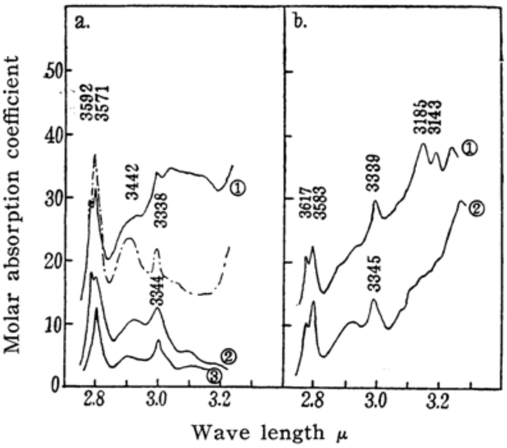


Fig. 3. Solvent effect and interation with triethylamine. Erythro 1, 2-diphenyl-2-methylaminoethanol-(1).

a). 1. CS$_2$ ——— 0.03 (2 cm.), —·—· 0.0044 mol./l. (0.3 cm.) 2. CHCl$_3$, 0.16 mol./l. (0.056 cm.) 3. Benzene, 0.16 mol./l. (〃).

b). 1. 0.02 mol./l. + (C$_2$H$_5$)$_3$N 0.26 mol./l.
2. + 0.5 mol./l. (0.3 cm.) in CCl$_4$.

---

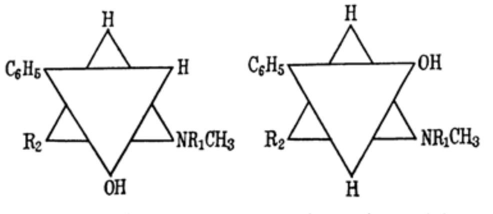
* According to the results obtained by Russell and Thompson (*J. Chem. Soc.*, **1955**, 483) absorption of ν(NH) in dibenzylamine is stronger than that in dialkylamine.

Discussion

The above results may be explained in the same manner as described for ephedrines[2]. The conformations capable of forming an intramolecular OH---N hydrogen bond are illustrated in Fig. 4 for diastereoisomers of N-methylephedrine and 1, 2-diphenyl-2-methylaminoethanol-(1). The appearance of the free OH absorption in the spectra for these two diastereoisomers will mean that all the compounds examined may be mixtures of rotational isomers, in one of which the OH and NR_1CH_3 groups are *trans* and in the others of which they are *gauche*.

$\Delta\nu$ of N-methylephedrine (151 cm^{-1}) is somewhat smaller than that of ephedrine (168 cm^{-1}). This may be explained qualitatively as follows. $N(CH_3)_2$ group will exert a stronger repulsive force from its bulkiness and, on the other hand, in a favorable steric position, a stronger attraction because of the stronger proton accepting power than $NHCH_3$ group in ephedrine. Since a repulsion between the methyl and phenyl groups may be the same in both compounds, the repulsion between the OH and $N(CH_3)_2$ groups may contribute more to the $\Delta\nu$ value of N-methylephedrine than the attraction between them. The equilibrium ratio of the rotational isomers may be about the same as that for ephedrine.

On the other hand, for ψ-N-methylephedrine $\Delta\nu$ (238 cm^{-1}) is much larger than that for N-methylephedrine and ψ-ephedrine (203 cm^{-1}). In this case the repulsion between the methyl and phenyl groups will give rise to a closer approach and accordingly a smaller $\Delta\nu$ than that of N-methylephedrine. However, considering the above-mentioned repulsion between the OH and $N(CH_3)_2$ groups $\Delta\nu$ of ψ-N-methylephedrine should be about the same as or smaller than that of ψ-ephedrine. Accordingly, the observed larger value of ψ-N-methylephedrine may be explained by the predominance of the other gauche type isomer than that shown in Fig. 4, in which the repulsion between the phenyl and $N(CH_3)_2$ groups will be larger than that between the phenyl and $NHCH_3$ groups in ephedrine. A possible explanation as regards the very weak intensity of the free OH vibration will be that the trans isomer may be fairly unstable because of the repulsion between bulky groups crowded together.



erythro (normal) threo (pseudo)

Fig. 4.

R_1	R_2	
H	CH_3	Ephedrine
CH_3	CH_3	N-Methylephedrine
H	C_6H_5	1, 2-Diphenyl-2-methylaminoethanol-(1)

For 1, 2-diphenyl-2-methylaminoethanol-(1) the origin of the doublet bands near 3600 cm^{-1} found for the erythro isomer should be discussed first. From the behavior of the doublet under various conditions described hitherto it will be noticed that the solvent effect seems to be different for each component. Such a tendency would suggest that the lower-frequency component might be caused by a sort of bonding of the OH group. Considering the smallness of $\Delta\nu$ (30 cm^{-1}) between the components, this bonding is not so strong as the ordinary OH---N hydrogen bonding. From this point of view proton acceptor other than $NHCH_3$ group should be considered. As an acceptor as such, the phenyl group attached to the asymmetric carbon atom adjacent to the other one having OH group might be considered. To confirm such an assumption a spectrum of benzylphenyl carbinol was taken in a dilute carbon tetrachloride solution. Only one sharp band was observed at 3610 cm^{-1} and therefore it may be said that the doublet is not caused by such an interaction. On the other hand, a spectrum of erythro 1, 2-diphenyl-2-aminoethanol-(1) showed also a doublet composed of bands at 3617 and 3590 cm^{-1}, a broad band at 3482 cm^{-1}, NH absorption at 3399 cm^{-1} and one more band near 3μ. The wave numbers of all the absorptions except one at 3617 cm^{-1} are larger than those of corresponding bands of erythro 1, 2-diphenyl-2-methylaminoethanol-(1). Those shifts are probably caused by a difference in nature of amino and methylamino groups. From these observations, it will be more reasonable to consider that the doublet is caused by some resonance effect or other.

It will be noticed from the spectra that the intensity of the free OH absorption at 3617 cm^{-1} for the threo isomer is stronger than the bonded OH absorption, and the intensities of the doublet for the erythro isomer are also stronger than that of the bonded one. Moreover, assuming the sum of the intensities of the components of the doublet as that of the free OH absorption subjected to no perturbation, an intensity ratio of the free OH absorption to the bonded one is much larger for the erythro isomer than for the threo isomer. Accordingly this will mean that a rotational isomer having the OH and $NHCH_3$ groups in trans position is more stable in the erythro isomer than in the threo one. In addition it may be said from the comparison of the intensity ratios that the trans isomer is more aboundant in 1, 2-diphenyl-2-methylaminoethanols than in ephedrines. These considerations on the equilibrium ratio of the rotational isomers can also be obtained by taking account of the repulsion between the larger phenyl groups in the conformation of the erythro compound shown in Fig. 4, although the presence of the stable trans isomer in the threo compound seems to be difficult to explain.

$\Delta\nu$ for the erythro isomer ($151\,cm^{-1}$) and the threo isomer ($193\,cm^{-1}$) are smaller than the corresponding isomers of ephedrine (168 and $203\,cm^{-1}$) and N-methylephedrine (157 and $238\,cm^{-1}$). This may be explained as follows. For the erythro isomer a larger repulsion between the phenyl groups of the gauche type molecule (Fig. 4) than that between the methyl and phenyl groups in ephedrine will give rise to a longer O–N distance and a smaller $\Delta\nu$ value than those in ephedrine. For the threo isomer, it can be expected that the repulsion between the phenyl groups will make $\Delta\nu$ larger than that of ephedrine. However, the experimental result is the reverse. Considering this fact another gauche isomer which has two phenyl groups in trans position may be more stable than that shown in Fig. 4 and show the smaller $\Delta\nu$ value as observed.

From the results obtained through this series of experiments, it can be concluded that the values of $\Delta\nu$ due to OH---N intramolecular hydrogen bond are more or less dependent on the kind and the nature of substituents attached to the asymmetric carbon atoms in ephedrine-like molecules. It has been observed, however, that $\Delta\nu$'s of the erythro (normal) isomers are always smaller than those of the threo (pseudo) isomers. The present finding of the presence of the intramolecular OH---N hydrogen bond in the erythro isomers as well as in the threo isomers may be related to the chemical fact that a crystalline ephedrine-copper complex can be prepared, although it is much less stable than ψ-ephedrine complex in aqueous organic solvent[4].

The author wishes to express his sincere thanks to Professor I. Nitta of Osaka University for his kind guidance and Dr. T. Shimanouchi of Tokyo University for his valuable advice. The Author's thanks are also due to Dr. S. Kuwada and Dr. A. Watanabe in this Laboratory for their continued encouragement.

Research Laboratory Takeda Pharmaceutical Industries, Ltd., Osaka

---

[4] *Z.* Földi, T. Földi and A. Földi, *Chemistry and Industry*, 1297 (1955).