# *Studies on the Infrared Spectra of Ephedrine and Related Compounds. I. On the Discrimination between Diastereoisomeric Ephedrines*

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The discrimination whether a compound like ephedrine, which has two asymmetric carbons, belongs to the erythro or threo series has been tried by various physical or chemical methods. For example, it was reported that a large difference in the rate of $N \rightarrow O$ acyl migration in N-acyl ephedrine and in N-acyl Ψ-ephedrine was available for the discrimination between diastereoisomeric ephedrines, N-methylephedrines and 1, 2-diphenyl-2-methylaminoethanols-(1)[1]. On the other hand, the fact that pKa of Ψ-ephedrine is larger than that of ephedrine was applied to the determination of the relative configuration of 8- and 9-carbon atoms in quinine and quinidine[2]. It was also reported that from the observations of the infrared absorption spectra no general relationship was obtained for the discrimination between diastereoisomers of β-oxyamino-acids[3] and chloramphenicols[4], although it had been postulated that in their spectra finger print region should show marked differences.

Many chemical evidences revealed that spatial configuration of erythro compound like ephedrine differed from that of Ψ-ephedrine[5] and that hydroxyl and methylamino groups were placed near each other in Ψ-ephedrine and far apart in ephedrine. However, recent investigations of crystal structure of ephedrine hydrochloride[6] and of reaction mechanism of ephedrine[7] confirmed spatial approach of the two polar groups also in ephedrine. Accordingly there seems to be a contradiction between these results and the old conclusions. If the earlier view of spatial configurations of diastereoisomeric ephedrines be correct, there should be hydrogen bond between the hydroxyl and methylamino groups only in Ψ-ephedrine. Then it will be expected reasonably that the existence of this hydrogen bonding should cause some characteristic difference in the infrared spectra of diastereoisomers.

One of the purposes of the present investigation is to find some correlation, if any, useful for the discrimination between diastereoisomers in the infrared spectra of ephedrines and related compounds.

## Experimental

**Materials.**—All compounds used in the present experiments were prepared by Dr. K. Tanaka

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[1] G. Fodor, V. Bruckner, J. Kiss and G. Ohegi, *J. Org. Chem.*, **14**, 337 (1949).

[2] V. Prelog and O. Haefliger, *Helv. Chim. Acta*, **33**, 2021 (1950).

[3] H.E. Carter, J.B. Harrison and D. Shapiro, *J. Am. Chem. Soc.*, **75**, 4705 (1953); E.D. Bergmann, H. Bendas and E. Resnick, *J. Chem. Soc.*, **1953**, 2564; W.A. Bolhofer, *J. Am. Chem. Soc.*, **71**, 1322 (1954).

[4] R.A. Cutler, C.M. Martini and F.C. Nachod, *J. Am. Pharm. Assoc. Sci. Ed.*, **43**, 697 (1954).

[5] L.H. Welsh, *J. Am. Chem. Soc.*, **71**, 3500 (1949); W.J. Close, *J. Org. Chem.*, **15**, 1131 (1950); K. Tanaka, *J. Pharm. Soc. Japan*, **70**, 212, 216, 220 (1950).

[6] G.D. Phillips, *Acta Cryst.*, **7**, 159 (1954).

[7] M. Murakami and T. Fukumoto, *J. Chem. Soc. Japan* (*Pure Chem. Sect.*), **76**, 270 (1955).

and Mr. S. Sugawa and their m.p.'s and $[\alpha]_D$'s were consistent with the already reported values.

**Solvents.**—*Chloroform.*—Washed with dilute NaOH solution, and water, distilled after drying with anhydrous sodium sulfate and before use, dried with phosphorous pentoxide for two hours.

*Carbon tetrachloride.*—Washed with conc. sulfuric acid, dilute NaOH solution and water. After drying with anhydrous sodium sulfate, distilled over phosphorous pentoxide through a 40 cm., glass helix-packed column. Used after confirmation of the elimination of water by the absence of OH absorption at $2.70\ \mu$ in a 2 cm. cell.

**Infrared Measurement.**—A Perkin-Elmer double beam infrared spectrophotometer Model 21 was used. Spectra of solid materials were taken in Nujol mull with NaCl optics. The thickness of cell spacer was 0.01 mm. Concentration of chloroform solution was about 20 mg./cc. and a sealed cell of 0.056 cm. thickness with NaCl windows was used. The absorption of the solvent was compensated by placing a variable thickness cell filled with the solvent in the reference beam. The spectra in the case of NaCl optics were taken under the following conditions; gain 5, response 1, suppression 4, resolution 3. The spectra of carbon tetrachloride solution were taken with LiF prism in a 2 cm. glass cell having calcium fluoride windows. Ammonia-treated casein paste was used to attach the windows to the glass cell. The absorption curves were obtained by subtraction of optical densities of solvent from that of solution. The following operating conditions were used (LiF); gain 7, response 2, slit $30\ \mu$, suppression 0, scanning speed 10–15 min./$\mu$. Under these conditions the absorption spectra of ethylene glycol and N-methyl acetamide in the dilute carbon tetrachloride solutions were in good agreement with those reported by other authors[8].

TABLE I

ABSORPTION BANDS OF SOLID MATERIALS IN $3\ \mu$ REGION

| Substance | Absorption bands ($cm^{-1}$) | | |
|---|---|---|---|
| *dl*-ephedrine hydrochloride | 3333 (3333)* | 2740 | 2460 |
| *l*- 〃 | 3328 (3330) | 2740 | 2460 |
| *dl*-*Ψ*-ephedrine hydrochloride | 3260 (3247) | 2710 | 2455, 2425 |
| *d*-*Ψ*- 〃 | 3250 (3230) | 2710 | 2465, 2425 |
| *dl*-ephedrine | 3300 (3300) | | 2340 (?) |
| *l*-ephedrine (liquid) | 3290 | 2786 | |
| 〃 (solid)** | | | 2330 (?) |
| *dl*-*Ψ*-ephedrine | 3300 (3290) | | 2350 |
| *d*-*Ψ*- 〃 | 3200 (3216) | | |
| *dl*- and *l*-1-chloro-1-phenyl-1-2-methyl-aminopropan hydrochloride | | 2670 | 2460 |
| *dl*- and *d*-*Ψ*-1-chloro-1-phenyl-2-methyl-aminopropan hydrochloride | | 2670 | 2470, 2430 |
| *dl*-N-benzoyl ephedrine | 3310 | 2660 | |
| *dl*-N-benzoyl *Ψ*-ephedrine | 3240 | 2660 | |
| *dl*-O-benzoyl ephedrine hydrochloride | | 2700 | 2450 |
| *dl*-O-benzoyl *Ψ*-ephedrine hydrochloride | | 2700 | 2415 |
| *l*-N-methylephedrine | *** | | 2350 (?) |
| *d*-*Ψ*-N-methylephedrine (liquid) | 3330 | 2780 | |
| *dl*-N-methylephedrine hydrochloride | 3215 | 2674 | 2494, 2421 |
| *dl*-erythro-1, 2-diphenyl-2-methylamino-ethanol-(1) hydrochloride | 3280 | | 2421, 2300 |
| *dl*-threo-1, 2-diphenyl-2-methylamino-ethanol-(1) hydrochloride | 3290 | 2667 | 2494, 2353 |

* Values in parentheses were taken with LiF prism in perfluorocarbon mull.

** Monohydrate.

*** A broad band superposed on CH absorption.

## Experimental Results and Discussion

**A. Absorption Spectra of Solid Materials**

**3600–1800 $cm^{-1}$ Region.**—In this region the appearance of absorption bands due to OH and NH stretching vibrations are expected. As shown in Table I, most of the compounds examined show only one band near 3300 $cm^{-1}$, but exceptions are diastereoisomers of 1-chloro substituted ephedrine hydrochlorides and of O-benzoyl ephedrine hydrochloride, which have no OH group and no absorption band near 3300 $cm^{-1}$. These two compounds, however, show a well-defined band near 2400 $cm^{-1}$, which is observed also in the

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[8] a) L.P. Kuhn, *J. Am. Chem. Soc.*, 74, 2492 (1952); b) M. Tsuboi, *Bull. Chem. Soc. Japan*, 22, 215 (1948).

spectra of ephedrine hydrochlorides, not so marked in those of ephedrines and absent in those of N-benzoyl compound having no NH group. Since a band near 3300 cm$^{-1}$ of N-methyl ephedrine and N-benzoyl ephedrines is undoubtedly due to OH group, it seems to be reasonable to assign $\nu$ (OH) to the band near 3300 cm$^{-1}$.

Following the above-mentioned assignment of $\nu$ (OH), it may be said that absorption due to free NH vibration, for which Randall et al.[9] quote an overall range of 3480–3050 cm$^{-1}$, is absent near 3300 cm$^{-1}$. Therefore, either a band near 2700 cm$^{-1}$ or one near 2400 cm$^{-1}$ may be due to perturbed NH vibration. The latter band seems to be due to the ionic form like $>NH_2^+$, at least in the case of hydrochlorides, because the evidences for the existence of such a band were found in the cases of bydrochlorides of triethylamine (2540 cm$^{-1}$)[10], pyridine (2425 cm$^{-1}$)[10], myosmine and nicotine (2560–2360 cm$^{-1}$)[11], and in the fact that N-benzoyl ephedrine without NH group shows no absorption near 2400 cm$^{-1}$. As to the absorption band near 2700 cm$^{-1}$ it seems to be related not to NH group, but to N-$CH_3$ group as will be seen in chloroform solution, since this band is observed forN-methylephedrine and N-benzoyl ephedrine, having no NH group.

Three absorption bands in the 1950–1800 cm$^{-1}$ region can be ascribed to a monosubstituted benzene ring from their position and intensity relationship[12].

It will be noticed that there are systematic differences in $\nu$ (OH) of hydrochlorides of diastereoisomeric ephedrines near 3300 cm$^{-1}$. That is, $\Psi$-ephedrine hydrochloried shows an absorption of frequency about 100 cm$^{-1}$ lower than that of ephedrine hydrochloride and the corresponding racemic modifications. The same is the case for N-benzoyl compounds, but not so marked in the cases of ephedrines and 1, 2-diphenyl-2-methylamino-ethanols-(1). From these observations and the generally accepted explanation that formation of hydrogen bond in a crystal causes a lowering of the OH absorption frequency from its normal position and that the magnitude of the shift is related to the strength of the hydrogen bond, it will be said that the hydrogen bond is formed in crystals of both of the corresponding diastereoisomers, it being only stronger in $\Psi$-ephedrine than in the normal one. Although such a tendency cannot be said to be general for all of the test compounds in crystalline state, it is worth noticing that a difference in the OH absorption frequency is found between diastereoisomers and between optically active, *d*- or *l*-compound and the corresponding recemic modification.

**1800–1600 cm$^{-1}$ Region.**—From Figs. 1 and 2 it is seen that a band common to all compounds appears at 1600 cm$^{-1}$. Absorption bands which are expected to appear in this region are those due to a benzene ring and NH deformation vibration. Since the latter band is generally very weak, the 1600 cm$^{-1}$ band may be assigned to C-C vibration of benzene ring in conjunction with 1500 cm$^{-1}$ band observed[12].

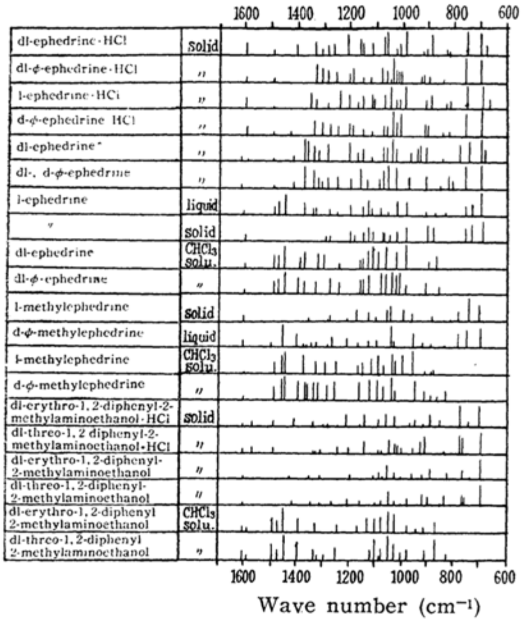

Fig. 1. Absorption spectra of ephedrine and related compounds in Nujol mull and in chloroform solution: 1600–600 cm$^{-1}$.

N-benzoyl compounds show a strong band near 1600 cm$^{-1}$, which may be due to C=O vibration of the benzoyl group (Fig. 2). For it can be considered that hydrogen bonding may lower the C=O frequency from 1670–1630 cm$^{-1}$, which is normal absorption frequency range for C=O group in disubstituted amide[12], to 1590–1613 cm$^{-1}$. Here again, pseudo compounds give a lower C=O frequency than that of the normal ones. On the other hand, O-benzoyl compounds also show a C=O band of slightly lower frequency (1715 cm$^{-1}$) than that for the C=O group in

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[9] H.M. Randall, R.G. Fowler, N. Fuson and J.R. Dangle, "Infrared Determination of organic structures", Van Nostrand (1949).

[10] R.C. Lord and R.E. Merrifield, *J. Chem. Phys.*, **21**, 166 (1953).

[11] B. Witkop, *J. Am. Chem. Soc.*, **76**, 5597 (1954).

[12] L.J. Bellamy, "The infrared spectra of complex molecules", Methuen & Co. London (1954).

methyl benzoate (1754 cm$^{-1}$)[13].

**Finger Print Region.**—From a survey of the spectra of all the compounds examined in the finger print region, it is noticed that there is a marked difference between the spectra of diastereoisomer for both optically active and corresponding racemic pairs. If there is any systematic difference in band position, this will be available for the discrimination between diastereoisomers. Bolhofer[3] attributed the erythro structure to the substituted $\beta$-phenyl-serines showing a band at 11.90–11.95 $\mu$ (840 cm$^{-1}$). However, his assignment stands in contradiction with observation by Cutler et al.[4] on the substituted chloramphenicols and that on the present series of compounds.

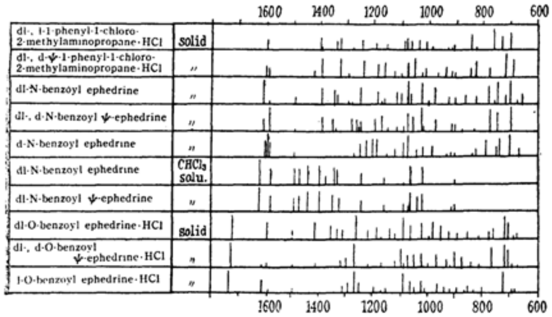

Fig. 2. Absorption spectra of ephedrine derivatives: 1800–600 cm$^{-1}$.

It is usually accepted that the absorption due to secondary alcohol occurs near 1100 cm$^{-1}$ and 1300 cm$^{-1}$ [12], the former being fairly strong. As seen in Figs. 1 and 2, there appears a strong band within a range of 1030–1060 cm$^{-1}$, the position of which varies depending on compounds. It will be noticed that the pseudo-compounds give a lower frequency absorption than that of the normal ones, except ephedrine and $\Psi$-ephedrine. This fact may be used to discriminate diastereoisomers in conjunction with the absorption in other region such as 3 $\mu$ region.

Besides these, the following observation may be added that $\Psi$-ephedrine, N-benzoyl $\Psi$-ephedrine, O-benzoyl $\Psi$-ephedrine hydrochloride and both diastereoisomers of 1-chloro-substituted ephedrine give the same spectra for both the optically active compound and its racemic modification. These facts may suggest that some factors like steric configuration of molecule and the existence of a polar group capable of forming hydrogen bond affect the formation of crystal of racemic compounds as Sensi and Fagioli[14] observed on chloramphenicols.

### B. Absorption Spectra in Chloroform Solution

In Fig. 3 absorption spectra in 3 $\mu$ region of chloroform solutions of ephedrines, N-methylephedrines, 1, 2-diphenyl-2-methylaminoethanols-(1) and N-benzoyl ephedrines are shown. There is a remarkable similarty among these spectra; that is, all of the compounds examined show two bands in a region 2.7–3.2 $\mu$, one of which is sharp (the higher frequency) and the other is broad (the lower frequency). The higher frequency band near 2.7 $\mu$ may be due to free OH vibration, but the lower one near 3.1 $\mu$ will be due to hydrogen-bonded OH vibration, free NH vibration or superposition of these. Since in N-methylephedrine the lower frequency absorption can be ascribed undoubtedly to the bonded OH vibration, the

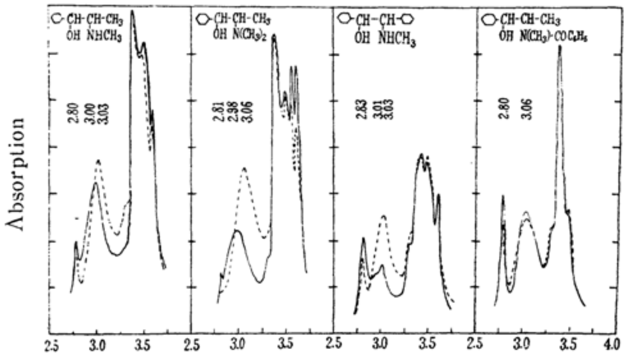

Fig. 3. Absorption of ephedrine and related compounds in chloroform solution (~0.1 mol./l.) near 3 micron.
——— erythro (normal), - - - - - threo (pseudo). NaCl prism.

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[13] E. J. Hartell, R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, **1948**, 1436.

[14] P. Sensi and O. Fagioli, *Gaz. Chim. Italiana*, **83**, 73 (1953).

same assignment seems to be reasonable for the other compounds. Moreover, the frequency difference between the sharp band and the broad one seems to be larger for pseudo-compounds than for normal ones, except in the case of N-benzoyl ephedrines.

The absorption bands near 3.4 μ are assigned to CH stretching vibration of methyl and -$CH_2$- groups. 3.59 μ band of ephedrine, 3.56 μ band of 1, 2-diphenyl-2-methylaminoethanol-(1) and 3.56 μ and 3.62 μ bands of N-methyl ephedrine, which are lower than any of CH vibration frequency of saturated hydrocarbon, could be regarded as due to $CH_3$-N group.

The absorption due to monosubstituted benzene derivatives in 2000–1800 cm$^{-1}$ region appear very clearly in the spectra of chloroform solution. Absorption spectra with frequency lower than 1600 cm$^{-1}$ are shown in Figs. 1 and 2. The spectra of the diastereoisomers show closer similarity than those in solid state. A strong band near 1000–1100 cm$^{-1}$ has the same position for both isomers, except for ephedrines.

### C. Absorption Spectra of Dilute Carbon Tetrachloride Solution[15]

As mentioned above a molecule like ephedrine may have an intramolecular hydrogen bond and this should be proved by spectra taken in a dilute carbon tetrachloride solution within the concentration range causing no intermolecular association. To ascertain more precisely the results of chloroform solution, spectra of diastereoisomers in 3 μ region were taken in carbon tetrachloride solution under a concentration of about 0.005 mol./l., by using LiF prism. The results are shown in Fig. 4.

In this case also, all compounds give very similar spectra, consisting of a higher frequency sharp band (3615–3621 cm$^{-1}$) and a lower frequency broad band (3329–3466 cm$^{-1}$). However, it is worthy of notice that only exceptionally erythro 1, 2-diphenyl-2-methylaminoethanol-(1) shows two sharp bands near 3600 cm$^{-1}$. The difference in the frequency of the sharp and the broad band is always greater in a pseudo compound ($\Delta\nu$=ca. 200 cm$^{-1}$) than in the corresponding normal one ($\Delta\nu$=ca. 150 cm$^{-1}$). Thus, the results obtained in chloroform solutions were fully confirmed. According to the generally accepted explanation the sharp bands (3615–3621 cm$^{-1}$) may be attributed to free OH vibration and the broad ones (3329–3466 cm$^{-1}$) to the hydrogen-bonded OH vibration. Since the concentration dependence of the ratio of the optical densities of the two bands was not appreciable and also since it was reported from the result of molecular weight determination in benzene solution that the association of the alkamines did not occure over the concentration range such as in the present experiments[16], it might be said that in a sense the hydrogen bond is that of an intramolecular type. Then, it will be concluded that a hydrogen bond exists in molecules of both of corresponding diastereoisomers, only strong in Ψ-ephedrine than in a normal one. This conclusion confirms the above-mentioned suggestion based on results of the experiments in the solid state and chloroform solution, and the discrimination between diastereoisomers of ephedrine and its derivatives can be carried out simply and clearly by comparing the magnitude of the frequency difference between the free and the hydrogen-bonded OH vibrations.

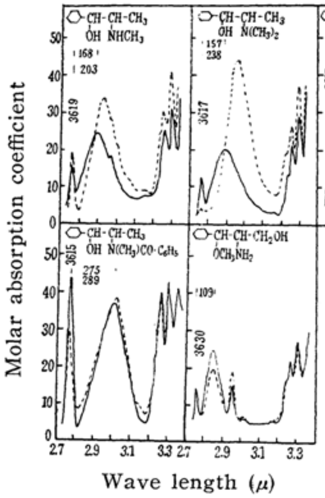

Fig. 4. Absorption of ephedrine and related compounds in carbon tetrachloride solution (∼0.005 mol./l.) near 3 micron.
——— erythro (normal),
- - - - - threo (pseudo). LiF prism.

On applying this method of discrimination between diastereoisomers to other compounds, it should be noted that the method is only applicable to compounds having two polar groups directly attached to the two adjacent asymmetric carbon atoms like ephedrines and forming a five-membered hydrogen bond ring. For example, N-benzoyl ephedrine isomers show almost the same frequency difference, because of the formation of a six-membered hydrogen bond ring, probably formed between OH and C=O group in the benzoyl radical (Fig. 4). Another example is shown in Fig. 4. 1-Phenyl-1-methoxy-2-aminopropanol-(3)

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[15] Partly reported as communication. T. Kanzawa, *Pharm. Bull.*, **3**, 71 (1955).

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

which may form hydrogen bond between the amino group attached to asymmetric carbon and the OH group in the terminal $CH_2OH$, shows almost identical band position for diastereoisomers.

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