*Aust. J. Chem.*, 1975, **28**, 49–56

# Physicochemical Study on Some Synthesized Oxazolidine Derivatives: Differentiation of Diastereomers

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*Abstract*

The synthesis of 15 diastereomeric oxazolidine derivatives of the type 2-(substituted phenyl)-3,4-dimethyl-5-phenyloxazolidine is reported. The specific as well as the molecular rotations of 31 diastereomeric oxazolidine derivatives of the same type of structure were determined. The *cis* compounds have higher specific and molecular rotation than the corresponding *trans* isomers. Substitution in the *ortho* or *para* position increased specific and molecular rotation while substitution in the *meta* position had an opposite effect.

The infrared spectra of 26 oxazolidine derivatives, having either a *cis* or a *trans* type of configuration, have been recorded in the range 2000–700 $cm^{-1}$.

## Introduction

The condensation of carbonyl compounds with amino alcohols to give oxazolidine derivatives has been reported in the literature. The behaviour towards carbonyl compounds of diastereomeric pairs of amino alcohols was studied by Bergmann[1] who reported the condensation of benzaldehyde with ephedrine and pseudoephedrine which, as secondary amines, gave oxazolidine derivatives. A number of *N*-substituted 2-aryloxazolidines were prepared[2] by refluxing equimolar amounts of amino alcohol and aromatic aldehyde in benzene under a Dean and Stark trap. Oxazolidine derivatives containing a phenyl group were found to be crystalline solids and when the nitrogen atom was substituted with a methyl group the products were colourless thin oils distilling in vacuum without decomposition. Some 3-aryloxazolidines[3] and a large number of oxazolidine derivatives[4] were synthesized, studied physiologically and stereochemically investigated.

A series of 5-aryl and 2-aryl oxazolidine derivatives were prepared by the reaction of aminoethanol derivatives, in the form of their hydrochloride salts, with the calculated amounts of the carbonyl compounds in the presence of 40% sodium hydroxide solution.[5] Hermann and his associates[6] reported the preparation of a number of oxazolidine derivatives from ephedrine and pseudoephedrine and different aromatic and alicyclic aldehydes. These authors noted the unstable nature of the diastereomeric pairs of the type 3,4-dimethyl-5-phenyloxazolidine by establishing their hydrolysis

[1] Bergmann, E. D., *Chem. Rev.*, 1953, **53**, 309.
[2] Uskeuko, N. K., and Baranon, S. N., *Ukr. Khim. Zh.*, 1953, **19**, 639 (*Chem. Abstr.*, 1955, **49**, 11623).
[3] Gorin, I. F., and Vysokosov, A. N., *Zh. Obshch. Khim.*, 1954, **24**, 18 (*Chem. Abstr.*, 1955, **49**, 13222).
[4] Bergmann, E. D., and Resnick, H., *J. Chem. Soc.*, 1956, 1662.
[5] Foldi, Z., *Acta Chim.* (Budapest), 1956, 339.
[6] Hermann, P., and Kirschner, G., *Justus Liebigs Ann Chem.*, 1958, **614**, 149.

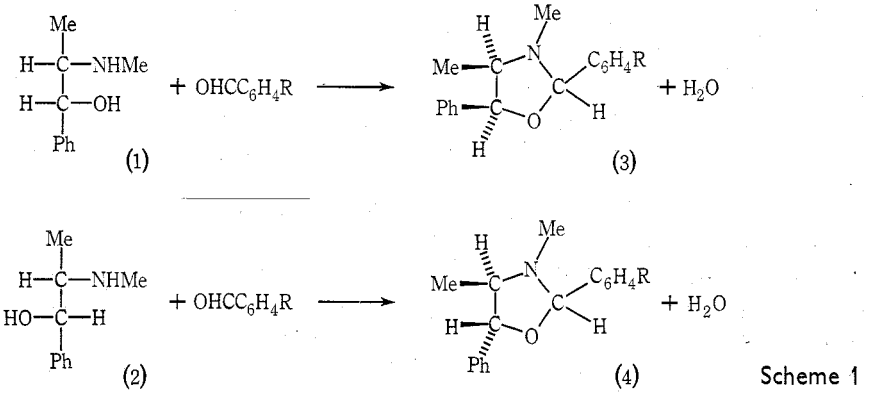
rate and concluded that the *cis* derivatives should be less stable than the corresponding *trans* isomers because of the steric hindrance due to methyl–phenyl interaction in the *cis* position.

Cleary[7] prepared some oxazolidine derivatives by azeotropic distillation in benzene. Soliman *et al.*[8] in a study of the behaviour of diastereomeric pairs of amino alcohols towards carbonyl compounds used anhydrous sodium sulphate, as a dehydrating agent, to effect the condensation.

Marginal antimalarial activity was demonstrated by amino alcohols obtained by room-temperature catalytic hydrogenation of oxazolidine derivatives prepared[9] by the condensation of 2-substituted aminoethanol and carbonyl compounds such as *p*-chlorobenzaldehyde and 1-methylpiperidin-4-one. In a search for drugs to counteract the clinical potassium-excreting and sodium-retaining effect of aldosterone Sharma *et al.*[10] undertook the preparation of compounds of the type spiro[androstane-17,5'-oxazolidine] and studied their n.m.r. spectra.

Searching the literature for assignments and interpretations of infrared absorption bands due to oxazolidine derivatives revealed the presence of few reports about the differentiation between oxazolidine ring structure and Schiff bases.[1,11] The structure of a Schiff base was verified by means of infrared spectroscopy as a result of the presence of an aliphatic OH as well as –C=N–. It was established by infrared absorption study that the products obtained from the condensation of aminoethanol and aromatic $\alpha,\beta$-unsaturated carbonyl compounds were Schiff bases and not oxazolidines.[12] However, most of these studies were made on a limited number of compounds.

To our knowledge there has been no attempt to differentiate between *cis* and *trans* diastereomeric oxazolidines, yielded by the condensation of (−)-ephedrine and (+)-pseudoephedrine and substituted benzaldehydes, by means of infrared absorption study.




Scheme 1

In the present work a number of oxazolidine derivatives of the type 2-(substituted phenyl)-3,4-dimethyl-5-phenyloxazolidine were prepared by the condensation of (−)-

[7] Cleary, R., Ph.D. Dissertation, Ohio State University, Columbus, 1964.
[8] Soliman, S. A., El-Nenaey, S. A., and Roushdi, I. M., *U.A.R. J. Chem.*, 1970, **13**, 1.
[9] Ager, J. H., and May, E. L., *J. Pharm. Sci.*, 1969, **58**, 499.
[10] Sharma, R. K., Doorenbos, N. J., and Bhecca, N. S., *J. Pharm. Sci.*, 1971, **60**, 1677.
[11] Daasch, L. W., and Hanninen, M. E., *J. Amer. Chem. Soc.*, 1950, **72**, 3674.
[12] Bergmann, E. D., *Rec. Trav. Chim. Pays-Bas*, 1951, **71**, 213.

ephedrine (1) or (+)-pseudoephedrine (2) and a series of substituted benzaldehydes to give the *cis* (3) and *trans* (4) diastereomers respectively according to Scheme 1. These compounds were used for a spectra–structure correlation study of the oxazolidine ring system and for a comparative study of the physical and chemical properties of the diastereomers.

## Experimental

*Apparatus and Materials*

The polarimeter used was a Zeiss Jena 185119 instrument equipped with a sodium lamp and a propagation tube 50 mm in length; (−)-ephedrine was obtained from Rhone–Poulenc; (+)-pseudoephedrine hydrochloride from Burroughs Wellcome.

The preparation of *m*-iodobenzaldehyde was carried out by the reaction of iodine with freshly distilled benzaldehyde in 80% sulphuric acid solution containing silver sulphate. The reaction product was recrystallized from ethanol–water, m.p. 58° (lit.[13] 58°).

Melting points were determined in a Gallenkamp melting point apparatus and are uncorrected.

*General Method for the Preparation of* cis- *and* trans-*2-(Substituted Phenyl)-3,4-dimethyl-5-phenyloxazolidine Derivatives*

To 0·01 mol of (−)-ephedrine or (+)-pseudoephedrine in 60·0 ml of dry benzene, an equimolar quantity of the respective substituted benzaldehyde was added and solution was effected by gentle heating if necessary. About 1·0 g of anhydrous sodium sulphate that had been heated at 105° for 4 h was added. The mixture was slowly brought to boiling and heated under reflux for 3 h. It was filtered while hot to separate the sodium sulphate and the filter was washed with hot benzene. The benzene in the combined filtrate and washings was distilled off and the remaining oily residue dissolved in hot ethanol. The oxazolidine derivative crystallized as the solution was cooled in the refrigerator. A further crop of crystals was obtained from the mother liquor.

*Compounds of the* cis *Series (from (−)-Ephedrine)*

(i) cis-*2*-(m-*Iodophenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, yellow needles from ethanol, m.p. 64·5–65·5°; yield 95% (Found: C, 53·5; H, 4·8; N, 3·9. $C_{17}H_{18}INO$ requires C, 53·8; H, 4·8; N, 3·7%).

(ii) cis-*2*-(*3,4-Dichlorophenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 84–85°, 86% yield (Found: C, 63·5; H, 5·4; N, 3·6. $C_{17}H_{17}Cl_2NO$ requires C, 63·4; H, 5·3; N, 4·3%).

(iii) cis-*2*-(*2,4-Dichlorophenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 85–86°, 90% yield (Found: C, 63·4; H, 5·6. $C_{17}H_{17}Cl_2NO$ requires C, 63·4; H, 5·3%).

(iv) cis-*2*-(o-*Methoxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 103–104°, 85% yield (Found: C, 76·9; H, 8·2. $C_{18}H_{21}NO_2$ requires C, 76·3; H, 7·5%).

(v) cis-*2*-(o-*Bromophenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 123–124°, 92% yield (Found: C, 61·0; H, 5·1. $C_{17}H_{18}BrNO$ requires C, 61·3; H, 5·4%).

(vi) cis-*2*-(p-*Ethoxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 90–91°, 90% yield (Found: C, 75·9; H, 8·2. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·7%).

*Compounds of the* trans *Series (from (+)-Pseudoephedrine)*

(vii) trans-*2*-(m-*Iodophenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 75–76°, 95% yield (Found: C, 53·5; H, 4·5; N, 3·9. $C_{17}H_{18}INO$ requires C, 53·8; H, 4·8; N, 3·7%).

(viii) trans-*2*-(o-*Methoxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, white needles from ethanol–water, m.p. 128–129°, 80% yield (Found: C, 76·2; H, 7·1; N, 4·1. $C_{18}H_{21}NO_2$ requires C, 76·9; H, 7·4; N, 4·9%).

(ix) *trans*-2-(*p*-Hydroxyphenyl)-3,4-dimethyl-5-phenyloxazolidine, white needles from ethanol–water mixture, m.p. 216–217° (lit.[7] 217°), 80% yield (Found: C, 75·7; H, 7·5; N, 5·5. Calc. for $C_{17}H_{19}NO_2$: C, 75·8; H, 7·1; N, 5·2%).

[13] Bakker, I. R., and Waters, W. A., *J. Chem. Soc.*, 1952, 150.

(x) trans-*2*-(m-*Hydroxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 142–143°. The yield of analytically pure white crystals after recrystallization from ethanol by the addition of water was 78% (Found: C, 75·0; H, 6·8. $C_{17}H_{19}NO_2$ requires C, 75·8; H, 7·1%).

(xi) trans-*2*-(o-*Hydroxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 80–81°, 85% yield (Found: C, 76·0; H, 7·1. $C_{17}H_{19}NO_2$ requires C, 75·8; H, 7·1%).

(xii) trans-*2*-(p-*Ethoxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 74–75°, 85% yield (Found: C, 76·2; H, 7·1. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·7%).

(xiii) *trans*-2-(*p*-Methylphenyl)-3,4-dimethyl-5-phenyloxazolidine, m.p. 62–63° (lit.[7] 62°). The solid was dissolved in hot ethanol and diluted to turbidity with water; yield 94% (Found: C, 81·0; H, 8·2. Calc. for $C_{18}H_{21}NO$: C, 80·9; H, 7·9%).

(xiv) trans-*2*-(*2,4-Dimethoxyphenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 78–79°, 90% yield (Found: C, 72·3; H, 7·9. $C_{19}H_{23}NO_3$ requires C, 72·8; H, 7·3%).

(xv) trans-*2*-(*3,4-Dichlorophenyl*)-*3,4-dimethyl-5-phenyloxazolidine*, m.p. 68–69°, 85% yield (Found: C, 64·0; H, 5·0. $C_{17}H_{17}Cl_2NO$ requires C, 63·4; H, 5·2%).

*Infrared Spectra*

The infrared spectra of the oxazolidine derivatives investigated were determined on a Perkin–Elmer 237B infrared spectrophotometer. The compounds were prepared as Nujol mulls.

*Determination of Optical Rotation*

Solutions were injected into the polarimeter tube by means of a hypodermic syringe. The zero of the instrument was determined with absolute methanol. Measurements were taken at a temperature of 25±2°. Results are listed in Table 3 below.

## Results and Discussion

Table 1 lists the major absorption bands in the range 2000–700 $cm^{-1}$ found to be characteristic of the oxazolidine ring structure. It can be readily seen that all the oxazolidine derivatives studied are characterized by three absorption bands whose ranges of correlation frequencies are narrow. The first band occurring in the range 1230–1195 $cm^{-1}$ is a strong absorption band and was found to be centred at 1200 $cm^{-1}$ in the majority of the compounds studied.

The second characteristic absorption band was located at 1150–1130 $cm^{-1}$ and found to be variable in nature. In most compounds studied, however, it is a strong band. The third band, located in the range 1090–1075 $cm^{-1}$, was also given by all oxazolidine derivatives investigated. In some cases more than one band is observed, but this may be due to splitting of a single broad band. The constancy and persistence of the occurrence of these three bands throughout the diastereomeric oxazolidine series permits assignment of absorption in these regions to the oxazolidine ring system. This assignment is in agreement with Bergmann's[1] findings, who in his attempt to differentiate between a Schiff base and simple oxazolidines derived from amino-ethanol, assigned absorption bands in the range 1200–1080 $cm^{-1}$ to the O–C–N structure of the oxazolidine ring system.

The majority of the oxazolidine derivatives investigated yielded two further characteristic absorption bands. The fourth band is a strong one and is located in the range 1190–1160 $cm^{-1}$, generally centred at 1175 $cm^{-1}$. This band is absent only when the substituent is in the *meta* position (compounds 13–18). However, the *m*-hydroxy derivative (compound 21) exhibited a small shoulder. The presence of such a band, therefore, may be used to indicate *ortho* or *para* substitution. The fifth characteristic band, in the range 1120–1105 $cm^{-1}$, is of medium intensity when compared with the

**Table 1. Infrared absorption bands characteristic of the oxazolidine ring system of the *cis* and *trans*-2-(substituted phenyl)-3,4-dimethyl-5-phenyloxazolidines**

| Compound | Configuration | Substituent | Frequency ($cm^{-1}$) (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|---|---|
| 1 | *cis* | H | 1200 | 1130 | 1080 | 1175 | 1120 |
| 2 | *trans* | H | 1200 | 1145sh | 1080sh | 1175sh | 1125 |
| 3 | *cis* | *p*-$CH_3$ | 1200 | 1145 | 1080 | 1185 | 1115 |
| 4 | *trans* | *p*-$CH_3$ | 1200 | 1145w | 1075sh | 1175w | 1120 |
| 5 | *cis* | *p*-OH | 1200 | 1145 | 1090 | 1170 | 1110 |
| 6 | *trans* | *p*-OH | 1225 | 1145w | 1100 | 1175 | 1125 |
| 7 | *cis* | *p*-$OCH_3$ | 1200 | 1130 | 1080 | 1170 | 1115 |
| 8 | *trans* | *p*-$OCH_3$ | 1200 | 1130 | 1080 | 1185 | 1110 |
| 9 | *cis* | *p*-$OC_2H_5$ | 1205sh | 1130w | 1080 | 1175 | 1110w |
| 10 | *trans* | *p*-$OC_2H_5$ | 1195 | 1140 | 1075 | 1160 | 1115 |
| 11 | *cis* | *p*-$NO_2$ | 1210 | 1135 | 1080 | 1180 | 1105 |
| 12 | *trans* | *p*-$NO_2$ | 1200sh | 1140 | 1075 | 1190 | 1105 |
| 13 | *cis* | *m*-Cl | 1190 | 1140 | 1090, 1080 | — | — |
| 14 | *trans* | *m*-Cl | 1200 | 1140 | 1090, 1080 | — | 1120 |
| 15 | *cis* | *m*-I | 1195 | 1135 | 1090 | — | — |
| 16 | *trans* | *m*-I | 1200 | 1140 | 1075 | — | 1120 |
| 17 | *cis* | *m*-$NO_2$ | 1195 | 1130 | 1090 | — | — |
| 18 | *trans* | *m*-$NO_2$ | 1195 | 1130 | 1090 | — | 1120 |
| 19 | *cis* | *o*-OH | 1210 | 1135sh | 1080 | 1170 | 1120 |
| 20 | *trans* | *o*-OH | 1210 | 1120w | 1080 | 1175 | 1110w |
| 21 | *trans* | *m*-OH | 1200 | 1140 | 1080 | 1175sh | 1120 |
| 22 | *cis* | *o*-Cl | 1225 | 1130 | 1085 | 1180 | — |
| 23 | *cis* | *o*-Br | 1220 | 1130 | 1090 | 1185 | — |
| 24 | *cis* | *o*-$NO_2$ | 1220 | 1130 | 1080 | 1190 | — |
| 25 | *cis* | spiro[A] | 1200 | 1145 | 1085 | 1180sh | 1120 |
| 26 | *trans* | spiro | 1200 | 1140 | 1080 | 1175sh | 1120 |

[A] 3,4-Dimethyl-5-phenyloxazolidine-2-spirocyclohexane.

**Table 2. Bands characteristic of the *cis* and *trans* derivatives**

| Compound | Substituent | Frequency ($cm^{-1}$) *cis* | *trans* | Frequency ($cm^{-1}$) *cis* | *trans* |
|---|---|---|---|---|---|
| 1, 2 | H | 1055 | 1040 | 1290 | 1260 |
| 3, 4 | *p*-$CH_3$ | 1060 | 1040 | 1290 | 1260 |
| 5, 6 | *p*-OH | 1075 | 1045 | 1275 | 1275 |
| 7, 8 | *p*-$OCH_3$ | 1050 | 1040 | 1290 | 1250 |
| 9, 10 | *p*-$OC_2H_5$ | 1055 | 1040 | 1300 | 1250 |
| 11, 12 | *p*-$NO_2$ | 1055 | 1035 | 1290 | 1260 |
| 13, 14 | *m*-Cl | 1055 | 1040 | 1280 | 1255 |
| 15, 16 | *m*-I | 1055 | 1040 | 1275 | 1255 |
| 17, 18 | *m*-$NO_2$ | 1055 | 1045 | 1290 | 1260 |
| 19, 20 | *o*-OH | 1055 | 1045 | 1260 | 1270 |
| 21 | *m*-OH | — | 1040 | — | 1255 |
| 22 | *o*-Cl | 1055 | — | 1280 | — |
| 23 | *o*-Br | 1055 | — | 1280w | — |
| 24 | *o*-$NO_2$ | 1060 | — | 1280 | — |
| 25, 26 | spiro[A] | 1060 | 1040 | 1270 | 1275 |

[A] 3,4-Dimethyl-5-phenyloxazolidine-2-spirocyclohexane.

first or second band. Among the compounds investigated some exceptions were noted (compounds 13, 15, 17 and 22–24).

Another characteristic absorption band of this series of compounds is located in the range 1060–1035 $cm^{-1}$. This band may be assigned to the C–O–C structure.[14] The data listed in Table 2 show that compounds with the *cis* configuration absorb at $1055 \pm 5$ $cm^{-1}$ and those with the *trans* configuration at $1040 \pm 5$ $cm^{-1}$.

Nakanishi[15] gives the range 1275–1175 $cm^{-1}$ for the in-plane bending vibration in a substituted phenyl system. The infrared absorption band characteristic of substituted phenyl[15] appeared in the spectra of the *cis* and *trans* oxazolidines investigated in the ranges 1290–1275 and 1260–1250 $cm^{-1}$ respectively. It is apparent here that the configuration does involve small shifts in the frequency of absorption in this region. As shown in Table 2, compounds having the *cis* configuration are, in general, characterized by higher absorption frequency in this region when compared with the *trans* stereomers. However, these small systematic differences observed are probably too small to be reliably useful to differentiate between the diastereomeric oxazolidine derivatives studied.

**Table 3. Specific and molecular rotation of the *cis* and *trans* derivatives**

| Substituent | *cis* series Cpd | $[\alpha]_D$ | $[M]$ | *trans* series Cpd | $[\alpha]_D$ | $[M]$ |
|---|---|---|---|---|---|---|
| H | 1[A] | −68·0° | −172·0 | 19[A] | +42·0° | +106·3 |
| *p*-$CH_3$ | 2[A,B] | −70·0 | −186·9 | — | — | — |
| *o*-OH | 3[B] | −96·1 | −258·6 | 20 | +64·0 | +172·2 |
| *p*-OH | 4[A,B] | −72·0 | −193·7 | 21[A] | +57·1 | +153·7 |
| *m*-OH | — | — | — | 22 | +40·0 | +107·6 |
| *o*-$OCH_3$ | 5 | −97·5 | −275·9 | — | — | — |
| *p*-$OCH_3$ | 6[B] | −60·0 | −169·8 | 23[C] | +46·0 | +130·2 |
| *p*-$OC_2H_5$ | 7 | −64·0 | −190·1 | 24 | +48·0 | +140·6 |
| *o*-Cl | 8[C] | −96·0 | −276·0 | — | — | — |
| *p*-Cl | 9[A,B] | −100·0 | −287·5 | — | — | — |
| *m*-Cl | 10[B] | −48·0 | −138·0 | 25[C] | +40·0 | +115·0 |
| *o*-Br | 11 | −125·0 | −416·3 | — | — | — |
| *m*-I | 12 | −50·0 | −189·5 | 26 | +26·8 | +101·9 |
| *o*-$NO_2$ | 13[B] | −100·0 | −298·0 | — | — | — |
| *p*-$NO_2$ | 14[A,B] | −96·0 | −286·1 | 27[A] | +50·0 | +149·0 |
| *m*-$NO_2$ | 15[B] | −44·0 | −131·1 | 28[C] | +32·0 | +95·4 |
| *m*-$CO_2H$, *p*-OH | 16[B] | −28·0 | −87·6 | 29[C] | +32·0 | +100·2 |
| *o*,*p*-di-Cl | 17 | −83·3 | −268·2 | — | — | — |
| *o*,*p*-di-$OCH_3$ | — | — | — | 30 | +16·0 | +50·1 |
| *m*,*p*-di-Cl | 18 | −60·0 | −193·2 | 31 | +33·3 | +107·2 |

[A] Ref. 7. [B] Ref. 8. [C] Soliman, S. A., unpublished data.

The specific and molecular rotations of the diastereomeric oxazolidine derivatives are listed in Table 3. In the formation of an oxazolidine derivative the sign of rotation of the diastereomeric amino alcohols, (−)-ephedrine or (+)-pseudoephedrine, was not affected by the condensation reaction and was retained by the produced *cis* or *trans* compounds. From these data it is possible to note that all the *cis* isomers have

[14] Bellamy, L. J., 'The Infrared Spectra of Complex Molecules' pp. 115, 76–8 (Methuen: London 1966).
[15] Nakanishi, K., 'Infrared Absorption Spectroscopy' p. 26 (Holden-Day: San Francisco 1962).

the greater magnitudes of specific and molecular rotation. The only exception noted is the diastereomeric pair 2-(*m*-carboxy-*p*-hydroxyphenyl)-3,4-dimethyl-5-phenyl-oxazolidine where the *cis* and *trans* configurations showed close specific rotation values of $-28{\cdot}0°$ and $+32°$ respectively.

Substitution in the *para* or *ortho* position with different substituents such as methyl, hydroxy, chloro, bromo and nitro resulted in an increase in specific as well as molecular rotation when compared with the corresponding constants of the parent unsubstituted oxazolidine derivative. However, etherification of a hydroxyl group in the *para* position with a methyl or an ethyl group decreases both specific and molecular rotation and this decrease is greater in the case of methylation. On the other hand, methylation of an *ortho*-hydroxyl group did not bring about any significant change in specific rotation. The specific as well as the molecular rotation of the *para*-substituted diastereomeric oxazolidine derivatives decrease significantly by further substitution in the *ortho* or *meta* position (compounds 16–18, 29 and 30).

Contrary to substitution in the *ortho* or *para* position, the introduction of a substituent in the *meta* position resulted in a significant decrease in the specific rotation of all compounds studied. Decrease in molecular rotation was also noted, except with two compounds, *trans*-2-(*m*-chlorophenyl)-3,4-dimethyl-5-phenyloxazolidine and *cis*-2-(*m*-iodophenyl)-3,4-dimethyl-5-phenyloxazolidine. No possible explanation can be offered for this discrepancy, but it may be attributed to the high formula weight of the iodo derivative and the relatively high specific rotation of the chloro derivative since these two constants are included in the formula of molecular rotation.

In a given substituted series, e.g. the hydroxy- and the nitro-substituted compounds, it is noted that the specific as well as the molecular rotations decrease in the order *ortho*, *para*, and *meta*.

**Table 4. Melting points (°C) of *cis* and *trans* derivatives**

| Subst. | *cis* | *trans* | Subst. | *cis* | *trans* |
|---|---|---|---|---|---|
| H | 75·0–75·5 | 68·0–68·5 | *m*-Cl | 61·0–61·5 | 48·0–48·5 |
| *p*-$CH_3$ | 45·5–46·5 | 62·0–63·0 | *p*-Cl | 81·0–81·5 | — |
| *o*-OH | 118·5–119·0 | 80·0–81·0 | *o*-$NO_2$ | 75·5 | — |
| *m*-OH | — | 142·0–143·0 | *m*-$NO_2$ | 77·0–77·5 | 56·0–56·5 |
| *p*-OH | 145·0–146·0 | 216·0–217·0 | *p*-$NO_2$ | 102·0–102·5 | 65·0–65·5 |
| *o*-$OCH_3$ | 103·0–104·0 | 128·0–129·0 | *o*,*p*-di-$OCH_3$ | — | 78·0–79·0 |
| *p*-$OCH_3$ | 89·0–89·5 | 70·0–71·0 | *o*,*p*-di-Cl | 85·0–86·0 | — |
| *p*-$OC_2H_5$ | 90·0–91·0 | 74·0–75·0 | *m*,*p*-di-Cl | 84·0–85·0 | 68·0–69·0 |
| *m*-I | 64·5–65·5 | 75·0–76·0 | *m*-$CO_2H$, *p*-OH | 105·0–106·0 | 113·0–113·5 |
| *o*-Br | 123·0–124·0 | — | spiro[A] | 77·0–78·0 | 72·5–73·5 |
| *o*-Cl | 124·5–125·5 | — | | | |

[A] 3,4-Dimethyl-5-phenyloxazolidine-2-spirocyclohexane.

The melting points of the oxazolidine derivatives investigated are listed in Table 4. Although the melting points of the diastereomeric amino alcohols (−)-ephedrine and (+)-pseudoephedrine are 34° and 119° respectively,[16] the data listed in this table indicate that, generally, the *cis* oxazolidines derived from (−)-ephedrine have higher

[16] 'The Merck Index' p. 410 (Merck: Rahway, N. J., 1968).

melting points than the corresponding *trans* isomers derived from (+)-pseudoephedrine.

**Acknowledgments**

Our thanks are due to Dr Ibrahim H. Abdallah, President of the Alexandria Co. for Pharmaceuticals and former Professor of Pharmaceutical Chemistry, for generously supplying chemicals and offering laboratory facilities.

Manuscript received 26 April 1974