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IDENTIFICATION AND STEREOCHEMISTRY OF (2S, 4S, 5R)- AND (2R, 4S, 5R)-2,3,4-TRIMETHYL-5-PHENYLOXAZOLIDINE, DEGRADATION PRODUCTS OF EPHEDRINE

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Abstract—The condensation of (−)-ephedrine with acetaldehyde gives two diastereomeric 2,3,4-trimethyl-5-phenyloxazolidines, of greatly differing thermodynamic stability. The structure and configuration of both the diastereoisomers was confirmed by chemical studies and by NMR spectroscopy.

Extraction of small quantities of ephedrine from aqueous media using freshly distilled diethyl ether resulted in some loss of the drug and the detection of new products. Aldehydic impurities in the ether condensed with the ephedrine to form substituted oxazolidines. When the main contaminant, acetaldehyde, was separately reacted with ephedrine the product gave two peaks on GLC of a ratio of about 10:1, and gave two "sets" of NMR signals with a ratio of about 20:1. The product was identified by spectroscopy (IR, NMR and MS) as a 2,3,4 - trimethyl - 5 - phenyloxazolidine and the major and minor components were thought to be related as diastereoisomers.[1]

In the present work we sought to confirm that the minor component of the oxazolidine (**4b**, Fig. 1) was a diastereoisomer of the major component and to determine their respective configurations by NMR, and by comparison with the corresponding analogues of pseudoephedrine.

†As a function of the NMR signal heights of one methyl doublet in each compound.

RESULTS AND DISCUSSION

The reaction of (−)-ephedrine with acetaldehyde. The formation of the oxazolidine **4a** from acetaldehyde and ephedrine probably proceeds via an open chain diol (**2**) or an iminium intermediate (**3**) (Fig. 1). The reaction as followed on NMR, showed the virtual disappearance of the ephedrine signals within 4 min and the appearance of signals due to **4a** and those due to a diastereoisomer **4b** which subsequently reduced in intensity as the signals due to **4a** increased (Fig. 2).

A duplicate reaction was examined on GLC. However, due to the high temperature (e.g. injection port 230°) the minor peak due to **4b** was seldom greater, even after only a few seconds, than its height at equilibrium (5 to 10% of the main oxazolidine peak due to **4a**). After distillation, the oxazolidine product **4** still gave two peaks on GLC; a

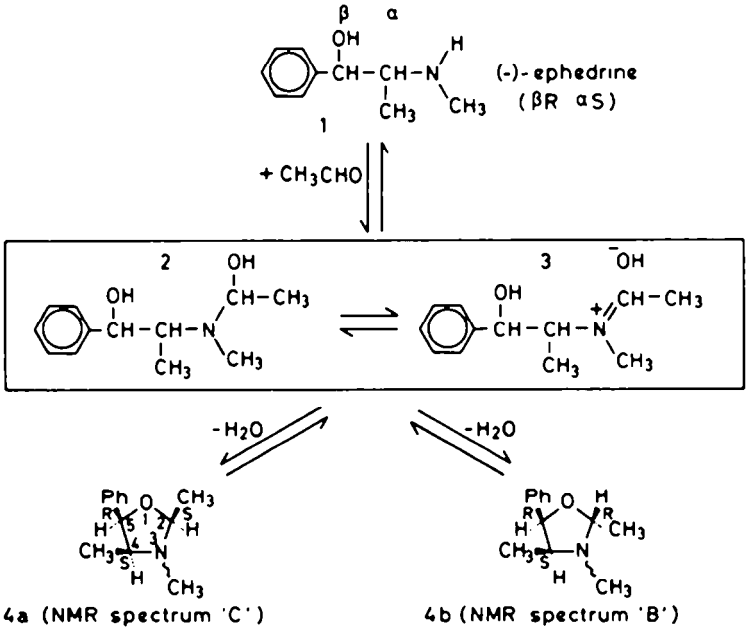

Fig. 1. Scheme for the formation of oxazolidines **4a** and **4b** from (—)-ephedrine and acetaldehyde. □ = Postulated intermediate-not isolated.

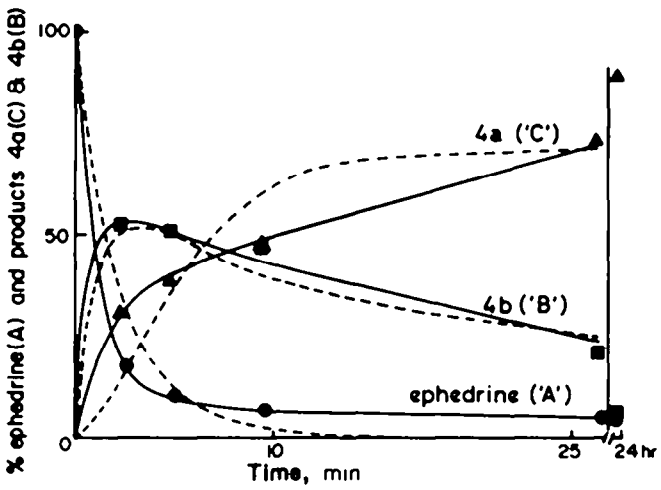

Fig. 2. The reaction of (−)-ephedrine ("A") with acetaldehyde to form oxazolidines **4a** ("C") and **4b** ("B") as follows by NMR spectral analysis (in $CDCl_3$). The dotted lines were a "best fit" by an analogue computer using the relationship A⇌B⇌C and the solid lines a "best fit" using B⇌A⇌C.

major peak (**4a**, 90–95%) and a minor peak (**4b**, 5–10%). The NMR spectrum of the product showed a minor (*ca.* 5%) and major (*ca.* 95%) set of signals identified as the oxazolidine diastereoisomers **4b** and **4a** respectively.

The initial high concentration of **4b** on adding acetaldehyde to ephedrine and eventual conversion of most of **4b** to **4a** (see Fig. 2) can be explained if there is a lower energy barrier for the formation of **4b** from the reactants than there is for **4a**, and if **4a** is thermodynamically more stable than **4b**. An equilibrium between ephedrine plus acetaldehyde and the transitory open chain intermediate, **2**, and between **2** and the oxazolidines **4a** or **4b**, will allow inversion of the O–C–N carbon centre and thus conversion of **4b** to **4a** (Fig. 2).

Simulation of the reaction on an analogue computer showed a "good fit" of the experimental data with the computed curves, using the relationship $B \underset{k_3}{\overset{k_1}{\rightleftharpoons}} A \underset{k_4}{\overset{k_2}{\rightleftharpoons}} C$ (see Fig. 2), where A = ephedrine, B = **4b** and C = **4a**; relative values of k were (as read off the analogue computer potentiometers): $k_1 = 7.23$, $k_2 = 3.64$, $k_3 = 1.63$ and $k_4 = 0.10$. (The absolute values could not be readily determined due to the difficulty of accurately measuring the acetaldehyde in the necessarily small volume of $CDCl_3$.) The relationship $A \underset{k_3'}{\overset{k_1'}{\rightleftharpoons}} B \underset{k_4'}{\overset{k_2'}{\rightleftharpoons}} C$ where "B" is considered an *intermediate* between ephedrine and **4a**, was unsatisfactory (for the "best fit" see Fig. 2).

The shape of the "C" curve is particularly characteristic of the systems studied. Where "C" arises from "A" via an intermediate "B" there must be an initial "lag" time for the build-up of "C", as "B" builds up, even if k_1' is fast and k_3' is slow. Where "C" arises from "A" independently of "B" both "C" and "B" can have an initial fast rate of formation. Thus the oxazolidine **4a** is formed independently of **4b**, although conversion of **4b** to **4a** does occur *via* ephedrine or some other intermediate.

An alternative structure for the "minor product" giving rise to the "B" signals observed in the NMR spectrum run after the reaction of ephedrine with acetaldehyde is structure **2**. However, this was rejected as a possibility because the "minor product" did not react with BSTFA at 35° (NMR evidence) or on GLC (ephedrine is silylated on the benzylic oxygen by BSTFA, at room temperature). Also the ratio of the "minor product" to **4a** is the same by NMR analysis (35°) as it is under the different conditions of GLC analysis (injection port 230°, oven temp. 100°); whereas structure **2** would be expected to lose water and cyclise on GLC. Furthermore the oxazolidines formed from ephedrine and formaldehyde or acetone, which possessed no asymmetric centre at C-2, give only one peak each on GLC and their NMR spectra show no "minor signals",[1] further indicating the involvement of this asymmetric centre in the formation of the "minor component" of **4**. Structure **2** is however postulated as a transitory intermediate in the formation of **4a** from ephedrine and acetaldehyde (see Fig. 1).

Reactivity of the hydroxyl and secondary amine functions with acetaldehyde. Further evidence that the "intermediate" set of NMR signals observed on adding acetaldehyde to (−)-ephedrine was not due to an iminium (**3**) or α-N-hydroxyethyl intermediate (**2**) was given by the very poor reaction of acetaldehyde with N-methylamphetamine and N-methylephedrine; only one functional group being available (NH and OH respectively) for reaction in each case. Similarly, little or no reaction occurred on adding acetaldehyde to the *O*-TMS derivative of (−)-ephedrine (NMR evidence). Thus both the β-OH and NH groups must be available for the reaction of acetaldehyde with the compound under study, to form the relatively stable oxazolidine in the case of ephedrine.

Configuration at C-4 and C-5 in oxazolidines **4a** *and* **4b**. Inversion of the benzylic (ephedrine-β-carbon ≡ oxazolidine-5-carbon) during the condensation of (−)-ephedrine with acetaldehyde to form the oxazolidine, is unlikely. There was no evidence from either GLC or NMR of more than two diastereoisomers being formed. The two diastereoisomers observed are explicable in terms of the two asymmetric centres of (−)-ephedrine retaining their geometry, and the formation of a new asymmetric centre (and thus two possible configurations) on the oxazolidine 2-carbon. Only one diastereoisomer was observed in each product from the condensation of formaldehyde and acetone with (−)-ephedrine (GLC and

NMR evidence[1]), in which the C-2 centres of these oxazolidines are not chiral.

The oxazolidine derived from acetaldehyde and (−)-pseudoephedrine was composed mainly of one diastereoisomer (*ca.* 95%) with an additional, minor diastereoisomer (*ca.* 5%) (GLC and NMR evidence), as was the condensation product of (+)-pseudoephedrine with acetaldehyde. The major oxazolidine diastereoisomers had an enantiomeric relationship (identical NMR spectra) as did the minor diastereoisomers. Neither the major, nor the minor diastereoisomers formed from the reaction of the pseudoephedrine isomers and acetaldehyde were the same as the diastereoisomers formed from (−)-ephedrine. Furthermore, acid hydrolysis of the oxazolidine obtained from (−)-ephedrine and acetaldehyde, yielded exclusively (−)-ephedrine (NMR, m.p. and optical rotation data). Thus neither the α- nor β-ephedrine asymmetric centres were racemised, either during the oxazolidine formation or hydrolysis.

Configuration at C-2 *in the oxazolidines.* The configuration of the oxazolidine 2-carbon of **4a** (NMR spectrum "C") and thus of **4b** (NMR spectrum "B") may be assigned by qualitative analysis of their NMR spectra since the configurations of the 4- and 5-carbons are the same as in the starting amine. The oxazolidine **4a** is more stable than **4b** (see Fig. 2) and conversion of **4b** to **4a** can occur via ephedrine or another intermediate. Thus configurational assignment rests on the following data:

(1) Because the 4-methyl and 5-phenyl groups are *cis* to one another (4S and 5R), the phenyl rotation is restricted such that it is always "edge on" to a group in the 2-position. Thus the anisotropic effect of the phenyl ring will augment the magnetic field, causing a deshielding effect on a group in the 2-position which will be greater if that group is *cis* rather than *trans* to the ring. Therefore the "C" 2-CH_3 indicates a *cis* configuration (i.e. 2S, 4S, 5R) for compound **4a** and *trans* (2R, 4S, 5R) for **4b**.

(2) If compound **4a** (spectrum "C") has a 2S, 4S, 5R configuration, the phenyl ring and both the 2- and 4-CH_3 groups will be on the same side of the plane of the oxazolidine ring and thus the NCH_3 group will adopt a position on the other side of this plane, i.e. *trans* to the phenyl ring and less deshielded than if it were *cis*. Conversely, **4b**, with the 2R, 4S, 5R configuration will favour the NCH_3 group *cis* to the phenyl ring, i.e. more deshielded. The "C" NCH_3 singlet being upfield by 0.14 ppm to the "B" NCH_3 singlet, is consistent with these deductions.

(3) A proton in the 2-position which is *cis* to the phenyl ring (edge) [see (1) above] will be deshielded to a much greater extent than one in the *trans* configuration. Compound **4a** (spectrum "C"-2S isomer) will have its 2-H proton deshielded by the *trans* phenyl group less than the corresponding proton in the diastereoisomer **4b**, with its 2-H atom *cis* to the phenyl ring. The "C" 2-H quartet being upfield by 0.8 ppm from the "B" 2-H quartet is consistent with the configuration proposal in (1) above.

Thus the major oxazolidine diastereoisomer from the reaction of (−)-ephedrine with acetaldehyde has the configuration 2S, 4S, 5R (**4a**) and the minor diastereoisomer 2R, 4S, 5R (**4b**).

EXPERIMENTAL

Methods. Nuclear magnetic resonance (NMR) spectra were recorded on a Perkin Elmer R32 spectrometer, incorporating a field lock on the TMS (tetramethylsilane) internal standard, as 10% solutions in $CDCl_3$. The coupling constants are quoted in Hertz, and the notations used are: s, singlet; d, doublet; q, quartet; m, multiplet; Ar, aromatic signals. Gas liquid chromatography (GLC) was carried out on a Perkin Elmer F11 instrument with a flame ionization detector; using a glass column, 1 m, 0.4 cm i.d., packed with 2.5% Carbowax 20 M and 5% potassium hydroxide coated on acid washed DMCS treated Chromosorb G (100–120 mesh); with an oven temp. of 100° and carrier gas (nitrogen) flow rate of 106 ml min^{-1} (pressure 105 kPa). GLC/mass spectrometry (GLC/MS) was performed on a Perkin Elmer model 270 instrument using a glass column, 1 m, 0.4 cm i.d., packed as above (system 1), or a 1 m column, 0.4 cm i.d. packed with 2% XE60 coated on Chromosorb G (80–100 mesh) at an oven temp. of 90°. Helium was the carrier gas (100 kPa) and the ionizing potential 70 eV. Analogue computing was carried out using an EAI model 180 computer (Electronics Associates) and specific rotations were determined using a Carl Zeiss Circle 0.01° Polarimeter.

Materials. (−)-Ephedrine anhydrous (Sigma), ephedrine hydrochloride (B.D.H.), acetaldehyde (B.D.H.), BSTFA (N,O-bis[trimethylsilyl]trifluoroacetamide) (Pierce Chemicals); (+)- and (−)-pseudoephedrine, N-methylamphetamine and N-methylephedrine were gifts from Burroughs Wellcome (England).

Formation of the 2,3,4-trimethyl - 5 - phenyloxazolidines **4a** *and* **4b**, *followed by NMR*

The NMR spectrum of (−)-ephedrine base was run (0.04 g, 0.24 m mole, in 0.4 ml $CDCl_3$)—spectrum "A". Acetaldehyde (12–15 μl, 0.21–0.26 m mole) was added and spectra recorded immediately and at varying intervals thereafter. The ephedrine signals rapidly decreased in intensity, whilst two new sets of signals appeared, "B" and "C", where "B" was more intense than "C" (see Fig. 2). Set "C" was due to the oxazolidine **4a** and set "B" due to a diastereoisomer **4b**. Over a period of 30 min, the signals due to **4b** ("B") decreased in intensity and those for **4a** ("C") increased, until at equilibrium **4a** was *ca.* 90%, **4b** *ca.* 5%, the remainder being ephedrine (Fig. 2).

The following data were abstracted from the NMR spectrum run eight minutes after the start of the reaction (less the aromatic signals; the field was locked at δ 7.28); set "B" due to **4b**: δ 0.62 (d, J = 6.2, $CHCHC\underline{H}_3$) 1.35 (d, J = 4.6, $CH'C\underline{H}_3$) 2.39 (s, $NC\underline{H}_3$) 3.49 (m, $C\underline{H}CHCH_3$) 4.76 (q, J = 4.6, $C\underline{H}'CH_3$) 5.29 (d, J = 5.0, $C\underline{H}CHCH_3$) and set "C" due to **4a**: δ 0.65 (d, J = 6.0, $CH'C\underline{H}_3$) 1.45 (d, J = 4.4, $CHCHC\underline{H}_3$) 2.20 (s, $NC\underline{H}_3$) 2.72 (m, $C\underline{H}CHCH_3$) 3.92 (q, J = 4.4, $C\underline{H}'CH_3$) 4.96 (d, J = 7.8, $C\underline{H}CHCH_3$). Characterization of this product has been reported previously.[1]

The reaction of (−)-*pseudoephedrine with acetaldehyde*

(−)-Pseudoephedrine (0.04 g, 0.24 m mole; extracted from the hydrochloride salt) was dissolved in chloroform (0.5 ml) and acetaldehyde (*ca.* 20 μl, *ca.* 0.35 m mole) added. After 15 min solvent and excess acetaldehyde were evaporated under vacuum and the NMR spectrum recorded in $CDCl_3$: δ 1.13 (d, J = 6.2, 3, $CHCHC\underline{H}_3$) 1.37 (d, J = 5.3, d, $CH'C\underline{H}_3$) 2.25 (s, 3, $NC\underline{H}_3$) 2.38 (m, 1, $C\underline{H}CHCH_3$) 4.21 (q, J = 5.3, 1, $C\underline{H}'CH_3$) 4.50 (d, J = 8.8, 1, $C\underline{H}CHCH_3$) 7.29 (s, 5, Ar), and a number of signals of about 5–10% of the intensity of the main signals, due to a less abundant diastereoisomer. The GLC/MS (system 1) was the same as that of the oxazolidine obtained from the reaction of (−)-ephedrine with acetaldehyde.[1]

The reaction of (+)-*pseudoephedrine with acetaldehyde*

The reaction was carried out as described above. The NMR spectrum was identical to that obtained from the above isomer.

Preparation of the O-*trimethylsilyl derivative of ephedrine and attempted reaction of it with acetaldehyde*

BSTFA (N,O-bis[trimethylsilyl]trifluoroacetamide, 250 μl—excess) was added to (−)-ephedrine base (0.055 g, 0.33 m.mole)

and the solution left at room temperature, overnight (*ca.* 18 hr). Excess silylating reagent was boiled off *in vacuo* (*ca.* 0.5–1.0 mmHg) at 40°C, and the NMR spectrum of the ephedrine—TMS derivative was δ 0.95 (d, 3, $CHC\underline{H}_3$) 2.35 (s, 3, $NC\underline{H}_3$) 2.68 (m, 1, $C\underline{H}CH_3$) 4.61 (d, 1, $ArC\underline{H}$) 7.29 (s, 5, $\underline{Ar}$). The O-TMS signal was not recorded as the spectrum was run using tetramethylsilane as the internal standard and locking signal. The mass spectrum of the derivative was consistent with that of the O-TMS ether (*cf.* N,O-diTMS ether); GLC/MS, *m/e* (% rel. abund.): 238 (M + 1, 0.3), M^+ absent, 222(1), 148(1), 91(1), 88(3), 75(2), 73(6), 59(4), 58(100), 45(2).

Acetaldehyde (*ca.* 20 μl, *ca.* 0.35 m mole) was added to the ephedrine-O-TMS derivative in $CDCl_3$ (0.4 ml) and the NMR spectrum run immediately and at intervals up to 210 min. No reaction was apparent.

Attempted reaction of acetaldehyde with N-methylephedrine

The method was as described above, only using N-methylephedrine (0.04 g, 0.34 m mole; extracted from the hydrochloride salt). No reaction was apparent.

Hydrolysis of the 2,3,4 - trimethyl - 5 - phenyloxazolidines, **4a** *and* **4b**, *to (−)-ephedrine*

2,3,4 - *Trimethyl* - 5 - *phenyloxazolidine* (**4a**:**4b** approx. 20:1 by NMR; 1.0 g, 5.24 mmole) was dissolved in ether (250 ml) and HCl gas bubbled in until no more precipitate was formed and a slight excess of HCl gas was in solution. Water (1 ml) was added and the mixture stirred overnight, after which the formation of ephedrine was complete (GLC). The ether was evaporated and the hydrochloride salt crystallized from ethyl acetate (0.98 g, 93% yield) m.p. 216–219° [cf. authentic (−)-ephedrine hydrochloride 217–220° and a mixed melting point with ephedrine hydrochloride, 216–219°, cf. (±)-ephedrine hydrochloride, 187–188°]: $[\alpha]_D^{22} = -34.1°$ in water, cf. authentic ephedrine hydrochloride $[\alpha]_D^{22} = -34.5°$. The NMR spectrum of the base (partitioned between aqueous potassium carbonate and $CDCl_3$) was identical to that of authentic (−)-ephedrine. The liquor obtained after filtration of the ephedrine hydrochloride, was evaporated, the residue dissolved in water (5 ml) and an NMR spectrum run after adding potassium carbonate and partitioning 1 ml with $CDCl_3$ (0.5 ml). The NMR spectrum showed the $CDCl_3$ soluble basic material to be at least 90% ephedrine.

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REFERENCE

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