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SYNTHESIS AND PROPERTIES OF ARALKYLAMINE C-NITROSO DIMERS

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Abstract—The action of 3-chloroperbenzoic acid on eleven aralkylamines yielded the C-nitroso dimers; physical properties of the compounds, including UV, IR, NMR and MS data are reported. The stability of the nitroso dimers was investigated. The 2-nitroso-1-phenylpropane dimer was converted into its hydrazo-, azo- and azoxy-derivatives.

INTRODUCTION

C-Nitroso compounds are both *in vitro* and *in vivo* metabolites of phentermine (2-amino-2-methyl-1-phenylpropane) and its *p*-chloro analogue (chlorphentermine), both of which possess a primary amino group attached to a tertiary carbon atom.[1] The initial oxidation step involves the transfer of one electron from the nitrogen lone pair to the oxygen molecule via a flavoprotein to give a free radical ion complex which dissociates to the nitroso compound via an N-hydroperoxide.[2] Alternatively, and as a less important route, the complex was reduced to yield a primary hydroxylamine. Amphetamine (2-amino-1-phenylpropane, **1a**) has a secondary carbon atom *alpha* to the nitrogen atom; it is extensively metabolised *in vitro* to 2-hydroxylamino-1-phenylpropane **1b**,[3] probably via a mechanism similar to the above.[4] However, the stability of the complex will be favoured by the presence of an α-C-H function (contrast phentermine and chlorophentermine) with consequent reduced steric hindrance so that the reductive route to the hydroxylamine will be favoured at the expense of the N-hydroperoxide route. Since C-nitroso compounds are chemically oxidised to the corresponding nitro compounds and also are isomerised to oximes under aerobic conditions,[5] only low concentrations of 2-nitroso-1-phenylpropane would be expected after *in vitro* metabolism of amphetamine. Some knowledge of the properties of this, and related nitroso compounds was required.

Various methods have been reported for the synthesis of aliphatic C-nitroso compounds with secondary and primary α-carbon atoms. Some compounds were prepared by oxidation of the corresponding amine[6] but most were obtained by oxidation of the corresponding hydroxylamine[7] or imine,[6a] by pyrolysis of the corresponding alkyl nitrite[8] or by the action of nitric oxide and chlorine on hydrocarbons in the presence of ultraviolet light.[9] The present paper describes a method of preparation of aralkylamine C-nitroso dimers by the direct oxidation of primary amines with 3-chloroperbenzoic acid (CPBA). This method has the advantage that the starting material is the normally readily available amine (often a drug), which is easily oxidised to the nitroso compound in one step, in good yield and with retention of the α-carbon asymmetry. The oxidation produced at least 95% nitroso dimer from most of the amines studied (NMR, GLC/TLC evidence), although recrystallisation reduced the yield to 30–70% when reactions were carried out on a small scale.

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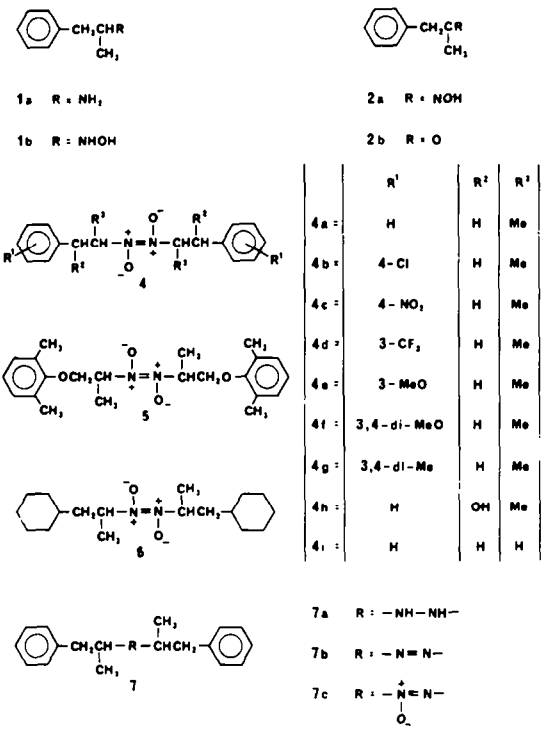
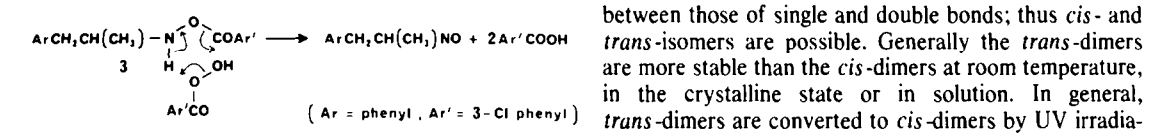


Synthesis—general method

The amine base was oxidised at 0–5° with a 2.5 molar quantity of 3-chloroperbenzoic acid (CPBA) in chloroform. The solution was then allowed to attain room temperature (20°) and evaporated *in vacuo* to a white residue which contained excess CPBA, 3-chlorobenzoic acid and nitroso compound. Partition between ether and aqueous potassium carbonate gave, on evaporation of the ether solution, the colourless *trans*-nitroso dimer which was recrystallised from a mixture of ether and n-pentane. In the overall reaction, two moles of CPBA condense with one of the amine. The reaction is thought to proceed via a 3-chlorobenzoyloxy ester intermediate **3** which reacts with the second mole of CPBA to yield the nitroso compound (Scheme 1). However, in contrast with the oxidation of secondary aralkylamines with CPBA[10] no ester intermediates could be isolated.

An oxidation was carried out using a large excess of 2-amino-1-phenylpropane **1a** (300 mg **1a**; 100 mg CPBA), in an attempt to produce the 3-chlorobenzoyloxy ester **3** which could be hydrolysed to 2-hydroxylamino-1-



Scheme 1.

phenylpropane **1b**. However, no hydroxylamine **1b** was detected (GLC, TLC/Tollens reagent) in the ethereal extract obtained after washing the oxidation mixture with potassium carbonate. After removing the excess amine with N hydrochloric acid, the main products were 1-phenyl-2-propanone oxime **2a** and 2-nitroso-1-phenylpropane dimer **4a** (NMR, GLC) but no ester **3** or 3-chlorobenzoic acid was present. Thus the amine **1a** was preferentially oxidised to the nitroso dimer **4a** rather than to the hydroxylamine **1b**. Oxidation of either (+)- or (−)-**1a** with CPBA did not racemise the optical centre. The observed specific rotations of the (+)- and (−)-nitroso dimers **1a** were $[\alpha]_D^{20} = +139°$ and $[\alpha]_D^{20} = -129°$ respectively; this difference could be due to optical impurity of the starting amines. The optical rotatory dispersion spectrum of (+)-**4a** was obtained and showed a Cotton effect with a positive maximum at 377 nm, $[\alpha]_{377}^{20} = +394°$. The circular dichroism spectrum of (+)-**4a** gave a positive maximum at *ca* 285 nm and a negative minimum at *ca* 320 nm, the converse being true for the (−)-isomer.

Dimeric properties and stability of the nitroso compounds

The nitroso compounds were concluded to be *trans*-nitroso dimers from evidence of their relative stability to heat and alkali, from their UV, IR, MS, and NMR data, and in one case, **4a**, from the apparent molecular weight determination by vapour pressure osmometry. These nitroso compounds required heating up to 10–20° above their melting point before they changed from colourless liquids (melted dimer) to deep blue oils (monomer[6a,8,11]); further heating caused isomerisation to the oxime usually as a mixture of *syn*- and *anti*-isomers (ratio 1:2 in the case of **4a–4d**). A 10% solution of (−)-**4a** in chloroform gave only a very pale blue colour when heated to 100° in a sealed tube; presumably, insufficient monomer was present at any one time to give the pronounced blue colour indicative of gross dissociation to the dimer.[6a,8,11] All the nitroso dimers studied were fairly stable in organic solution at room temperature (20°) for several hours, but they isomerised to the oxime on prolonged warming [e.g. 2% breakdown of (−)-**4a** in 2 h at 35°C in chloroform (NMR evidence)].

Compound **4a** was not isomerised by either aqueous N sodium hydroxide or N hydrochloric acid although acidic and basic media are reported to accelerate the isomerism of primary and secondary nitroso compounds to oximes. Insolubility of the dimer in aqueous media may partly account for the stability. However, when (−)-**4a** was refluxed in 0.5% alcoholic sodium hydroxide, converson to the oxime **2a** was complete in thirty minutes, with a small amount of 1-phenyl-2-propanone **2b** also produced which probably came from acid hydrolysis of the oxime **2a** during purification. The average molecular weight of the nitroso dimer (−)-**4a** in chloroform at 37°C, by vapour pressure osmometry was 284.4 indicative of 9 molecules of monomer per 91 molecules of dimer or approximately 5% by weight of monomer.

C-Nitroso dimers exist in an azodioxide form (e.g. structure **4**) as shown by X-ray crystallography[13] where both the N–O and N–N bond lengths are intermediate between those of single and double bonds; thus *cis*- and *trans*-isomers are possible. Generally the *trans*-dimers are more stable than the *cis*-dimers at room temperature, in the crystalline state or in solution. In general, *trans*-dimers are converted to *cis*-dimers by UV irradiation while heat isomerises the *cis*-dimers to *trans*-dimers.[8,11,14] All the nitroso dimers examined herein had strong UV absorptions, λ_{max} 290–294 nm, $\log \epsilon$ = *ca.* 3.9 except **4c** which absorbed at λ_{max} 272 nm, $\log \epsilon = 4.36$, (cf. *trans*-nitroso dimers generally absrob at *ca.* 290 nm, $\log \epsilon = 4.0$ in chloroform or carbon tetrachloride, the *cis*-dimers rearranging to the *trans*-isomer in these solvents[8,11,14]); they had characteristic absorptions in the 1180–1240 cm^{-1} region of the IR (cf. *trans*-nitroso dimers have strong absorptions in the region 1176–1290 cm^{-1}; *cis*-isomers absorb strongly as a double band 1323–1334 cm^{-1} and 1330–1420 cm^{-1}, whereas monomeric aliphatic nitroso compounds absorb strongly in the region 1539–1621 cm^{-1}[8,11,14]). Many of the nitroso dimers (**4a–4d**, **4g** and **6**) showed a strong double band in the region 1180–1200 cm^{-1} and 1200–1250 cm^{-1} rather than one band at 1200–1225 cm^{-1} reported previously[11] for other alkyl *trans*-nitroso dimers; the remainder (**4e**, **4f**, **4h**, **4i** and **5**) had strong or overlapping absorptions which may conceal two bands.

Stability of the nitroso dimers and related hydrazo **7a** *azo* **7b** *and azoxy* **7c** *derivatives of* **4a** *on GLC and TLC*

All the nitroso compounds isomerised completely to the corresponding oximes on GLC (GLC/MS evidence); some gave one peak (**4a**, **4b**, **4d**, **4e** and **4g**), others gave one peak with a "shoulder" due to partial separation of the *syn*- and *anti*-oxime isomers. The nitroso compounds were stable on TLC and the *meso*- and (+)/(−) isomers of **4a–4d**, **4f** and **4g** were resolvable in the system used. The azo **7b** and azoxy **7c** derivatives of **4a** were stable on TLC and GLC. The hydrazo compound **7a** partially decomposed to the azo compound **7b** on GLC. Similar GLC oxidations of some primary hydroxylamines occur.[15]

Formation of diastereoisomers due to dimerisation of (±)-aralkyl nitroso compounds

The oxidation of racemic aralkylamines produced diastereomeric nitroso dimers, i.e. (±)- and *meso*-dimers. The (+)- and (−)-isomers of **4a** had identical IR, UV and NMR spectra and melting points. The IR spectrum of *meso*-**4a** differed from that of the (+)- or (−)-isomers in the fingerprint region and *meso*-**4a** absorbed at a slightly longer wavelength in the UV region, *viz.* λ_{max} 294 nm, cf. (+)- and (−)-**4a**, λ_{max} 292 nm. The NMR spectra of the *meso*- and (+)- or (−)-nitroso compounds differed, particularly in the chemical shifts of the methyl and methylene groups. In the spectrum of **4a**, for example, the chemical shifts of the *meso*- and (+)- or (−)-isomer methyl groups differed by 0.14 ppm with the *meso*-signal upfield (δ being the same for symmetrical functions of the same dimer molecule), and the chemical shifts of the methylene groups (appearing as a double quartet due to non-equivalence of the methylene hydrogens[16]) of the *meso*- and (+)- or (−)-isomers differed by 0.11 ppm with the *meso*-methylene signal downfield. The direction and magnitude of these differences was generally applicable to most of the other phenylpropane nitroso compounds (**4a–4g**). Equimolar quantities of (+)- and (−)-**4a**, in $CDCl_3$ at 35°, gave the same NMR spectrum as either isomer alone; however, on raising the temperature to 60°, signals due to the *meso*-**4a** isomer and *syn*- and *anti*-oxime

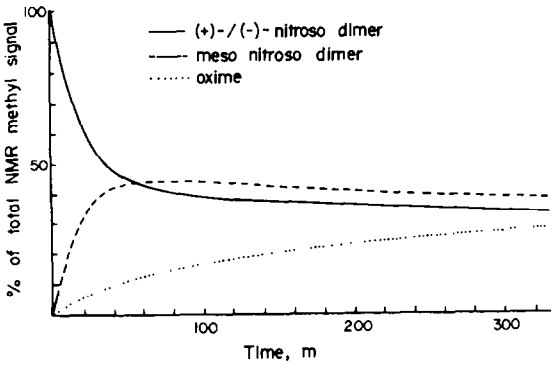


Fig. 1. Formation of *meso*-2-nitroso-1-phenylpropane dimer **4a** and 1-phenyl-2-propanone oxime **2a** from an equimolar solution of (+)- and (−)-**4a** at 60°C in $CDCl_3$—followed by NMR.

appeared. After about 90 min an equilibrium of seven parts *meso*- to six parts of the (+)/(−) nitroso dimer was established although two parts of the oxime **2a** had also been, and continued to be, formed at the expense of both nitroso dimer isomers (Fig. 1). In a kinetic study on a 10% solution of (−)-**4a** in $CDCl_3$ the oxime **2a** concentration was 100% after 134 h.

Where racemic aralkylamines were oxidised, the final ratio of *meso*-to(+)- and (−)-nitroso dimers varied. NMR spectra were run of each of the crude reaction products after removing the acidic fraction (i.e. the total neutral plus any basic products): only the *meso*-isomer of **5** was present, but both diastereoisomers were present in varying but approximately equal proportions in **4a–4d, 4f** and **4g**. NMR of the recrystallised products showed **4g, 5** and **6** to be pure *meso*-isomers, whilst the remainder still showed a mixture of both diastereoisomers with the *meso*-form predominating. Where optically pure isomers were not available, the interpretation of the NMR spectrum of each of the diastereoisomers was made on the basis of relative chemical shifts and coupling constants obtained from the spectra of *meso*- and (+)/(−)-**4a**.

The IR spectra of *meso*-**4a** and (+)- or (−)-**4a** differed in the region where the *trans*-nitroso dimer function absorbed. The *meso*-isomer spectrum had well-resolved peaks at 1160, 1180, 1195 cm^{-1} whereas that of the (+)-isomer had a narrower and poorly resolved "multiplet" at 1185 cm^{-1}. The *meso*-isomer showed a single peak at 1075 cm^{-1} whereas the (+)-isomer had well resolved peaks at 1075, 1085 and 1095 cm^{-1}; in addition, the single peak in the *meso*-spectrum at 755 cm^{-1} was split in the (+)-spectrum (740, 750 cm^{-1}). Melting points of mixtures of (+)- and (−)-**4a** revealed a eutectic relationship often obtained with racemic mixtures.[17] The (+)- and the (−)-isomers of **4a** each melted at 100–102°, however, equal mixtures of the (+)- and (−)-isomers melted at 76–79°C, the melt being fairly sharp with little prior softening; the *meso*-isomer melted at 94–96°.

Reduction of the nitroso dimer, **4a**, *and synthesis of its hydrazo-***7a** *azo-***7b** *and azoxy-***7c** *derivatives*

Zinc metal and ammonium chloride solution (pH 6.8) reduced (−)-**4a** to a mixture of the hydrazo **7a**, azo **7b** and azoxy **7c** compounds, the primary amine **1a**, some oxime **2a**, and a negligible amount of hydroxylamine **1b** (GLC, TLC/Tollens reagent). Lithium aluminium hydride (LAH) similarly reduced (−)-**4a**, but yielded a much greater proportion of the hydroxylamine **1b**. Similar results were obtained on LAH reduction of **4d, 4i** and **5**. In contrast, there was much less reduction of the *anti*-oxime **2a** with LAH under identical conditions and the only products were the hydroxylamine **1b** and amine **1a**. An alcoholic solution of sodium borohydride did not reduce (−)-**4a** at room temperature or on refluxing. *Meso*-**4a** was catalytically reduced under one atmosphere of hydrogen, in methanolic sulphuric acid; 5% platinum on charcoal was the catalyst. The products, which were extracted from acidic solution, were the azoxy compound **7c** and an unidentified product (GLC R_T 7.2 min. cf. **7c**, 16.2 min.); the hydrazo compound **7a** plus a small amount of amine **1a** were extracted after basification.

Reduction of (−)-**4a** with zinc dust and 2N hydrochloric acid produced the hydrazo compound **7a** and the primary amine **1a**. Extraction of the acidic reaction mixture with chloroform removed hydrazodi-(1-methyl-2-phenylethane) **7a** hydrochloride and unreacted nitroso starting material **4a** which were readily separated by washing with ether. The hydrazo compound (**7a**, salt or base) could be oxidised with yellow HgO in chloroform to give azodi-(1-methyl-2-phenylethane) **7b** in good yield (*ca.* 95%-TLC/GLC, NMR), or with a 2.2 molar quantity of CPBA in chloroform to form azoxydi-(1-methyl-2-phenylethane) **7c** in good yield (*ca.* 80–90%). The hydrazo **7a**, azo **7b** and azoxy **7c** compounds were prepared from both the *meso*-isomer and (+)- or (−)-isomers of **4a**.

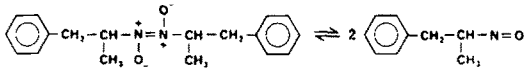
In the present study, oxidation of the *meso*-hydrazo compound **7a** with HgO gave the *meso*-azo compound **7b**. However, oxidation of the *meso*-hydrazo compound **7a** with CPBA gave a pair of enantiomorphs of the azoxy compound **7c** (viz. [(+)NNO(−)]- and [(+)ONN((−)]-), which is distinct from the pair of enantiomorphs which would be produced on CPBA oxidation of a racemic mixture of (+)- and (−)-**7a** (viz. [(−)NNO(−)]- and [(+)NNO(+)]-), although they are related as diastereoisomers. Azo and azoxy compounds can exist in *cis*- and *trans*- forms although one isomer is often more stable than the other;[18] therefore, such isomers are possible of each of the four enantiomorphs of **7c**, and of (+)-, (−)- and *meso*-**7b**. However, the present work shows that only one geometrical isomer (i.e. either *cis*- or *trans*-) of each diastereoisomer of **7b** and **7c** was formed, or is stable, from NMR evidence.

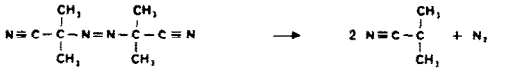
IR absorption bands due to N–O stretching in the N-oxidised amphetamine series were identified by comparison of the nitroso dimer **4a** and azoxy compound **7c** spectra with those of the primary amine **1a**, the hydrazo compound **7a** and the azo compound **7b**. Thus, in the spectrum of **7c**, there was a very strong band at 1505 cm^{-1} (considerably stronger than the medium band at 1500 cm^{-1} in the spectrum of **7b**), and a medium/strong band at 1310 cm^{-1} identified as asymmetric and symmetric stretch of the $\overset{+}{N}$–$\overset{\cdot}{O}$ group.[19] Similarly, the *trans*-nitroso dimer absorption bands could be identified.

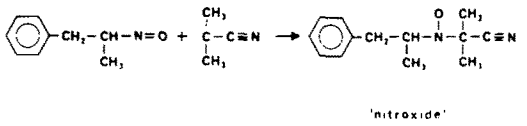
Possible application of ESR to the detection of C-nitroso compounds in metabolic extracts

C-Nitroso compounds act as efficient free radical traps to form nitroxides which give strong ESR spectra.[20] A solution of (−)-**4a** reacted in this way with azoisobutyronitrile (AIBN), a free radical precursor. At 40° the AIBN loses nitrogen to form free radicals which are trapped by the nitroso compound; probably the monomer (Scheme 2). Neither 2-hydroxylamino-1-phenylpropane **1b** nor 1-phenyl-2-propanone oxime **2a**

formed nitroxides with AIBN. ESR may thus be a potential method for detecting C-nitroso compounds in metabolic extracts and in the presence of other metabolites. However, preliminary work indicates that a minimum sample of 0.1 mg of pure **4a** is required to give an identifiable spectrum with AIBN and since viscous solutions (e.g. from concentrated extracts of hepatic fractions) tend to broaden absorption lines,[21] some purification may be required if even this quantity is to be detected in metabolic extracts.







Scheme 2.

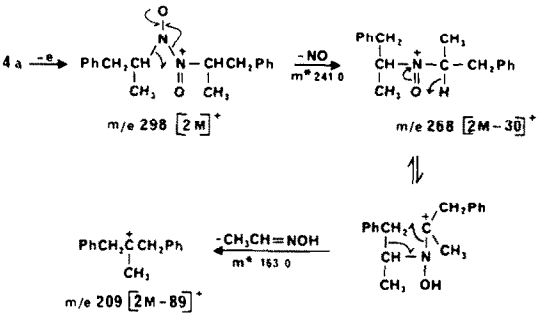
Mass spectrometry

Attempts were made to characterize the nitroso compounds synthesized in this study by their GLC retention times and mass spectral behaviour but when the compounds were examined by GLC or combined GLC/MS, they were found to rearrange to their corresponding oximes. However, they gave characteristic spectra when introduced by direct probe into the mass spectrometer and if scanned to a sufficiently high mass value, gave ions corresponding to the dimer molecular ion ($2M^{+\cdot}$) in most instances (**4a–4d**, **4f**, **4g**, **4i**, **5** and **6**). In some spectra (**4a–4d**, **4g**, **4i** and **6**), ions of mass $[2M-30]^+$ were observed, and the presence of appropriate metastable ions in most of these spectra confirmed that the $2M^{+\cdot} \rightarrow [2M-30]^+$ transition was a direct fragmentation which can be interpreted as the expulsion of an NO radical from the $2M^{+\cdot}$ ion. Nitroso compounds **4a** and **4i** fragmented further yielding $[2M-89]^+$ and $[2M-75]^+$ ions respectively. Metastable ions were again present in the spectra which indicated that these last two ions were derived from the $[2M-30]^+$ fragment and not the bimolecular ion.

A mechanism which explains the formation of a $2M^{+\cdot}$ ion, and the loss of 30 mass units from the bimolecular ion of **4a** is suggested in Scheme 3. A similar fragmentation pathway may occur with compound **4i** such that the bimolecular ion first expels an NO radical which then loses a formaldoxime molecule to produce the carbonium ion, $PhCH_2\dot{C}HCH_2Ph$, *m/e* 195, $[2M-75]^+$; metastables located at *m/e* 213.3 and 158.4 support the pathway:

$$m/e\ 270 \xrightarrow{-NO} m/e\ 240 \xrightarrow{-CH_2=NOH} m/e\ 195$$

Nitroso compound **6** also formed a bimolecular ion (*m/e* 310) which expelled an NO radical yielding the fragment *m/e* 280 (m* 252.9). In addition, the $2M^{+\cdot}$ ion expelled an OH radical to yield the fragment ion *m/e* 293 (m* 276.9).



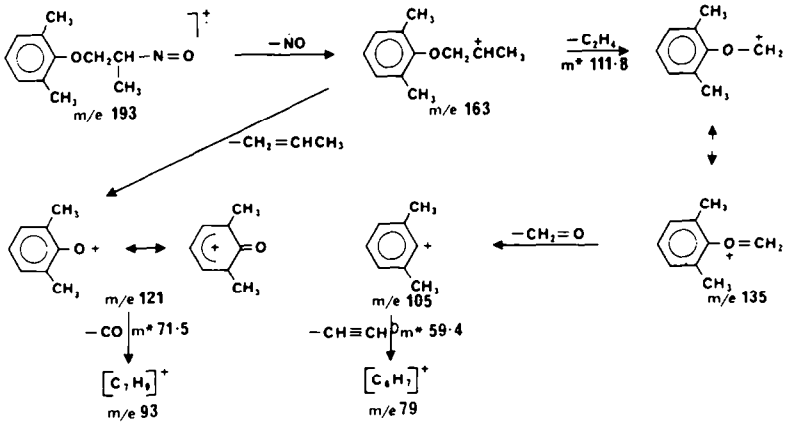
Scheme 3.

Speculation on the structure of this $[2M-17]^+$ ion is not warranted. Nitroso compounds **4f** and **5** both gave $2M^{+\cdot}$ ions of very low relative abundance (<0.2%) but in neither instance was a $[2M-30]^+$ fragment observed. In each instance, however, other fragment ions of mass greater than $M^{+\cdot}$ were recorded (see Experimental); they were also of low relative abundance and are formed by obscure mechanisms.

The monomer molecular ion ($M^{+\cdot}$) was present in the spectra of all the nitroso compounds examined with the exception of the only non-aralkyl nitroso compound **6**. The relative abundance of each monomolecular ion of **4a–4i** and **5** was seldom greater than 30%, in contrast with the isomeric oximes where $M^{+\cdot}$ was seldom less than 30% abundant. Monomolecular ions of **4a–4g** fragmented in identical fashion by first expelling an NO radical followed by an ethylene molecule. The resulting benzylium (or tropylium) ion fragmented further in predictable[22] fashion. The benzylium ion could be formed directly from the molecular ion but metastable ions were present in most spectra which supported the $M^{+\cdot} \rightarrow [M-30]^+ \rightarrow [M-58]^+$ sequence. The monomolecular ion of nitroso compound **4i** was relatively weak (5%) and, in typical fashion, it lost 30 mass units to yield the base peak at *m/e* 105. This latter ion apparently rearranges in the mass spectrometer; it fragmented further to the ion *m/e* 79 ($C_6H_7^+$) by expelling an acetylene molecule. A metastable ion in support of this pathway was present at *m/e* 59.4. The monomolecular ion of **4i** also degraded in the mass spectrometer to the benzylium ion *m/e* 91 which fragmented further as expected.[22]

The mass spectrum of nitroso compound **5** contained a monomolecular ion, *m/e* 193, which fragmented in a more complex manner than the previously described monomolecular ions. Appropriate pathways which explain the formation of most ions are suggested in Scheme 4. The monomolecular ion of **4h** was of low abundance (*m/e* 165, 2%). The $[M+1]^+$ ion, presumably $PhCHOHCH(CH_3)\dot{N}=OH$, was more abundant (5%). As in the other nitroso spectra, the $[M-30]^+$ ion (*m/e* 135, 45%) and the $[M-58]^+$ ion (*m/e* 107, 51%) were abundant ions, but the base peak was located at *m/e* 77, due undoubtedly to the ease with which the *m/e* 107 ion fragments further.

The monomer molecular ion (*m/e* 155) of nitroso compound **6** lacked the stabilizing effect of an aromatic ring and was not detected in the mass spectrum. An $[M+1]^+$ ion, however, was present (cf. monomolecular ion of **4h**). The ion $[M-30]^+$ was fairly abundant but there was no significant ion of *m/e* 97 $[M-58]^+$, presumably due to its instability and facile decomposition. Strong ions



Scheme 4.

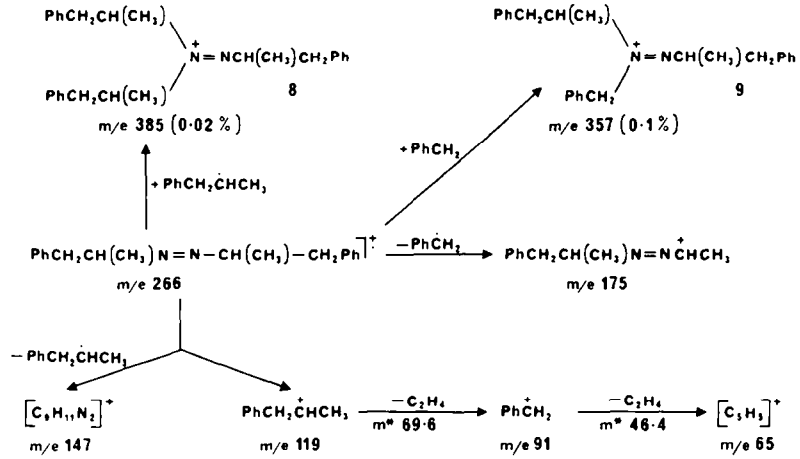
were present at *m/e* 83, 69, 55 and 41, all of which can be envisaged as deriving from the $[M-30]^+$ fragment.

In many of the nitroso spectra, additional ions were seen. Most nitroso compounds expelled an OH radical or a water molecule from the monomolecular ion giving rise to $[M-17]^+$ and $[M-18]^+$ fragments. In the spectra of compounds **4a–4d**, **4f** and **4g**, appropriate metastable ions were present which supported the concept of a direct $M^+ \rightarrow [M-18]^+$ fragmentation. In the spectra of **4g** and **5** the $M^+ \rightarrow [M-17]^+$ fragmentation was accompanied by a metastable transition. In addition, an ion of *m/e* 58 ($CH_3\dot{C}$=NOH) was found in some nitroso spectra. This fragment is also observed in the spectra of certain aralkyl oximes.[23] Undoubtedly, some nitroso to oxime isomerization occurs in the mass spectrometer and these additional ions are thought to arise as a result of such a rearrangement even though the probe temperature was kept as low as possible when the spectra were being recorded. In contrast with the nitroso compounds, however, the spectra of the corresponding oximes did not contain $[M-30]^+$ ions of significant intensity, nor ions of mass greater than M^+.

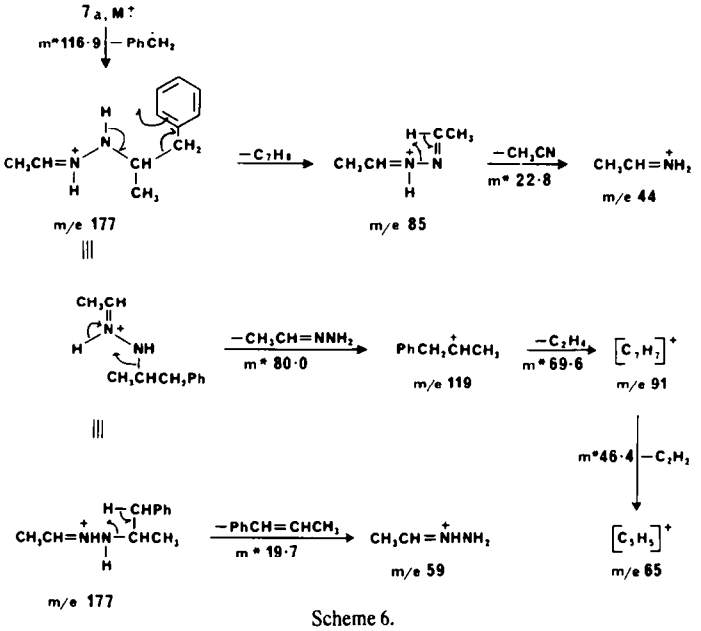
The mass spectra of the hydrazo **7a**, azo **7b** and azoxy **7c** derivatives of 2-nitroso-1-phenylpropane **4a** were recorded and used for characterization purposes. The azo compound **7b** gave a molecular ion (*m/e* 266) of low relative abundance (0.5%). Diagnostic fragments were present in the spectrum at *m/e* 175 (3%), 147 (2%), 119 (54%), 91 (100%) and 65 (4%). All are readily accounted for (Scheme 5). Two other ions, *m/e* 385 and 357, were present in very low abundance; both were formed apparently as the result of ion-radical interactions. Interaction of the molecular ion (*m/e* 266) with the $PhCH_2C\dot{C}HCH_3$ radical would yield the ion *m/e* 385 **8**, while a similar reaction involving the benzyl radical would give the ion *m/e* 357 **9**. The azoxy derivative **7c** gave only a weak molecular ion (*m/e* 282, 0.5%) and fragment ions of similar or lower intensities at *m/e* 252 $[M-NO]^+$, *m/e* 265 $[M-OH]^+$, *m/e* 209 and 207. The strongest ions in the spectrum were located at *m/e* 119, 91 and 65 (cf. Scheme 5). Another diagnostic ion was located at *m/e* 191 (6%) and was the result of the expulsion of a benzyl radical from the molecular ion. The hydrazo compound **7a** gave a spectrum containing many metastable ions which were of assistance in interpreting fragmentation pathways. Important ions in the spectrum were located at *m/e* 268 (16%), 177 (100%), 119 (30%), 85 (21%), 65 (7%), 59 (28%) and 44 (18%). An additional ion at *m/e* 134 (4%) is concluded to be a doubly-charged ion. Possible mechanisms for the formation of fragments *m/e* 119, 85, 59 and 44 from the molecular ion of **8a** are suggested in Scheme 6.

ADDENDUM

Lindeke *et al.*[25] recently described the formation of "2-nitroso-1-phenylpropanes", eg. **4a**, by alkaline potassium



Scheme 5.



Scheme 6.

ferricyanide oxidation of hydroxylamine **1b**, but did not fully characterise the products. They state that "fraction 1" (of the nitroso dimers obtained by oxidation of N-hydroxy amphetamine), isomerises to give an NMR spectrum similar to that of "fraction 2". They imply that "fraction 1" is a *cis*- dimer isomer and by implication that "fraction 2" is a mixture of *cis* and *trans*-isomers of 2-nitroso-1-phenylpropane dimer. Presumably the authors used racemic hydroxylamine-**1b**. Oxidation would therefore produce (+)-, (−)- and *meso*- diastereomeric dimers. We have shown that *meso-trans*-**4a**- nitroso dimer gradually equilibrates to an approximately equal mixture of (+)-, (−)- and of *meso*-**4a** dimers on standing in chloroform. The solid so obtained, after separation of any oxime **2a** formed, would give a lower melting point than that of the pure *meso-trans*-**4a**. (Lindeke *et al.*[25] found their "fraction 2" had a much lower melting point than "fraction 1".) Thus from the IR, NMR and melting point data produced by Lindeke *et al.*[25] their "fraction 1" is probably the *meso-trans*-dimeric isomer of 2-nitroso-1-phenylpropane, and their "fraction 2" is a mixture of *meso*-, (+)- and (−)-dimeric isomers of the nitroso compound.

EXPERIMENTAL

M.p (capillary tubes) are uncorrected. IR spectra were recorded on a Unicam SP1000 spectrophotometer as Nujol mulls or films. NMR spectra were recorded on a 90 MHz Perkin Elmer R32 spectrometer as 10% solutions in $CDCl_3$ with 1% TMS as the locking signal; the δ values are measured centres of the groups and coupling constants quoted (where possible) in Hz (the methylene protons of **4a–4g**, **6** and **7a–7c** are reported separately as CH_A and CH_B). UV spectra were obtained using a Unicam SP800 spectrophotometer; ORD spectra were recorded on a Bellingham Stanley/Bendix Erikson Polaromatic 62 spectrophotometer equipped with a 250 w Supersil Xenon lamp with constant nitrogen purging and operating at room temperature; and CD spectra were recorded on a Roussel-Jouan Dichrographe Model 1. Direct inlet MS were obtained using an AEI MS-9 or MS-12 or a Perkin Elmer 270 mass spectrometer with a 70 eV ionising potential and probe and temperatures of 90–200°C. Combined GLC/MS spectra were recorded on a Perkin Elmer model 270 GLC/mass spectrometer with a glass column length 1 m, o.d. 0.64 cm containing 2% Carbowax 20 M on Chromosorb W 100–120 mesh, acid washed and DCMS treated; helium (20 lb. in^{-2}) was used as the carrier gas; the oven temperature was 180–200°C and the ionising potential 70 eV. GLC was carried out on a Perkin Elmer F11 instrument which incorporated a flame ionisation detector. A glass column was used of length 1 m o.d. 0.64 cm packed with 2% Carbowax 20 M on Chromosorb G 100–120 mesh, acid washed and DMCS treated; nitrogen was the carrier gas (80 ml min^{-1}) and an oven temperature of 160°C. TLC was carried out on plates spread to a thickness of 0.25 mm with silica gel HF_{254} and run in: benzene (18) ethyl acetate (6) water (0.5). Vapour pressure osmometry was performed on a Mechrolab Vapour Pressure Osmometer model 301 A using recrystallised benzil for the calibration curve and a thermister bead temperature of 37°C. ESR spectra were run on a Varian E4 ESR spectrometer. Molar quantities of all the nitroso compounds were calculated with respect to the dimer.

(+)-2-*Nitroso*-1-*phenylpropane* **4a**

A solution of 3-chloroperbenzoic acid (CPBA) (0.32 g, 1.86 mmole) in chloroform was added over 15 min to a cooled (0–5°) chloroform solution of (+)-2-amino-1-phenylpropane base (extracted from the (+)-sulphate 0.14 g, 0.38 mmole with 20% NaOH). The reaction mixture was allowed to stand over ice for a further 15 min and then at room temperature for an additional 60 min. The chloroform was then removed on a rotary film evaporator (40°) to yield a white solid which was dissolved in ether and extracted with excess 10% KCO_3 solution. The ether layer was dried (Na_2SO_4) and evaporated to yield a white solid. Recrystallisation from ether/pentane gave the title compound (0.064 g, 57% yield), m.p. 100–102°; NMR ($CDCl_3$) δ 1.28 (d, J = 6.6, 3, CH_3) 2.65 (q, J_{AC} = 7.6, 1, CH_A) 3.01 (q, J_{BC} = 7.1, J_{AB} = 13.8, 1, CH_B) 5.53 (m, 1, CH_2-CH_C) 7.19 (s, 5, Ar); IR (Nujol) ν max 695, 740, 750, 1025, 1075, 1085, 1095, 1185 and 1240 (nitroso *trans*-dimer), 1376, 1395, 1455, 1505, 2860–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 298 (M$^+$, 3), 268 (20), 209 (1), 149 (8), 120 (10), 119 (40), 117 (10), 92 (11), 91 (100), 77 (10), 65 (11), 51 (11), 41 (21), 39 (10), mestables (m*) at 241.0, 163.0, 69.6, 46.4; UV (ethanol) λ_{max} 292, log ϵ = 3.91; $[\alpha]_D^{20}$ = +139°; ORD λ_{max}^{EtOH} 377 nm $[\alpha]_{377}^{20}$ = +394°, λ_{max}^{EtOH} = +337° nm $[\alpha]_{337}^{20}$ = −40°. (Found: C, 72.32; H, 7.45; N, 9.17. $(C_9H_{11}NO)_2$: requires C, 72.48; H, 7.38; N, 9.40%).

(−)-2-*Nitroso*-1-*phenylpropane* **4a**

This was prepared as described immediately above from (−)-1 a base (5.0 g, 37.0 mmole) and CPBA (15.0 g, 87.0 mmole) as a white solid (2.98 g, 54% yield), m.p. 100–102°; NMR and IR were as reported for the (+)-isomer; UV (ethanol) λ_{max} 292 nm, log ϵ = 3.91; $[\alpha]_D^{20}$ = −129°.

Meso-(±)-2-*nitroso*-1-*phenylpropane* **4a**

This was prepared as described above for (+)-**4a** from (±)-**1a** base (2.0 g, 14.8 mmole) and CPBA (6.8 g, 34.8 mmole) as white nitroso dimer (1.24 g, 56% yeild), the first crystallisation (0.65 g) being pure *meso*-dimer m.p. 94–96°; NMR ($CDCl_3$) δ 1.14 (d, J = 6.6, 3, CH_3) 2.77 (q, J_{AC} = 6.8, 1, CH_A) 3.17 (q, J_{BC} = 8.0, J_{AB} = 13.8, 1, CH_B) 5.60 (m, 1, CH_2–CH_C) 7.20 (s, 5, Ar); IR (Nujol) ν_{max} 700, 755, 1020, 1075, 1160–1180–1195 and 1225 (nitroso *trans*-dimer), 1380, 1395, 1460, 1500, 2860–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 298 (M^+, 1), 268 (7), 149 (16), 119 (51), 117 (14), 116 (13), 92 (22), 91 (100), 77 (14), 65 (21), 51 (16), 41 (24), 39 (21), metastables (m*) at 69.6, 46.4; UV (ethanol) λ_{max} 294 nm, log ϵ = 3.91.

(±)-2-*Nitroso*-1-(4′-*chlorophenyl*) *propane* **4b**

This was prepared as described for (+)-**4a** from (±)-2-amino-1-(4′-chlorophenyl)propane hydrochloride (0.54 g, 2.62 mmole) and CPBA (1.13 g, 6.55 mmole) as recrystallised, mixed (+)-, (−)- and *meso*-dimers (0.40 g, 83% yield) m.p. 106–109°; NMR δ 1.17 (d, 3, CH_3) 2.76 (q, 1, CH_A) 3.16 (q, 1, CH_B) *ca.* 5.53 (m, 1, CH_2–CH) *ca.* 7.00–7.32 (m, 4, Ar) (*meso*-isomer); δ 1.32 (d, 3, CH_3) 2.68 (q, 1, CH_A) 3.08 (q, 1, CH_B) *ca.* 5.53 (m, 1, CH_2–CH) *ca.* 7.00–7.32 (m, 4, Ar) ((+)- and (−)-isomers); IR (Nujol) ν_{max} 665, 720, 800, 850, 1020, 1030, 1095, 1190 and 1225 (nitroso *trans*-dimer), 1380, 1395, 1465, 1500, 2850–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 368 (0.1), 366 (0.2), 338 (1.2), 336 (1.5), 185 (6), 183 (19), 165 (9), 155 (26), 154 (11), 153 (70), 150 (16), 127 (32), 126 (15), 125 (100), 117 (10), 91 (10), 89 (16), 58 (14), 41 (31), 39 (13), metastables (m*) at 148.8, 138.4, 136.4, 104.1, 102.1; UV (ethanol) λ_{max} 294 nm, log ϵ = 3.88. (Found: C, 58.84; H, 5.32; N, 7.80. $(C_9H_{10}NOCl)_2$ requires C, 58.86; H, 5.45; N, 7.63%).

(±)-2-*Nitroso*-1-(4′-*nitrophenyl*)*propane* **4c**

This was prepared as described for (+)-**4a** from (±)-2-amino-1-(4′-nitrophenyl)propane hydrochloride (0.37 g, 1.71 mmole) and CPBA (0.74 g, 4.30 mmole) as mixed (+)-, (−)- and *meso*-dimers (0.29 g, 87% yield), m.p. 134–138°; NMR ($CDCl_3$) δ 1.16 (d, 3, CH_3) 2.87 (q, 1, CH_A) 3.28 (q, 1, CH_B) *ca.* 5.6 (m, 1, CH_2–CH) *ca.* 7.3 and 8.1 (m, 4, Ar) (*meso*-isomer), δ 1.36 (d, 3, CH_3) 2.80 (q, 1, CH_A) 3.19 (q, 1, CH_B) *ca.* 5.6 m, 1, CH_2–CH) *ca.* 7.3 and 8.1 (m, 4, Ar)((+)- and (−)-isomers); IR (Nujol) ν_{max} 695, 745, 855, 865, 1110, 1185 and 1220 (nitroso *trans*-dimer), 1350, 1475, 1525, 1610, 2860–3020 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 388 (M^+, 0.04), 358 (0.08), 330 (0.06) 194 (11), 176 (9), 165 (10), 164 (55), 137 (13), 136 (100), 118 (26), 117 (31), 116 (10), 115 (18), 106 (34), 103 (12), 91 (31), 90 (32), 89 (30), 78 (59), 77 (27), 65 (12), 63 (24), 58 (19), 51 (22), 50 (16), 41 (21), 39 (30); m* 330.3, 159.7, 112.8, 82.6; UV (ethanol). λ_{max} 272, log ϵ = 4.36. (Found: C, 55.74; H, 5.20; N, 14.43. $(C_9H_{10}N_2O_3)_2$ requires C, 55.67; H, 5.15; N, 14.43%).

(±)-2-*Nitroso*-1-(3′-*trifluoromethylphenyl*)*propane* **4d**

This was prepared as described for (+)-**4a** from (±)-2-amino-1-(3′-trifluoromethylphenyl) propane hydrochloride (0.12 g, 0.50 mmole) and CPBA (0.21 g, 1.22 mmole) as recrystallised mixed (+)-, (−)- and *meso*-dimers (0.046 g, 42% yield), m.p. 86.5–87.5°; NMR ($CDCl_3$) δ 1.14 (d, J = 6.1, 3, CH_3) 2.83 (q, J_{AC} = 6.1, J_{AB} = 13.9, 1, CH_A) 3.23 (q, J_{BC} = 8.5, 1, CH_B) *ca.* 5.58 (m, 1, CH_C) *ca.* 7.2–7.6 (m, 4, Ar) (*meso*-isomer); δ 1.32 (d, J = 6.1, 3, CH_3) 2.72 (q, J_{AC} = 6.9, 1, CH_A) 3.09 (q, J_{BC} = 7.6, J_{AB} = 13.9, 1, CH_B) *ca.* 5.58 (m, 1, CH_2–CH_C) *ca.* 7.2–7.6 (m, 4, Ar) (+)- and (−)-isomers); IR (Nujol) ν_{max} 705, 800, 1030, 1080, 1130–1190 and 1230 (nitroso *trans*-dimer), 1335, 1455, 2860–3020 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 434 (M^+, 0.002), 404 (0.025), 374 (0.005), 259 (0.015), 246 (0.012), 217 (10), 199 (10), 187 (23), 160 (10), 159 (100), 109 (7), 58 (13), 41 (15), metastables (m*) at 182.5, 135.2, 74.7; UV (ethanol) λ_{max} 294, log ϵ = 3.91. (Found: C, 55.26; H, 4.61; N, 6.42. $(C_{10}H_{10}NOF_3)_2$ requires C, 55.30; H, 4.61; N, 6.45%).

(±)-2-*Nitroso*-1-(3′-*methoxyphenyl*)*propane* **4e**

This was prepared as described for (+)-**4a** from (+)-2-amino-1-(3′-methoxyphenyl) propane bitartrate (0.30 g, 1.26 mmole) and CPBA (0.54 g, 3.13 mmole) as 0.17 g of crude nitroso which would not readily crystallise. GLC and NMR analysis showed the product to be approximately 97% of the title compound. The following data was obtained from this product; NMR ($CDCl_3$) δ 1.29 (d, 3, CH_3) 2.63 (q, 1, CH_A) 3.01 (q, 1, CH_B) 3.74 (s, 3, OCH_3) 5.54 (m, 1, CH_2–CH) 6.74 and 7.16 (m, 4, Ar); IR (film) ν_{max} 695, 780, 1045, 1160, 1210 (broad band, nitroso *trans*-dimer), 1270, 1380, 1500, 1590, 1605, 2835, 2865–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 179 (M^+, 5), 150 (13), 149 (77), 148 (12), 134 (10), 122 (15), 121 (100), 91 (37), 78 (14), 65 (10), 51 (10), 41 (20), 39 (10), metastables (m*) at 98.3, 68.4, 46.4; UV (ethanol) λ^{275}_{max}, log ϵ = 3.92, λ^{280}_{max}, log ϵ = 3.96, λ^{290}_{max}, log ϵ = 3.83.

(±)-2-*Nitroso*-1-(3′,4′-*dimethoxyphenyl*)*propane* **4f**

This was prepared as described for (+)-**4a** by Dr. P. H. Morgan from (±)-2-amino-1-(3′,4′-dimethoxyphenyl) propane (2.4 g, 12.31 mmole) and CPBA (4.2 g, 24.35 mmole) as recrystallised mixed (+), (−) and *meso*-dimers 1.0 g, 39% yield), m.p. 133–134°; NMR ($CDCl_3$) δ 1.16 (d, J = 6.2, 3, CH_3) 2.72 (q, J_{AC} = 6.8, 1, CH_A) 3.12 (q, J_{BC} = 8.1, J_{AB} = 13.9, 1, CH_B) *ca.* 3.81 and 3.84 (2s, 6, $2OCH_3$) *ca.* 5.6 (m, 1, CH_2–CH_C) *ca.* 6.75 (s, 3, Ar) (*meso*-isomer), δ 1.31 (d, J = 6.2, 3, CH_3) 2.62 (q, J_{AC} = 7.4, 1, CH_A) 3.02 (q, J_{BC} = 7.0, J_{AB} = 13.9, 1, CH_B) *ca.* 3.81 and 3.84 (2s, 6, $2OCH_3$) *ca.* 5.6 (m, 1, CH_2–CH_C) *ca.* 6.75 (s, 3, Ar) ((+)- and (−)-isomers); IR (Nujol) ν_{max} 810, 855, 1020, 1035, 1140, 1155, 1205 (nitroso *trans*-dimer), 1245, 1260, 1440, 1470, 1500, 1520, 1590, 1610, 2840–3000 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 418 (M^+, 0.2), 362 (0.14), 293 (0.78), 283 (0.14), 256 (0.10), 209 (65), 180 (12), 179 (100), 178 (14), 164 (14), 152 (10), 151 (78), 148 (10), 138 (13), 107 (16), 91 (21), 78 (11), 77 (18), 51 (12), 41 (13), 39 (15), metastables (m*) at 176.4, 127.4; UV (ethanol) λ_{max} 281 nm, log ϵ = 4.09. (Found: C, 63.06; H, 7.20; N, 6.59. $(C_{11}H_{15}NO_3)_2$ requires: C, 63.14; H, 7.23; N, 6.63%).

(±)-2-*Nitroso*-1-(3′,4′-*dimethylphenyl*)*propane* **4g**

This was prepared as described for (+)-**4a** from 2-amino-1-(3′,4′-dimethylphenyl) propane sulphate (0.13 g, 0.61 mmole) and CPBA (0.28 g, 1.62 mmole) as recrystallised *meso*-dimer (0.7 g, 65% yield) m.p. 86–88°; NMR ($CDCl_3$) δ 1.17 (d, J = 6.4, 3, CH–CH_3) 2.19 (s, 6, Ar–$2CH_3$) 2.69 (q, J_{AC} = 7.2, 1, CH_A) 3.11 (q, J_{BC} = 7.2, J_{AB} = 13.6, 1, CH_B) 5.54 (m, 1, CH_2–CH_C) 6.95 (m, 3, Ar); IR (Nujol) ν_{max} 755, 815, 1030, 1120, 1190 and 1225 (nitroso *trans*-dimer), 1375, 1390, 1450, 1465, 1510, 2865–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 354 (M^+, 0.2), 324 (0.7), 177 (21), 147 (40), 144 (12), 120 (13), 119 (100), 117 (13), 105 (15), 91 (22), 77 (13), 51 (10), 44 (11), 41 (32), 39 (16), metastables (m*) at 296.5, 142.8, 96.3, 69.6, 46.4; UV (ethanol) λ_{max} 294, log ϵ = 3.89. (Found: C, 73.99; H, 8.49; N, 7.73. $(C_{11}H_{15}NO)_2$ requires: C, 74.58; H, 8.47; N, 7.91%).

(±)-1-*Hydroxy*-2-*nitroso*-1-*phenylpropane* **4h**

This was prepared as described for (+)-**4a** from (±)-*erythro*-2-amino-1-hydroxy-1-phenylpropane hydrochloride (1.24 g, 6.61 mmole) and CPBA (2.9 g, 16.81 mmole) and separated from benzaldehyde and other products on a silica gel column (solvent: benzene 18, ethyl acetate 6) to give the nitroso dimer (0.015 g, 1.4% yield), m.p. 126–127°; NMR ($CDCl_3$, 1%) δ 1.23 (d, J = 6.9, CH_3) 5.12 (d, J = 3.3, Ar–CH) 5.47 (m, CH–CH_3) 7.35 (s, Ar) (isomer not determined); IR (KCl) ν_{max} 675, 695, 760, 1025, 1055, 1080, 1210 (nitroso *trans*-dimer), 1370, 1385, 1455, 3450 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 166 (5), 165 (M^+, 2), 135 (45), 118 (27), 117 (27), 107 (51), 106 (67), 105 (72), 91 (26), 79 (46), 78 (23), 77 (100), 60 (61), 59 (35), 57 (46), 51 (46), 50 (22), 43 (58), 41 (25). (Found: C, 64.39; H, 6.63; N, 8.37% $(C_9H_{11}NO_2)_2$ requires: C, 65.45, H, 6.67; N, 8.48%).

2-*Nitroso*-1-*phenylethane* **4i**

This was prepared as described for (+)-**4a** from 2-amino-1-phenylethane base (0.22 g, 1.82 mmole) and CPBA (0.8 g, 4.64 mmole) as the recrystallised dimer (0.2 g, 82% yield), m.p. 92.0–92.5°; NMR ($CDCl_3$) δ 3.11 (m, 2, Ar–CH_2) 4.48 (m, 2, CH_2–N=) 7.24 (s, 5, Ar); IR (Nujol) ν_{max} 700, 745, 755, 930, 1225 (nitroso *trans*-dimer), 1300, 1380, 1460, 2850–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 270 (M^+, 2), 240 (9), 195 (1), 149 (1), 135 (5), 117 (8), 106 (12), 105 (100), 103 (13), 91 (27), 79 (22), 77

(23), 51 (9), metastables (m*) at 213.3, 158.4, 69.2, 59.4, 46.4; UV (ethanol) λ_{max} 290, log ϵ = 3.95. (Found: C, 71.08; H, 6.86; N, 10.06. $(C_6H_9NO)_2$ requires: C, 71.11; H, 6.67; N, 10.37%).

(±)-2-Nitroso-1-(2',6'-dimethylphenoxy) propane **5**

This was prepared as described for (+)-**4a** from (±)-2-amino-1-(2',6'-dimethylphenoxy) propane hydrochloride (0.12 g, 0.56 mmole) and CPBA (0.24 g, 1.39 mmole) as the recrystallised *meso*-dimer (0.05 g, 46% yield), m.p. 128.5–129.5°; NMR ($CDCl_3$) δ 1.46 (d, J = 6.8, 3, CH–CH_3) 2.29 (s, 6, Ar2CH_3) 3.84 (q, J_{AC} = 4.4, 1, CH_A) 4.30 (q, J_{BC} = 8.0, J_{AB} = 9.9, 1, CH_B) 5.89 (m, 1, CH_2–CH_C) 6.97 (s, 3, Ar); IR (Nujol) ν_{max} 765, 1025, 1065, 1090, 1185 and 1205 (nitroso *trans*-dimer and ether), 1250, 1260, 1370, 1380, 1470, 2820–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 386 (M^+, 0.02), 385 (0.02), 369 (0.02), 313 (0.1), 278 (5), 277 (3), 241 (0.5), 193 (28), 163 (53), 135 (8), 122 (33), 121 (82), 107 (12), 105 (100), 103 (11), 91 (26), 79 (22), 77 (41), metastables (m*) at 160.5, 11.8, 101.3, 93.8, 71.5, 59.4; UV (ethanol) λ_{max} 292 nm, log ϵ = 3.95. (Found: C, 68.30; H, 7.91; N, 7.09. $(C_{11}H_{15}NO_2)_2$ requires: C, 68.39; H, 7.77; N, 7.25%).

(±)-2-Nitroso-1-cyclohexylpropane **6**

This was prepared as described for (+)-**4a** from (±)-2-amino-1-cyclohexylpropane hydrochloride (3.0 g, 16.9 mmole) and CPBA (7.5 g, 43.5 mmole) as an off-white solid (1.51 g, 58% yield) crystallised from *n*-heptane in an acetone/solid CO_2 bath; m.p. 64–68°; NMR ($CDCl_3$) δ 0.60–2.30 (broad multiplet, C_6H_{11}–CH_2 [CH_2 located *ca.* δ 2.10 by SDC at δ 5.55–CH]) 1.29 (d, J = 6.2, CH_3) 5.55 (m, CH–CH_3); IR (Nujol) ν_{max} 1005, 1120, 1185 and 1225 (nitroso *trans*-dimer), 1365, 1450, 2840–3000 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 310 (M^+, 0.8) 293 (0.13), 280 (1.3), 198 (0.3), 184 (1.1), 156 (6), 126 (6), 125 (25), 83 (47), 69 (78), 67 (15), 57 (18), 55 (100), 43 (16), 41 (85), 39 (21), metastables (m*) at 276.93, 252.90, 86.91, 36.45, 24.36; UV (ethanol) λ_{max} 295 nm, log ϵ = 3.91. (Found: C, 69.36; H, 10.68; N, 8.73. $(C_9H_{17}NO)_2$ requires: C, 69.68; H, 10.97; N, 9.03%).

Attempt to prepare **1b** *by partial oxidation of* **1a** *with CPBA*

Compound **1a** (0.3 g, 2.22 mmole) was oxidised with CPBA (0.1 g, 0.58 mmole) in chloroform, over ice, similarly to the preparation of (+)-**4a**. The final ethereal solution gave rise to the amine peak **1a** and an oxime peak (i.e. **4a** and/or **2a**) on GLC but no hydroxylamine peak **1b**; neither did the ethereal layer give a positive reaction with Tollens reagent. The solution was subsequently washed with 2N hydrochloric acid to remove the amine **1a** and after evaporation of the solvent, the residue was examined by NMR and found to contain **2a** (*syn* and *anti*) and **4a** in a ratio of approximately 4:3.

Effect of heat on (−)-2-nitroso-1-phenylpropane dimer **4a**

(a) *Solid.* Compound **4a** was heated rapidly in a melting point apparatus. The colourless dimer melted and at about 20° above its m.p. became pale blue, deepening in colour until at 160–170° the blue colour irreversibly changed to a straw colour. The oil did not crystallise on cooling; NMR ($CDCl_3$) δ 1.80 (s, CH_3 *syn*- and *anti*-) 3.48 (s, CH *anti*) 3.72 (s, CH *syn*-) 7.24 (s, Ar *syn*- + *anti*-), ratio of *syn*:*anti* 1:2, identified as isomers of 1-phenyl-2-propanone oxime **2a** by reference to an authentic sample.

(b) *Solution.* A solution of (−)-**4a** (10% w/v in $CDCl_3$) was warmed in a sealed tube for 2 hr at 35°C; 2% decomposition to the oxime **2a** occurred (NMR). The VTP (variable temperature probe) facility on an R32 spectrometer was used to raise the temperature of the solution to 100° and spectra recorded at various intervals. The solution was pale blue at 100°, but no other spectrum was observed except that due to residual starting material (−)-**4a** and the oxime **2a**.

*Effect of heat (60°) on an equimolar solution of (+)- and (−)-***4a**

The NMR spectrum was recorded, of an equimolar mixture of (+)- and (−)-**4a** (0.02 g each) in $CDCl_3$ (0.4 ml) at 35°. The VTP control, on the NMR spectrometer, was set at 60° 8 min after preparing the solution and the spectrum recorded such that the methyl signal (*ca.* 1.2 ppm) was scanned exactly 5 min after setting the VTP control. Spectra were recorded initially at 5 min intervals and after 1 hr at 15 min intervals until an equilibrium between the (+)-/(−)-and *meso*-isomers was established. Methyl signal heights for the (+)-/(−)-isomers, the *meso*-isomer and the oxime **2a** formed were plotted as a percentage of total methyl signal heights against time, where zero was taken to be the moment when the VTP control was initially set to 60° (see Fig. 1). A solution of (−)-**4a** (0.04 g) in $CDCl_3$ (0.4 ml) was also studied as described for the mixed isomers above.

*Melting point study on mixtures of (+)- and (−)-***4a**

Melting points of the (+)- and (−)-**4a** dimers were determined for ratios of mixtures from 1:9 to 9:1. The temperature at which the solid started to melt and finally melted were recorded. The ratios of (+)- to (−)-**4a** and their melting points (°C) are: 1:9, 80–98°; 2:8, 77–94°; 3:7, 75–93°; 4:6, 75–88°; 5:5, 76–80°; 6:4, 76–91°; 7:3, 75–94°; 8:2, 77–96°, 9:1, 78–98°; pure (+)- and pure (−)-**4a** both melt at 100–102°.

*Effect of aqueous sodium hydroxide on (−)-***4a**

Compound **4a** (0.1 g, 0.34 mmole) was dissolved in ether (15 ml) and shaken with N sodium hydroxide (20 ml) for 60 min. The nitroso dimer **4a** was subsequently recovered unchanged (m.p. 99°).

*Effect of ethanolic sodium hydroxide on (−)-***4a**

Compound **4a** (0.04 g, 0.13 mmole) was refluxed in sodium hydroxide (0.09 g, 2.25 mmole), water (1 ml) and 96% ethanol (20 ml) for 30 min. The volume was then reduced by half on a rotary film evaporator, water (20 ml) was added, the solution neturalised with 2N hydrochloric acid, and extracted with ether (3 × 50 ml). The dried (Na_2SO_4) ethereal extract was evaporated to dryness and examined on GLC, TLC and NMR; the main product was **2a** with some 1-phenyl-2-propanone **2b**.

Attempted reduction of **4a**

(a) *With sodium borohydride.* Compound **4a** (0.015 g, 0.05 mmole) was dissolved in 96% ethanol (2 ml) and added to a solution of sodium borohydride (0.4 g, 10.8 mmole) in 96% ethanol (2 ml). No reduction was observed after 4 hr at 20°C or on subsequent refluxing for 5 min (GLC, TLC).

(b) *With zinc dust and ammonium chloride solution* (pH 6.8). An ethanolic solution of **4a** (0.025 g, 0.084 mmole, in 2 ml) was shaken with zinc dust (0.03 g, 0.46 mmole) and a solution (2 ml) containing ammonium chloride (2.7%) adjusted to pH 6.8 with 2N ammonia, for 2 hr at 20°C. The products were extracted with ether and were the amine **1a**, the hydrazo **7a**, azo **7b** and azoxy **7c** compounds (analysed by GLC and TLC); a negligable amount of the hydroxylamine **1b** was detected.

(c) *With lithium aluminium hydride (LAH).* Compound **4a** (0.1 g, 0.34 mmole) was reduced with LAH (0.015 g, 0.43 mmole) in dry ether for 20 min, over ice. After destroying the excess LAH with water, the solution was extracted with ether (2 × 10 ml) and the ethereal extract examined on GLC and TLC. Approximately 20% each of the hydrazo **7a**, azo **7b** and azoxy **7c** compounds, 15% of the hydroxylamine **1b**, and 5% amine **1a** were formed; the remainder was oxime **2a** or unchanged nitroso compound **4a** (GLC, GLC/MS). Note: A similar reduction of the oxime **2a** yielded a solution of the amine **1a** and the hydroxylamine **1b**, however, only about 10% overall reduction occurred (GLC).

Catalytic hydrogenation

The *meso*-isomer of **4a** (1.0 g, 3.36 mmole) was catalytically reduced under 1 atm of hydrogen, in concentrated sulphuric acid (5 ml) and 96% ethanol (50 ml), using 5% platinum on charcoal (50 mg) as the catalyst. The hydrogen was generated from a M sodium borohydride solution in a Brown hydrogenator.[24] After 18 h water (100 ml) was added, the catalyst removed and the neutral products extracted with ether (2 × 100 ml). The ether layer was dried (Na_2SO_4) and the ether removed *in vacuo* to yield a yellow oil (0.7 g), which was examined on GLC and NMR. The aqueous layer was neutralised with sodium bicarbonate and extracted with ether (2 × 100 ml). The ether extract was dried (Na_2SO_4) and the basic products precipitated with an ethereal oxalic acid solution to yield a white solid (0.12 g) which was

further partitioned between sodium carbonate solution and ether and analysed by GLC. The basic fraction contained mainly the hydrazo **7a** derivative (*ca.* 90%, GLC), and the neutral fraction about 85% of the azoxy **7c** derivative and 15% of an unidentified compound (GLC R_T 7.2 mins cf. $7cR_T$ 16.2 mins) and some 1-phenyl-2-propanone **2b** (GLC, NMR).

Zinc dust and 2N *hydrochloric acid*

See the preparation of (−)-hydrazodi-(1-methyl-2-phenylethane) below.

(−)-*Hydrazodi*-(1-*methyl*-2-*phenylethane*) **7a**

Compound **4a** (0.4 g, 1.34 mmole) was ground up with zinc dust (4.0 g, 61.5 mmole), 2N hydrochloric acid (30 ml) was triturated into the powder and the suspension transferred to a conical flask. Methanol (10 ml) was added and the solution stirred for 24 h. The suspension was then filtered, washed with water and the filtrate extracted with chloroform (2 × 60 ml). The aqueous layer was discarded and the chloroform extract dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The solid residue was washed with ether (3 × 50 ml, discarding the washings) to yield the title compound as the monohydrochloride (0.17 g, 42% yield), m.p. 174–180°; NMR ($CDCl_3$) δ 1.23 (d, 3, CH_3) 2.67 (q, 1, CH_A) 3.31 (q, 1, CH_B) *ca.* 3.6 (m, 1, CH_2–CH) 7.19 (s, 5, Ar) (mono HCl salt), δ 0.96 (d, J = 6.2, 3, CH_3) 2.47 (q, J_{AC} = 6.7, 1, CH_A) 2.72 (q, J_{BC} = 6.3, J_{AB} = 13.2, 1, CH_B) *ca.* 2.95 (m, 1, CH_2–CH_C) 7.19 (m, 5, Ar) (base); IR (Nujol) ν_{max} 695, 705, 740, 1130, 1390, 1455, 1470, 1595, 2470, 2600–3100, 3180 cm^{-1} (mono HCl salt); MS (direct inlet) *m/e* (% rel. abund.): 268 (M^+, 15), 177 (100), 119 (30), 91 (83), 85 (21), 59 (28), 44 (18), 36 (20), metastables (m*) at 116.9, 80.0, 69.6, 46.4, 22.8, 19.7. (Found: C, 70.58; H, 7.98; N, 9.25; Cl, 12.27. $C_{18}H_{25}N_2Cl$ requires: C, 70.94, H, 8.21; N, 9.20; Cl, 11.66%).

Meso-*hydrazodi*-(1-*methyl*-2-*phenylethane*) **7a**

This was prepared as described above from *meso*-**4a** (1.0 g, 3.36 mmole) and zinc dust (10.0 g, 154 mmole) to give the title compound as the monohydrochloride, (0.48 g, 48% yield), m.p. 151–160° with decomp.; NMR ($CDCl_3$) δ 1.02 (d, 3, CH_3) 2.48 (q, 1, CH_A) *ca.* 2.7 (q, 1, CH_B) *ca.* 3.0 (m, 1, CH_2–CH) 7.20 (m, 5, Ar) (base), and the spectrum of the salt is the same as that of the (−)-isomer; IR (Nujol) ν_{max} 700, 740, 750, 1085, 1100, 1150, 1380, 1460, 1585, 2500, 2600–3100, 3200 cm^{-1} (mono HCl salt).

(−)-*Azodi*-(1-*methyl*-2-*phenylethane*) **7b**

(−)-Hydrazodi-(1-methyl-2-phenylethane) hydrochloride (7a, 0.05 g, 0.19 mmole) was shaken with yellow mercuric oxide (100 mg—excess) in chloroform (3 ml). The oxidation was followed on GLC and after the apparent disappearance of the hydrazo compound **7a**, the reaction was left for a further 4 h. Excess mercuric oxide was removed by centrifugation, subsequently washed with ether, the ether fractions dried (Na_2SO_4) and evaporated to yield a colourless oil which was at least 95% of the title compound (GLC, TLC and NMR); NMR ($CDCl_3$) δ 1.16 (d, 3, CH_3) 2.74 (q, 1, CH_A) 2.96 (q, 1, CH_B) 3.74 (m, 1, CH_2–CH) 7.17 (m, 5, Ar); IR film ν_{max} 700, 740, 1375, 1460, 1500, 1610, 2860–3100 cm^{-1}; MS (direct inlet) *m/e* (% rel. abund.): 385 (0.02), 357 (0.1), 267 (0.2), 266 (M^+, 0.5), 265 (0.2), 238 (0.2), 175 (3), 147 (2), 119 (54), 91 (100), 41 (20), metastables (m*) at 113.1, 69.6, 46.4.

Meso-*azodi*-(1-*methyl*-2-*phenylethane*) **7b**

This was prepared from *meso*-**7a** hydrochloride (0.05 g, 0.19 mmole) as described above for (−)-**7b** to yield a colourless oil; NMR ($CDCl_3$) δ 1.07 (d, J = 6.4, 3, CH_3) 2.81 (q, J_{AC} = 7.0, 1, CH_A) 3.07 (q, J_{BC} = 7.2, J_{AB} = 13.6, 1, CH_B) 3.71 (m, 1, CH_2CH_C) 7.19 (m, 5, Ar), IR (film) as for (−)-isomer; GLC/MS—similar to the MS of (−)-**7b**.

[(−)NNO(−)]-*Azoxydi*-(1-*methyl*-2-*phenylethane*) **7c**

(−)-Hydrazodi-(1-methyl-2-phenylethane) **7a** (extracted from the mono hydrochloride (0.17 g, 0.56 mmole) with 20% sodium hydroxide and chloroform) was oxidised with CPBA (0.4 g, 2.32 mmole) in chloroform and over ice. After 30 min the reaction was allowed to reach room temperature and left for a further 1.5 hr. The chloroform was then evaporated on a rotary film evaporator, the residue taken up in ether (100 ml), and extracted with excess 10% potassium carbonate solution. The ether layer was dried (Na_2SO_4), and the ether evaporated *in vacuo* to give the title compound (0.13 g, 82% yield) as a pale yellow oil; NMR ($CDCl_3$) δ 1.04 (d, 3, CH_3) 1.44 (d, 3, CH_3') 2.45 (q, J_{AC} = 7.3, 1, CH_A) 2.76 (q, J_{BC} = 6.0, J_{AB} = 13.3, 1, CH_B) 2.88 (q, $J_{A'C'}$ = 6.5, 1, $CH_{A'}$) 3.23 (q, $J_{B'C'}$ = 8.1, $J_{A'B'}$ = 13.7, 1, $CH_{B'}$) 4.26 (m, 1, CH_2–CH_C) 4.56 (m, 1, CH_2–$CH_{C'}$) 7.20 (m, 10, Ar); IR (film) ν_{max} 705, 750, 1310 (azoxy), 1380, 1460, 1500 (azoxy), 2660–3100 cm^{-1}; GLC/MS similar to direct inlet MS given for the diastereoisomer.

[(+)NNO(−)]- *and* [(+)ONN(−)]-*Azoxydi*-(1-*methyl*-2-*phenylethane*) **7c**

This was prepared from *meso*- **7a** (0.48 g, 1.58 mmole) and CPBA (1.2 g, 6.96 mmole) as described above for (−)-**7c** to give the title compound (0.41 g, 92% yield) as a pale yellow oil; NMR ($CDCl_3$) δ 0.89 (d, 3, CH_3) 1.38 (d, 3, CH_3') 2.60 (q, J_{AC} = 6.7, 1, CH_A) 2.83 (q, $J_{A'C'}$ = 6.2, 1, $CH_{A'}$) 2.88 (q, J_{BC} = 6.7, J_{AB} = 13.6, 1, CH_B) 3.22 (q, $J_{B'C'}$ = 8.4, $J_{A'B'}$ = 13.9, 1, $CH_{B'}$) 4.29 (m, 1, CH_2–CH_C) 4.55 (m, 1, CH_2–$CH_{C'}$) 7.30 (s, 10, Ar); IR (film) as reported for the (−)-isomer; MS (direct inlet) *m/e* (% rel. abund.): 282 (M^+, 0.5), 265 (0.07), 252 (0.2), 209 (0.2), 207 (0.2), 191 (6), 156 (2), 139 (3), 135 (3), 134 (3), 119 (58), 118 (23), 117 (8), 92 (8), 91 (100), 65 (5), 41 (9), metastables (m*) at 123.8, 113.1, 69.6, 46.4. (Found: C, 76.85; H, 7.86; N, 10.18; $C_{18}H_{22}N_2O$ requires: C, 76.60; H, 7.80; N, 9.93%).

ESR spectra of various possible 2-*amino*-1-*phenylpropane* **1a** *metabolites or metabonates*

Solutions in carbon tetrachloride (1 mg/0.3 ml) of (−)-**4a**, **1b** and *anti*-**2a** were examined by ESR. Resonance signals were not observed for any of the compounds. About 1–2 mg of azoisobutyronitrile (AIBN) was added to each sample and the solutions scanned again at 40°C. The solution of **4a** plus AIBN gave a spectrum: triplet of partially resolved doublets, a_N = 14.31 G, a_H = 1.0 G; magnetic field 2375 G, microwave frequency 9.188 Gc; while the solutions of the oxime **2a** and hydroxylamine **1b** gave no signals.

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