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SYNTHESIS OF SOME N-OXYGENATED PRODUCTS OF 3,4-DIMETHOXYAMPETAMINE AND ITS N-ALKYL DERIVATIVES

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Abstract—The synthesis of N-monoalkylhydroxylamines, N,N-dialkylhydroxylamines, nitrones, oxaziridines, nitroso and other N-oxidised products of 3,4-dimethoxyamphetamine and its N-methyl and N-benzyl derivatives is described, including a new and simple method for preparing N,N-dialkylhydroxylamines and a method for the isolation and analysis of an α-unsubstituted nitrone.

INTRODUCTION

Many primary and secondary aliphatic amines are metabolised *in vitro* and *in vivo* to products in which the nitrogen exists in a variety of oxidation states.[1] The N-oxygenated compounds which have been isolated as metabolites or metabonates of amines include N-monoalkylhydroxylamines,[1e,2] N,N-dialkylhydroxylamines,[3] ketoximes and aldoximes,[1e,1d,2b] nitrones,[4] and nitroso and nitro derivatives.[5] To provide reference compounds of suspected metabolites, investigation into the available methods of synthesis of these type compounds was undertaken.

3,4-Dimethoxyamphetamine has been shown to possess both amphetamine and mescaline-like activity in rats.[6] The N-hydroxy derivative has been prepared and screened for behavioural and neuropharmacological effects.[7] Our interest in the psychopharmacological activity of amphetamine and its derivatives and in the metabolism of this type of compound led us to choose 3,4-dimethoxyamphetamine and its N-methyl and N-benzyl derivatives as the model compounds in this study.

RESULTS AND DISCUSSION

Future investigations will involve the metabolism of these compounds; therefore all of the probable metabolites and metabonates were prepared (Table 1). 3,4-Dimethoxyphenylacetone (**2**) and the corresponding oxime (**3**) were prepared by reported procedures from the intermediate nitropropene (**1**).[7] The alcohol (**5**) was obtained by $NaBH_4$ reduction of **2**. Although compounds **2**, **3** and **5** are known, the recorded physical and spectroscopic data, important in identification of possible metabolites, are incomplete and therefore are included in the present report. The remaining derivatives were prepared as follows:

Amines. 3,4-Dimethoxyamphetamine (**4**) was prepared by LAH reduction of the nitropropene (**1**), a reported reaction,[8] and from the ketone (**2**) by the reductive amination procedure using sodium cyanoborohydride ($NaBH_3CN$), developed recently by Borch *et al.*[9] The latter method was also utilised in preparing N-methyl-3,4-dimethoxyamphetamine (**8**) from **2** and methylamine. Reduction of the imine (**11**), obtained from the condensation of the primary amine (**4**) and benzaldehyde, with $NaBH_4$ afforded N-benzyl-3,4-dimethoxyamphetamine (**12**).

Hydroxylamines. N-Monoalkylhydroxylamines have been synthesised by a variety of reductive methods; (a) from nitroalkanes by hydrogenation over $Pd/BaSO_4$,[10] by aluminium amalgam reduction,[1e] and by diborane reduction of the nitro salts;[11] (b) from nitroolefins by controlled reduction with LAH,[12] and by catalytic hydrogenation over Pd/C in ethanol;[13] (c) from oximes of aliphatic aldehydes and ketones by hydrogenation over Pt/C in aqueous ethanolic HCl,[14] by reduction with diborane,[15] by reduction with $NaBH_4$ on silica gel support,[16] and by reduction with $NaBH_3CN$.[9] In one of few reports of oxidative methods, N-cyclohexylhydroxylamine has been synthesized by H_2O_2 oxidation of cyclohexylamine.[17] Other methods include acid hydrolysis of oxaziridines[18] and nitrones,[19] pyrolysis of tertiary amine oxides,[20] and recently by reaction of a primary alkyl halide with a special reagent, N - tosyl - O - 2,4,6 - trimethylbenzylhydroxylamine, and cleaving the resulting protected N-alkylhydroxylamine to the product.[21]

Of these methods, many are disadvantageous because of low yields, failure of the reduction to stop at the hydroxylamine stage resulting in difficulty separating mixtures of amine and hydroxylamine products, lack of readily accessible starting materials, or hard-to-handle reagents. In view of the results of the present investigation, the method of choice appears to be that of Borch *et al.*,[9] in which oximes are reduced with $NaBH_3CN$ to give good yields of hydroxylamines simply by stirring at ambient temperature a methanolic solution (pH = 3–5) of the reactants. The low temperature and the mildly acidic conditions of the reaction, and the complete absence of over-reduction to the amine are distinct advantages when working with the often unstable alkylhydroxylamines.

In our hands, this method afforded a 62% yield of purified N-hydroxy-3,4-dimethoxyamphetamine (**6**) from the oxime (**3**), with no over-reduction to amine as evidenced by GLC analysis. Furthermore, a 50% yield of recrystallised **6** was obtained from the reductive hydroxylamination of the ketone (**2**).

Reports in the literature concerning the synthesis of N,N-dialkylhydroxylamines consist mainly of three methods. Nitrones may be reduced with LAH[18a,22] or by controlled catalytic hydrogenation[23] to give the desired products. Careful reaction of alkylhalides with hydroxylamine gives low yields of symmetrically dialkyl-substituted hydroxylamines.[24] Several secondary amines have been oxidised with benzoyl peroxide and the resulting N-benzoyl ester hydrolysed with NaOEt to the corresponding dialkylhydroxylamine,[25] although the alkaline conditions of the hydrolysis step breaks down

many aliphatic hydroxylamines.[22] More recently, Beckett *et al.* used 3-chloroperbenzoic acid to oxidise aliphatic secondary amines, and reduced the resulting N-3-chlorobenzoyl ester with LAH to the N-hydroxy derivative.[22]

Drawbacks to this method were the low yields caused by concomitant production of the nitrone in the oxidation step, and the difficulty experienced in separating the desired product from the parent amine, which arose from over-reduction of the ester.

Compound **9**, the N-hydroxy derivative of N-methylamphetamine, was prepared in less than 5% yield by this method. Also, about 10% of the total N-oxidation products occurred as the nitroso compound (**7**), resulting from either oxidative N-demethylation of the starting N-methylamine and subsequent oxidation of the primary amine or from oxidative degradation of the nitrone (**10**). N-Benzyl - N - hydroxy - 3,4 - dimethoxyamphetamine (**16**) was synthesised by this method in about 5% yield while about 60% of the total oxidation products was nitrone (**13**). Reduction of the nitrone with LAH afforded a 62% yield of **16**. In view of the above results, a simple, straightforward preparative method of N,N-dialkylhydroxylamines in good yields was sought.

3,4-Dimethoxyphenylacetone (**2**) was reductively N-alkylhydroxylaminated using the appropriate N-alkylhydroxylamine and $NaBH_3CN$. By this method, N - methyl - N - hydroxy - 3,4 - dimethoxyamphetamine (**9**) was synthesized in 50% yield (recrystallised) from the ketone (**2**) and N-methylhydroxylamine. The reaction was also successful when a mixture of N-hydroxy-3,4-dimethoxyamphetamine (**6**) and formaldehyde or benzaldehyde were used, giving 50 and 36% yields of recrystallised **9** and **16**, respectively. No special efforts were made to optimise yields, although the crude solids obtained were usually quite pure and in yields of 80–90% before recrystallisation.

Nitrones. Reported methods[19,26] were utilised in preparing the two nitrones, **10** and **13**. As stated previously, **13** was isolated from the 3-chloroperbenzoic acid oxidation of the secondary amine (**12**). Also, condensation of the primary hydroxylamine (**6**) with benzaldehyde and removal of the water by refluxing in benzene, gave an 85% yield of **13**. The same reaction using formaldehyde gave **10** as an oil which was found to be unstable to moisture, TLC and GLC analysis, and heat. Heating the oil at 60° under vacuum caused decomposition. Therefore, purification was effected by treatment of the crude reaction mixture with activated charcoal; after complete removal of the solvent, an oil was obtained which gave satisfactory elemental and spectral analyses. There are few reports of this type of nitrone (α-unsubstituted or N-alkylated derivatives of formaldoxime) in the literature. The condensation product of phenylhydroxylamine and formaldehyde was not isolable but formed a dinitrone *in situ*.[27] N - (2 - Hydroxy - 1 - naphthylmethyl)nitrone was reported as a stable product of the reaction between β-napthol, formaldehyde, and hydroxylamine.[28] The condensation of N-methylhydroxylamine and formaldehyde to give N-methylnitrone has recently been reported incidentally and without detail.[29] More recently, representatives of this group of nitrones have been synthesised by reacting aliphatic nitroso compounds with diazomethane.[30] However, this method was restricted to aliphatic nitroso compounds which possess no α-hydrogens since under the conditions of the reaction nitroso compounds with an α-hydrogen would wholly or partially convert to the isomeric aldoximes. The α-unsubstituted nitrones are of special interest in that they may represent important transitory intermediates in metabolic oxidative N-demethylation of N-methyl amines.

Nitroso compound. The nitroso compound (**7**) was synthesised in 40% yield by 3-chloroperbenzoic acid oxidation of **4**.[31] The solid nitroso exists as a *trans*-dimer as two diastereoisomers (the starting amine was racemic). The solid initially isolated from the reaction, prior to recrystallisation, melted at 122–124° and appeared to be the *meso*-isomer from NMR analysis.[31] Upon heating in solution the nitroso dimers may equilibrate through the monomer.[31] Therefore, upon recrystallisation, the *meso*-isomer must have undergone an equilibrium to the RR and SS since sharp melting crystals (133–134°) were recovered which NMR analysis showed to be a 2:1 mixture of the diastereoisomers, the *meso*-isomer being present in the larger amount. Concentration of the mother liquor provided more sharp melting crystals (104–105°) which were shown to be a mixture, 4:1 [*meso*/(RR/SS)]. Therefore these dimers apparently exist as complex diastereoisomeric compounds with sharp m.ps.

The nitroso dimer of **7** was warmed with α-azo-isobutyronitrile and the ESR spectrum recorded. The latter compound produces carbon-centered radicals upon heating to 40°; these reacted with **7** to give a stable nitroxide radical exhibiting a typical nitroxide ESR spectrum. This is a reaction characteristic of nitroso and nitrone compounds,[32] and may be of use in detecting the production of nitroso compounds in metabolic investigations.

Oxaziridines. These structures were first synthesized by Emmons in 1957, by the oxidation of imines with peracetic acid;[18a] subsequently, 3-chloroperbenzoic acid has been reported to be a superior oxidising agent.[33] Oxidation of N-benzylidene-3,4-dimethoxyamphetamine (**11**) with this reagent gave a product as an oil which upon heating sufficiently for vacuum distillation isomerised to the corresponding nitrone. Therefore the oil was purified by column chromatography; the product was a mixture of the two possible diastereoisomers in a 3·5:1 ratio as indicated by NMR analysis. No attempt to separate or assign sterochemistry to the diastereoisomers was made. Similarly, **15** was synthesised from N - (4 - nitrobenzylidene) - 3,4 - dimethoxyamphetamine. One pure, solid diastereoisomer was isolated from the crude diastereoisomeric mixture, although, again, no attempt was made to assign stereochemistry. Since hydrolysis of oxaziridines provides N-monoalkylhydroxylamines, this route has been demonstrated as a method of preparing optical isomers of hydroxylamines from enantiomers of the parent amines.[18c,d]

CONCLUSIONS

Sodium cyanoborohydride is a very versatile reducing reagent due to its stability and utility in aqueous or alcoholic solutions from pH 3 to 10 (Borch *et al.*[9]). They further reported that the intermediate imines formed in the course of reductive alkylations of amines are readily reduced at pH = 6 – 8 whereas aldehyde and ketone reduction becomes significant at pH = 3 – 4. The only pH requirement for reduction of the imine, and of enamines, was the presence of sufficient H^+ concentration to provide protonation of the basic centre to give the easily reducible imminium cations. The same mechanism may be assumed for reduction of the oximes since this reaction also

proceeds at a much faster rate as the H^+ concentration increases.

In like manner, we have found that nitrones may be reduced at pH = 5–6; the rate becomes faster as the H^+ concentration increases since nitrones become protonated.[18a] Therefore, by mixing an aldehyde or ketone with hydroxylamine or an N-monosubstituted hydroxylamine, the presumed protonated oxime or nitrone intermediate (Fig. 1) is easily reduced by $NaBH_3CN$ at pH = 5–6 to the N-monoalkylhydroxylamine or N,N-disubstituted hydroxylamine, respectively. This method represents a new and simple method of preparation of these compounds; the mild acidic conditions are favourable for the production and isolation of the often unstable hydroxylamines. Further experiments are being conducted to ascertain the general applicability of this method to the synthesis of other mono- and dialkyl and arylhydroxylamines.

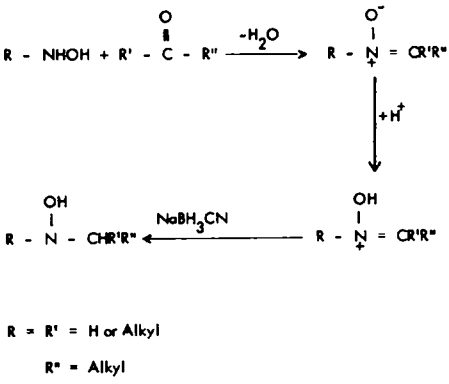


Fig. 1. Proposed reaction route for the reductive alkylation of hydroxylamines.

EXPERIMENTAL

Methods. All m.ps are uncorrected. UV spectra were recorded on a Unicam SP 800 and IR spectra on a Unicam SP 1000 spectrophotometer. NMR spectra were recorded on a Perkin Elmer R-32 spectrometer. The solns for NMR analysis were about 10% and TMS was used as an internal standard. Deuterium exchange using D_2O was routinely performed on all compounds possessing labile H atoms. Spin decoupling and indor techniques were applied to the NMR analyses of the heterosteric ABC spin system[34] which is present in the compounds ($3,4(OCH_3)_2C_6H_3CH_2\underline{C}H\underline{C}H_3$—). ESR spectra were recorded on a Varian E4 ESR spectrometer. Mass spectra were obtained from a Perkin Elmer Model 270 spectrometer or were performed by the Mass Spectrometry Service, University of London. Elemental analyses were determined by either Dr. A. J. Layton, University College, London, or The Butterworth Microanalytical Consultancy Ltd., Teddington, Middx. GLC analyses were carried out on a Perkin Elmer F-11 instrument equipped with a flame ionization detector: systems used were; (A) glass column, length 0·5 m, o.d. 0·25 in, containing 7·5% Carbowax 20M on Chromosorb W, 80–100 mesh, acid washed and DMCS treated, N_2 as carrier gas at 1 kg/cm^2; (B) glass column, length 1 m, o.d. 0·25 in, containing 10% UCW 98 on Chromosorb W, 100–120 mesh, acid washed and DMCS treated, N_2 as carrier gas at 1 kg/cm^2; (C) glass column, length 1 m, o.d. 0·25 in, containing 2% Carbowax 20M on Chromosorb G, 100–120 mesh, acid washed and DMCS treated, N_2 as carrier gas at 1·2 kg/cm^2; (D) glass column, length 1 m, o.d. 0·25 in, containing 3% OV-17 on Chromosorb G, 80–100 mesh, acid washed and DMCS treated, N_2 as carrier gas at 1·4 kg/cm^2. The column temperatures used are cited in the text. The pH of the reactions was monitored using a WPA Saffron Walden C-10 pH meter.

Materials. Reference samples of 3,4-dimethoxyamphetamine and the N-methyl and N-benzyl derivatives were kindly provided by Smith, Kline & French Laboratories, Philadelphia, Pa. 3,4-Dimethoxyphenylacetone was prepared by reported procedures[8] (see below) from 3,4-dimethoxybenzaldehyde (Koch-Light) and purchased from Aldrich Chemical Co. Ltd. Sodium cyanoborohydride was obtained from Aldrich and was used without further purification. All the compounds possessing asymmetric centres are reported as racemates. Unless otherwise specified, no attempt was made to determine whether oxalate salts were full or hemi.

Procedures

trans-1-(3',4'-*Dimethoxyphenyl*)-2-*nitropropene* (1). A soln of 80 g (0·48 mol) 3,4-dimethoxybenzaldehyde, 40 g (0·53 mol) nitroethane and 20 g ammonium acetate in glacial AcOH was refluxed for 2 hr and the cooled soln poured over crushed ice. The resulting yellow solid was recrystallised from EtOH to give 42 g (40%) of the product, m.p. 72–74° (lit.[8] m.p. 73°).

3,4-*Dimethoxyphenylacetone* (2). A mixture of 59 g (1·05 g-atom) of Fe (electrolytic powder), 33·5 g (0·15 mol) of 1, and 0·2 g $FeCl_3$ in 60 ml water was refluxed with vigourous stirring as 24 ml (0·28 mol) of conc HCl was added dropwise over the course of 1 hr. Refluxing and stirring were continued for 6 hr after which 200 ml benzene and 20 g celite were added to the cooled, stirred mixture. The solids were filtered off and the benzene layer separated and washed once with dil. HCl and twice with water. The benzene was removed by rotary evaporation and the residual oil vacuum distilled to give 23·5 g (81%) of the ketone, shown to be 97% pure by GLC analysis (R_t = 1·5 min at 200° and 4·75 min at 170°, system A): b.p. 126–128° (0·35 mm), (lit.[7] b.p. 129–133° (0·4 mm)); UV (EtOH) λ_{max}, 281 (E = 3120) and 231 nm (sh) (E = 7310); IR (liquid film) 3040–2940, 2867, 1740 (C=O), 1612, 1540, 1485 and 1440 (doublet), 1373, 1270 (broad), 1165 and 1041 cm^{-1}; NMR ($CDCl_3$) δ 2·08 (s, 3, $C\underline{H}_3$), 3·53 (s, 2, $C\underline{H}_2$), 3·74 (s, 6, $OC\underline{H}_3$) and 6·66 ppm (d, 3, $C_6\underline{H}_3$).

3,4-*Dimethoxyphenylacetone oxime* (3). A mixture of 5 g (0·026 mol) of 2 and 2·3 g (0·034 mol) hydroxylamine hydrochloride in 10 ml water was stirred at room temp. while 1·75 g (0·017 mol) Na_2CO_3 in 5 ml water was added over a 10 min period. The resulting soln was stirred for 3 hr, extracted with ether, and after removal of the ether, the oily residue was distilled under vacuum to give 5·1 g (95%) of the product, b.p. 160–165° (0·1 mm), (lit.[7] b.p. 165–175° (0·6 mm)), shown to be 98% pure by GLC analysis (R_t = 8·0 min at 200° and 33·4 min at 170°, system A). After standing for two months the oil crystallised, m.p. 45–50°. Recrystallisation from ether-pet ether (40–60°) provided shiny, colourless crystals, m.p. 61–62·5, (lit.[35] m.p. 62·5–63°); UV (EtOH) λ_{max}, 282 (E = 2960) and 233 nm (E = 12,500); IR (liquid film) 3520 (free O–H), 3400–3200 (H-bonded O–H), 3060–2880, 1685 (C=N), 1613, 1540, 1480 (broad), 1275 (broad), 1165, 1043 and 972 cm^{-1}; NMR ($CDCl_3$) δ 1·82 (s, 3, $C\underline{H}_3$), 3·42 (s, 2, $C\underline{H}_2$), 3·80 (s, 6, $OC\underline{H}_3$), 6·72 (s, 3, $C_6\underline{H}_3$) and 9·71 ppm (broad s, 1, $O\underline{H}$); ms, *m/e* 209(83) molecular ion, 207(36), 192(29), 176(24), 161(43), 151(100), 137(23), 121(10), 107(33), 91(24), 77(26), 57(13), 51(20), 44(43).

3,4-*Dimethoxyamphetamine* (4)

(a) *By reduction of the nitroolefin* (1). To a stirred suspension of 19 g of LAH in 750 ml dry ether was added dropwise 27 g (0·121 mol) of 1 dissolved in 500 ml of a benzene-ether mixture (1:10). The mixture was refluxed during the addition and subsequently for 5 hr. Celite (12 g) was added and the excess LAH was decomposed by addition of a saturated aqueous solution of potassium sodium tartrate. The solid mass was filtered, the filter cake washed well with ether and the combined ether fractions were dried over $MgSO_4$. After removal of the ether by rotary evaporation, the residual oil was vacuum distilled to give 15·3 g (65%) of the product, shown to be pure by GLC analysis (R_t = 3·2 min at 170°, system A, and 8 min at 130°, system C); b.p. 100–104° (0·04 mm), (lit.[8] b.p. 95–97 (0·05 mm)); IR (liquid film) 3390 (free N–H), 3330 and 3240 (H-bonded N–H), 3040–2920, 2870, 1610, 1534, 1483, 1434, 1345, 1278 and 1250 (doublet), 1169 and 1038 cm^{-1}; NMR ($CDCl_3$) δ 1·09 (d, 3, J = 6·2, $C\underline{H}_3$), 2·37–2·75 (m, 2, $C\underline{H}_2$), 2·62 ($N\underline{H}_2$), 2·93–3·22 (m, 1, $C\underline{H}$), 3·83 (d, 6, J < 1, $OC\underline{H}_3$) and 6·75 ppm (m, 3, $C_6\underline{H}_3$).

A hydrochloride was prepared and recrystallised from

EtOAc-acetonitrile, m.p. 145–148°, (lit.[36] m.p. 147·5–148°). An oxalate was prepared and recrystallised from methanol-EtOAc, m.p. 232–234°(dec.).

(b) *By reductive amination of the ketone* (2). A mixture of 5·32 g (0·0275 mol) of 2, ammonium acetate (21·2 g, 0·275 mol) and 2 g (0·032 mol) $NaBH_3CN$ in 100 ml MeOH was stirred for 8 hr at room temp. The pH was adjusted to 2 with 5N HCl, the MeOH removed by rotary evaporation, and the residue taken up in 2N NaOH (100 ml) and extracted with chloroform. The chloroform extracts were then extracted with 2N HCl. The acidic aqueous phase was made alkaline and extracted with ether (3 × 50 ml), the ethereal extracts dried over $MgSO_4$, and concentrated to give 2·37 g (45%) of pure (by GLC analysis) product.

1-(3′,4′-*Dimethoxyphenyl*)-2-*propanol* (5)

A soln of 1 g (0·0052 mol) of 2 in 30 ml dry ether was added dropwise to a stirred suspension of 0·5 g LAH in 50 ml of ether. The mixture was refluxed for 30 min after completion of the addition. Celite (3 g) was added and the excess LAH was decomposed with water. The solid mass was filtered from the soln and washed well with ether. The ethereal soln was dried over $MgSO_4$ and concentrated to give 0·91 g (90%) of an oil, shown by GLC analysis to be 95% pure (R_t = 6·45 min at 170°, system A). After standing 1 month, the oil solidified and was recrystallised from ether-pet. ether (40–60°) to give colourless needles: m.p. 43–45°, (lit.[37] m.p. 43–45°); IR (liquid film) 3520–3350 (OH), 3010–2890, 2840, 1610 and 1590 (doublet), 1512, 1460 (broad), 1409, 1260 and 1243 (doublet), 1158 and 1142 (doublet) and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1·22 (d, 3, J = 6·2, CH_3), 1·89 (broad s, 1, OH), 2·60–2·70 (m, 2, CH_2), 3·77–4·20 (m, CH, partially masked by OCH_3), 3·86 (d, 6, J < 1, OCH_3) and 6·77 ppm (m, 3, C_6H_3).

N-*Hydroxy*-3,4-*dimethoxyamphetamine* (6)

(a) *By* $NaBH_3CN$ *reduction of the oxime* 3. To a stirred soln of 2·08 g (0·01 mol) of 3, and $NaBH_3CN$ (0·63 g, 0·01 mol) in 15 ml MeOH at room temp was added dropwise 2N HCl at a rate sufficient to maintain a pH of 3–4. After 10–15 min the pH changed less rapidly (the reaction consumes acid) and the mixture was allowed to stir an additional 3 hr. The pH was lowered to 1 and the MeOH removed by rotary evaporation. The residue was taken up in 10 ml water and the pH adjusted to 8 with 20% K_2CO_3 and extracted with 6 × 20 ml ether. The ethereal extracts were dried over $MgSO_4$ and concentrated to afford an oil which solidified upon trituration with pet. ether (40–60°) to give 1·9 g (90%) of a white solid, m.p. 68–74°. Recrystallisation from ether-pet. ether (40–60°) provided 1·3 g (62%) of the product, m.p. 74–75·5° (lit.[18d] m.p. 75–77°). (See Ref. 18*d* for complete spectral data on this compound).

(b) *By reductive hydroxylamination of* 3,4-*dimethoxyphenylacetone.* A stirred soln of 15·5 g (0·08 mol) of 2 and 7 g (0·101 mol) hydroxylamine hydrochloride in 60 ml 30% aqueous MeOH was adjusted to pH 6 by addition of 6N KOH. $NaBH_3CN$ (2·6 g, 0·041 mol) was added and the resulting mixture was stirred at room temp for 3 hr, dil HCl being added dropwise to maintain the pH at 6. The pH was then lowered to 1, and after the subsidence of the evolution of gas bubbles from the excess $NaBH_3CN$ reacting with acid, the mixture was diluted with 100 ml water. The pH of this soln was adjusted to 8 with 6N KOH, saturated with NaCl, and extracted with 6 × 50 ml of ether. The ethereal extracts were extracted with 5% HCl (2 × 40 ml), the acidic extracts made alkaline (pH = 8), and extracted with 5 × 50 ml of ether. These ethereal extracts were dried over $MgSO_4$ and concentrated to give an oil which solidified after trituration with pet. ether (40–60°). The solid, 11·1 g (66%), m.p. 64–68°, was recrystallised from diisopropyl ether to afford 8·22 g (49%) of the product, m.p. 75–77° (lit.[18d] m.p. 75–77°).

A neutral oxalate was prepared and recrystallised from MeOH-ether, m.p. 137–139° (lit.[14a] m.p. 135–136°).

†Since GLC analysis proved the absence of primary amine 4 in the starting material, the by product nitroso compound 7 must have arisen from oxidative demethylation to 8, to produce the primary amine 4, which subsequently was oxidised to 7.

1-(3′,4′-*Dimethoxyphenyl*)-2-*nitrosopropane* (7)

The synthesis and physical data of this compound are reported elsewhere.[31] The method employed 3-chloroperbenzoic acid oxidation of 4 to give a 40% yield of the product. The UV, IR, NMR and Mass spectrum were consistent with the dimeric nitroso structure. An ESR spectrum was obtained by heating at 40° a 10% solution of 7 in carbon tetrachloride to which had been added 1–2 mg of α-azo-isobutyronitrile. The spectrum consisted of a triplet of slightly resolved doublets, a_N = 14·9 G, a_H < 1 G. The amplitude of magnetic field modulation was 0·125 G, the power level was 2 mW, and the microwave frequency was 9·188 GC. The sweep rate was 25 G/min and the time constant was 0·3 sec. Midpoint of the spectrum was 3273 G.

N-*Methyl*-3,4-*dimethoxyamphetamine* (8)

To a soln of methylamine (1·9 g, 0·06 mol) in 25 ml abs MeOH was added 4·8 ml (0·02 mol) of 4·17 N HCl/MeOH followed by 1·94 g (0·01 mol) of 2 and 0·5 g (0·008 mol) of $NaBH_3CN$. The resulting mixture was stirred at room temp over Type 3A molecular sieve for 72 hr. The soln was adjusted to pH = 1, filtered, and the MeOH removed by rotary evaporation. The residue was taken up in 50 ml water, made alkaline with 6 N KOH, saturated with NaCl, and extracted with 3 × 75 ml ether. The ethereal extracts were extracted with 2N HCl (2 × 50 ml), the acidic extracts made alkaline and extracted with ether. These ethereal extracts were dried over $MgSO_4$ and concentrated to give 1·93 g (92%) of an oil shown by GLC analysis to be pure (R_t = 2·85 min at 170°, system A) and identical with authentic N-methyl-3,4-dimethoxyamphetamine.

A hydrochloride was prepared and recrystallised from EtOAC-acetonitrile, m.p. 117–119° (lit.[38] m.p. 123–124°). An oxalate was prepared and recrystallised from MeOH–ether, m.p. 103–104°.

N-*Hydroxy*-N-*methyl*-3,4-*dimethoxyamphetamine* (9)

(a) *By oxidation of* N-*methyl*-3,4-*dimethoxyamphetamine.* To 4·18 g (0·02 mol) of 8 in 100 ml CH_2Cl_2 at 0° was added with stirring 8·68 g (0·05 mol) of 3-chloroperbenzoic acid in 50 ml CH_2Cl_2. Stirring was continued after the addition was complete for 30 min at 0°, then for 2 hr at room temp. The mixture was then filtered of the precipitated 3-chlorobenzoic acid and the filtrate washed with 3 × 50 ml 10% K_2CO_3 and once with water. The organic phase was dried over $MgSO_4$ and the volume reduced by rotary evaporation, leaving an oily residue which was shown by IR to possess an ester C=O band (1730 cm^{-1}). The oil was dissolved in 20 ml ether and placed in an ice bath to promote crystallisation of the by-product, 7.† After separation of the nitroso compound, the ethereal soln was added dropwise to LAH (1 g) in 200 ml dry ether at room temp. After stirring for 30 min, 5 g celite was added and the excess LAH was decomposed by addition of water. The solid mass was filtered from the soln, washed well with ether, and the combined ether solns dired over $MgSO_4$. Addition of a saturated ethereal soln of oxalic acid caused precipitation of a white solid which was isolated by decantation. The solid was dissolved in 50 ml of pH = 4 buffer and extracted with 5 × 50 ml ether in an effort to separate the less basic product from the primary amine 8, which arises from over-reduction of the intermediate ester. The ethereal extracts were dried over $MgSO_4$ and again the oxalate was formed and recrystallised from acetone to give 90 mg (2%) of the neutral oxalate, m.p. 136–138°: IR (KBr) 1630 (broad), 1543, 1490, 1314, 1285, 1248, 1172, 1153, 1032, 800 and 760 cm^{-1}. (Found: C, 57·0; H, 7·7; N, 5·1. Calc. for $C_{26}H_{40}N_2O_{10}$: C, 57·8; H, 7·46; N, 5·18%).

(b) *By reductive* N-*methylhydroxylamination of* 3,4-*dimethoxyphenylacetone.* To a soln of 2·09 g (0·022 mol) N-methylhydroxylamine hydrochloride (Aldrich) in 2 ml water was added 4·0 g (0·0206 mol) of 2 in 10 ml MeOH. 5% KOH aq was added until the pH was 6. Then $NaBH_3CN$ (1·58 g, 0·025 mol) was added and the resulting mixture was stirred at room temp for 3 hr, 5% HCl being added in order to maintain the pH between 5 and 6. The pH was adjusted to 1 and after the evolution of gas bubbles had subsided, the soln was diluted with 50 ml water and washed with 2 × 25 ml ether. The acidic soln was made alkaline (pH = 8) with 5% KOH, saturated with NaCl, and extracted with 5 × 50 ml ether. The ethereal extracts were dried over $MgSO_4$ and con-

centrated to give an oil which solidified upon trituration with pet. ether (40–60°). The solid was recrystallised from ether–pet. ether (40–60°) to afford 2·30 g (50%) of the product: m.p. 48–51°; IR ($CHCl_3$) 3590 (free O–H), 3220 (broad, H-bonded O–H), 3020–2915, 2845, 1609 and 1592 (doublet), 1516, 1468, 1262, 1239, 1159 and 1142 (doublet), and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1·00 (d, 3, J = 6·4, CH_3), 2·28–3·30 (m, CH_2), 2·60–3·20 (m, CH), 2·70 (s, 3, NCH_3), 3·87 (s, 6, OCH_3), 6·77 (m, 3, C_6H_3) and 7·64 ppm (broad s, 1, OH); ms, *m/e* 226(2·7), 225(1·8) molecular ion, 207(1·2), 192(1), 178(3·8), 163(2·1), 152(45), 151(28), 137(6), 121(3), 107(10), 91(7), 77(8), 74(100), 56(25), 45(7), 42(17). (Found: C, 64·0; H, 8·7; N, 6·1). Calc. for $C_{12}H_{19}NO_3$: C, 63·97; H, 8·50; N, 6·22%).

(c) *By reductive N-alkylation of* **6** *with formaldehyde.* A soln containing 1·05 g (0·005 mol) of **6** and 0·72 g (0·0074 mol) (0·6 ml of a 38% solution) of formaldehyde in 20 ml MeOH was adjusted to pH = 6 with dil HCl. $NaBH_3CN$ (0·6 g, 0·01 mol) was added and the mixture was stirred at room temp and maintained at pH = 6 by addition of dil. HCl for 3 hr. The mixture was made acidic (pH = 1), diluted to 100 ml and washed with 2 × 20 ml ether. The aqueous phase was made alkaline (pH = 8) with 5% KOH and extracted with 4 × 50 ml ether. These ethereal extracts were dried over $MgSO_4$ and concentrated to give an oil which was shown by NMR analysis to be quite pure product. The oil was dissolved in dry ether and a saturated soln of oxalic acid was added. The ppt which formed was filtered, washed with ether, and recrystallised from n-propanol to afford 0·68 g (51%) of the neutral oxalate, m.p. 137–138·5°, which was shown by mixed m.p. to be identical to the oxalate prepared in (a).

N-(1-(3′,4′-*Dimethoxyphenyl*)*prop*-2-*yl*)*nitrone* (**10**)

A mixture of 0·8 g (0·0038 mol) of **6**, 1 ml of a 38% soln of formaldehyde (0·4 g, 0·013 mol), and 100 ml benzene was refluxed until the water from the formalin soln and the condensation reaction had been completely removed. The water removal was achieved by use of a Dean-Stark trap. The benzene was removed by rotary evaporation and the residual solvent removed *in vacuo* at 25° for 8 hr. The product formed quantitatively and was stable if stored under dry N_2 with exclusion of moisture. However, breakdown of the compound occurred when subjected to heating *in vacuo*, TLC or GLC analysis. Therefore, the product was purified by two treatments of a benzene soln with activated charcoal and the benzene completely removed in the same manner as described above: UV (EtOH) λ_{max}, 340 (E = 870), 282(E = 2170) and 233 nm (E = 8160); IR (liquid film) 3415 (broad), 3010–2900, 2840, 1590 and 1573 (doublet), 1512, 1455, 1420, 1328, 1260, 1238, 1150, 1058 and 1028 cm^{-1} (doublet); NMR ($CDCl_3$) δ 1·47 (d, 3, J = 6·0, CH_3), 2·73 (q, 1, J_{ab} = 14, J_{ac} = 5·6, $H_aCH_bCH_c$), 3·18 (q, 1, J_{ab} = 14, J_{bc} = 10, $H_aCH_bCH_c$), 3·84 (s, 6, OCH_3), 5·95 (m, 1, $H_aCH_bCH_c$) 6·04 and 6·24 (two doublets, 2, J_{ab} = 8·0, H_aCH_b = N–) and 6·78 ppm (s, 3, C_6H_3); ms, *m/e* 223(6) molecular ion, 221(3), 194(8), 189(22), 188(56), 164(30), 163(33), 152(22), 151(100), 137(5), 135(14), 121(11), 107(25), 91(25), 77(23), 72(16), 65(19), 56(47), 51(17), 44(24), 39(22). (Found: C, 64·4; H, 7·8; N, 6·2. Calc. for $C_{12}H_{17}NO_3$: C, 64·55; H, 7·68; N, 6·27%).

A small sample of the oil (50 mg) was dissolved in 5 ml of dry MeOH containing $NaBH_3CN$ (50 mg), the pH adjusted to 4 with anhyd methanolic HCl and the mixture stirred at room temp for 2 hr. The soln was diluted with water to 30 ml, made alkaline (pH = 8) with 5% KOH, and extracted with ether. After drying over $MgSO_4$, the ethereal extracts were concentrated and GLC analysis of the N,O-bis-trimethylsilyl trifluoroacetamide (Pierce Chem. Co.) derivative of the resulting oil and the authentic compound confirmed **9** as the major product (85%), R_t = 6·3 min at 180°, system D.

N-*Benzylidene*-3,4-*dimethoxyamphetamine* (**11**)

To 8·37 g (0·043 mol) of **4** in 60 ml abs MeOH and 10 g Type 3A molecular sieve was added dropwise with stirring 6·85 g (0·065 mol) benzaldehyde. After completion of the addition, stirring was continued and the mixture was gently heated at 50° for 1 hr. GLC analysis of the reaction media indicated complete conversion to the imine after 30 min. The mixture was filtered and the MeOH removed by rotary evaporation giving a thick oil which was vacuum distilled to give 9·5 g (79%) of the product: b.p. 146–150° (0·05 mm); R_t = 11·1 min at 200°, system A, R_t = 4·5 min at 200°, system B; IR (liquid film) 3040–2860, 1664, 1608, 1545, 1475 (broad), 1433, 1397, 1278 and 1250 (doublet), 1162 (broad), and 1038 cm^{-1}; NMR ($CDCl_3$) δ 1·33 (d, 3, J = 6·6, CH_3), 2·84 (d, 2, J = 6·4, CH_2), 3·50 (m, 1, CH), 3·76 (d, 6, J = 9·6, OCH_3), 6·71 (m, 3, $C_6H_3(OCH_3)_2$), 7·25–7·50 (m, 3, *meta* H and *para* H of C_6H_5), 7·55–7·80 (m, 2, *ortho* H_2 of C_6H_5) and 7·98 ppm (s, 1, N=CH).

N-*Benzyl*-3,4-*dimethoxyamphetamine* (**12**)

To a stirred soln of 15 g (0·053 mol) of **11** in 150 ml abs MeOH was added dropwise 1·03 g (0·027 mol, 100% excess) of $NaBH_4$ in 50 ml MeOH. After completion of the addition, the mixture was refluxed for 15 min, cooled, and diluted with 300 ml water. The amine, which oiled out, was extracted with ether (3 × 100 ml), the ethereal extracts dried over $MgSO_4$, and concentrated to give 15 g of the crude product, shown by GLC analysis to be 95% pure. The oil was distilled under vacuum to provide 13·7 g (91%) of the pure product: b.p. 142–146° (0·05 mm); shown by GLC analysis to be identical to the reference compound, R_t = 13 min at 200°, system A, R_t = 5·2 min at 200°, system B, R_t = 4·65 min at 200°, system C; NMR ($CDCl_3$) δ 1·10 (d, 3, J = 6·2, CH_3), 1·57 (s, 1, NH), 2·64 (m, 2, CH_2CH), 2·77–3·10 (m, 1, CH), 3·60–3·98 (m, partially masked by OCH_3, 2, $NCH_2C_6H_5$), 3·84 (d, 6, J = 3·0, OCH_3), 6·63–6·83 (m, 3, $C_6H_3(OCH_3)_2$) and 7·24 ppm (s, 5, C_6H_5); MS (HCl salt), *m/e* 286(0·65), 285(0·35) (molecular ion), 179(1·2), 178(1·0), 152(7), 151(7), 135(15), 134(100), 121(2), 107(4), 91(98), 77(5), 65(10), 58(6), 45(16).

A hydrochloride was prepared and recrystallised from methanol-ether, m.p. 171–173°. An oxalate was prepared, m.p. 188–190°.

α-*Phenyl*-N-(1-(3′,4′-*dimethoxyphenyl*)*prop*-2-*yl*)*nitrone* (**13**)

(a) *By oxidation of* N-*benzyl*-3,4-*dimethoxyamphetamine.* To a stirred soln of 5 g (0·0175 mol) of **12** in 150 ml dry acetone at 0–5° was added 7·6 g (0·044 mol) 3-chloroperbenzoic acid in 50 ml dry acetone. Stirring was continued after completion of the addition for 30 min at 0–5° and then for 1 hr at room temp. The acetone was removed by rotary evaporation, the residue dissolved in 100 ml ether and washed with 2 × 25 ml 10% K_2CO_3. The ethereal soln was dried over $MgSO_4$ and concentrated to yield a mixture of yellow oil and colourless crystals. Trituration with cold ether dissolved the oil and the crystals of nitrone were separated and dried to give 3·28 g (63%): m.p. 130–132°; UV (EtOH) λ_{max}, 303 (shoulder) (E = 15,000), 291 (E = 20,220), 284 (E = 20,490) and 224 nm (E = 17,200); IR ($CHCl_3$) 3365 (broad), 3020–2940, 2845, 1589, 1516, 1455, 1318, 1263, 1239, 1143 and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1·54 (d, 3, J = 6·2, CH_3), 2·75 (q, 1, J_{ab} = 14, J_{ac} = 4·4, $H_aCH_bCH_c$) 3·31 (q, 1, J_{ab} = 14, J_{bc} = 9·3, $H_aCH_bCH_c$), 3·70 (d, 6, J = 4, OCH_3), 4·08 (m, 1, $H_aCH_bCH_c$), 6·73 (m, 3, $C_6H_3(OCH_3)_2$), 7·07 (s, 1, N=CH), 7·37 (m, 3, *meta* H_2, *para* H of C_6H_5), and 8·18 ppm (m, 2, *ortho* H_2 of C_6H_5); ms, *m/e* 300(0·07), 299(0·12) (molecular ion), 298(0·05), 283(1·03), 281(0·25), 178(100), 164(2), 163(15), 151(8), 148(1·5), 147(4), 132(18), 121(2), 107(9), 105(7), 104(2), 91(7), 77(6). (Found: C, 71·1; H, 7·0; N, 4·7. Calc. for $C_{18}H_{21}NO_3$: C, 72·21; H, 7·07; N, 4·68%).

(b) *By condensation of* **6** *with benzaldehyde.* A mixture of 0·3 g (0·0014 mol) of **6** and 0·17 g (0·0016 mol) benzaldehyde in 100 ml benzene was refluxed utilising a Dean-Stark trap to collect the water given off by the reaction. After 30 min, the benzene was removed by rotary evaporation and the residue triturated with diisopropyl ether. The white solid which formed was recrystallised from diisopropyl ether to afford 0·358 g (64%) of the product, m.p. 129–131°.

2-(1′(3″,4″-*Dimethoxyphenyl*)*prop*-2′-*yl*)-3-*phenyloxaziridine* (**14**)

To a stirred soln of 4·41 g (0·0156 mol) of **11** in 20 ml CH_2Cl_2 at room temp was added dropwise 3·23 g (0·0187 mol) 3-chloroperbenzoic acid dissolved in 40 ml CH_2Cl_2. After stirring for 8 hr, the precipitated 3-chlorobenzoic acid was removed by filtration and the filtrate washed with 2 × 50 ml 10% K_2CO_3 and once with water. The organic layer was dried over $MgSO_4$ and concentrated to give 4·31 g of a wine-coloured oil. Since oxaziridines are known to thermally isomerise to the corresponding

nitrones,[18a] the oil was purified by column chromatography. The 4·31 g sample was placed on a column (24 mm × 36 cm) containing 100 g silica gel and eluted with benzene-$CHCl_3$. The recovered oil weighed 2·27 g and was shown by NMR and TLC analysis to be a mixture (about 4:1) of the two possible diastereoisomers. The sample was again chromatographed on 100 g silica gel and eluted with pet. ether-benzene mixtures (4:1, 3:1, 2:1, and 1:1). Analysis of the fractions collected indicated negligible separation of the diastereoisomers. Therefore, the fractions were combined and treated twice with activated charcoal. The solvent was removed by rotary evaporation and the resulting oil placed under vacuum (0·05 mm) at 50° for 6 hr. The product (1·69 g, 36%) was shown by NMR to be a 3·5:1 mixture of the pure diastereoisomers: UV (EtOH) λ_{max} 278 (E = 3300), 230 shoulder (E = 10,200) and 217 nm shoulder (E = 12,200); IR (liquid film) 3027–2865, 2823, 1611, 1595, 1520, 1467, 1268, 1242, 1162, 1147 and 1033 cm^{-1}, NMR ($CDCl_3$) δ 1·08 (d, J = 6, CH_3 for lesser isomer), 1·41 (d, J = 6, CH_3 for greater isomer), 2·46 (m, 1, CH_2CH), 2·80 (distorted d, 2, J = 7, CH_2CH), 3·40 (s, 3, OCH_3), 3·85 (s, 3, OCH_3), 3·92 (s, C_6H_4CH for greater isomer), 4·52 (s, C_6H_5CH for lesser isomer), 6·62 (broad m, 3, $C_6H_3(OCH_3)_2$), 7·03 (m, 2, *ortho* H of C_6H_5), and 7·34 ppm (m, 3, *meta* H and *para* H of C_6H_5); MS, *m/e* 301(0·6), 300(2·4), 284(0·4), 226(0·8), 195(1·6), 179(13), 178(100), 163(11), 151(27), 137(2), 132(6), 121(3), 107(10), 106(9), 105(16), 103(3), 91(8), 85(3), 77(21), 57(10), 51(10), 43(9), 42(5), 41(10). (Found: C, 71·8; H, 7·5; N, 4·5. Calc. for $C_{18}H_{21}NO_3$: C, 72·23; H, 7·07; N, 4·68%).

2 - (1' - (3",4" - *Dimethoxyphenyl*)*prop* - 2' - *yl*) - 3 - (4" - *nitrophenyl*)*oxaziridine* (**15**)

This compound was prepared by oxidation of 3·94 g (0·012 mol) of N - (4 - nitrobenzylidene) - 3,4 - dimethoxyamphetamine with 2·42 g (0·014 mol) 3-chloroperbenzoic acid in a procedure identical to that for **14**. Following the work-up procedure, 3·84 g of a viscous yellow oil was obtained which was shown by NMR analysis to consist of a 4·3:1 mixture of the two possible diastereoisomers. Initial attempts to crystallise the oil failed. The oil was dissolved in 30 ml diisopropyl ether, stoppered, and allowed to stand at 4° for 2 mo, after which time yellow plates had formed in the oil. The crystals which were isolated and washed with cold diisopropyl ether weighed 1·53 g (37%): m.p. 109·5–111°; IR ($CHCl_3$) 3030–2880, 2840, 1610, 1591, 1520, 1464, 1348, 1261, 1220, 1158, 1142 and 1028 cm^{-1}; NMR ($CDCl_3$) δ 1·41 (s, 3, J = 6, CH_3), 2·50 (m, 1, CH_2CH), 2·78 (m, 2, CH_2), 3·52 (s, 3, OCH_3), 3·87 (s, 3, OCH_3), 3·98 (s, 1, $CHC_6H_4NO_2$), 6·46–6·79 (m, 3, $C_6H_3(OCH_3)_2$), 7·14 ($m_{aa'bb'}$, 2, J_{ab} = 8·4, $J_{aa'}$ and $J_{ab'}$ < 1, *ortho* H of 4-$NO_2C_6H_4$) and 8·13 ppm ($m_{aa'bb'}$, 2, J_{ab} = 8·4, *meta* H of 4-$NO_2C_6H_4$); MS, *m/e* 345(3), 344(14) molecular ion, 328(1), 193(6), 179(16), 178(100), 163(9), 152(11), 151(37), 150(23), 137(4), 121(2), 107(8), 104(7), 91(5), 77(9), 65(5), 51(8), 42(8). (Found: C, 63·2; H, 6·0; N, 8·0. Calc. for $C_{18}H_{20}N_2O_5$: C, 62·78; H, 5·85; N, 8·14%).

N - *Hydroxy* - N - *benzyl* - 3,4 - *dimethoxyamphetamine* (**16**)

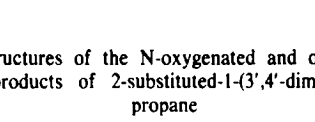
(a) *By oxidation of* N-*benzyl*-3,4-*dimethoxyamphetamine*. The yellow oily ester, N - (3 - chlorobenzolyoxy) - N - benzyl - 3,4 - dimethoxyamphetamine (2·89 g, 0·0066 mol), obtained from the 3-chloroperbenzoic acid oxidation of N-benzyl-3,4-dimethoxyamphetamine as described previously, was dissolved in 150 ml dry ether and added dropwise to a stirred slurry of LAH (0·5 g) in 200 ml dry ether at room temp. Stirring was continued for 2 hr. Celite (2 g) was added to the mixture and the excess LAH was decomposed by addition of water. After filtration of the celite and solid salts, the ethereal soln was dried over $MgSO_4$ and concentrated to give an oil. IR analysis showed absence of the C=O band and the presence of O–H stretching in the region of 3200–3500 cm^{-1}. After failure of attempts to cause the oil to solidify, it was dissolved in ether and the oxalate was prepared in the usual manner. The precipitated salt was recrystallised from MeOH-ether to give 0·14 g (5%), m.p. 169–171°; it gave no depression of m.p. when mixed with that prepared below in method b.

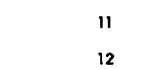
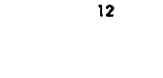
(b) *By* LAH *reduction of the nitrone* **13**. To 1 g of a stirred LAH slurry in 100 ml dry ether at room temp was added dropwise 1·88 g (0·0063 mol) of **13** dissolved in 50 ml benzene. The mixture was stirred for 1·5 hr, celite (2 g) was added and the excess LAH was decomposed with water. After filtration and drying of the ethereal soln over $MgSO_4$, removal of the ether provided an oil which solidified upon standing to yield 1·78 g (94%), m.p. 100–104°. Recrystallisation from ether-pet. ether (40–60°) gave 1·18 g (62%) of the product, m.p. 105–107°: IR ($CHCl_3$) 3590 (free O–H) sharp, 3230 (H-bonded O–H) broad, 3040–2900, 2843, 1609, 1592, 1514, 1468, 1261, 1150 and 1030 cm^{-1}; NMR ($CDCl_3$) δ 1·07 (d, 3, J = 6·2, CH_3), 2·45 (m, 1, $H_aCH_bCH_c$), 2·97 (m, $H_aCH_bH_c$), 3·15 (m, $H_aCH_bCH_c$), 3·83 (s, $CH_2C_6H_5$), 3·83 (s, OCH_3), 5·97 (broad s, 1, NOH), 6·58–6·89 (m, 3, $C_6H_3(OCH_3)_2$) and 7·30 (s, 5, C_6H_5); MS, *m/e* 302(0·8), 301(0·7) molecular ion, 283(0·9), 210(0·2), 191(0·6), 179(2), 178(5), 163(2), 152(43), 151(30), 150(75), 134(6), 131(6), 121(2), 107(5), 92(9), 91(100), 77(4), 65(5). (Found: C, 71·6; H, 7·7; N, 4·5. Calc. for $C_{18}H_{23}NO_3$: C, 71·73; H, 7·69; N, 4·65%). An oxalate was prepared and recrystallised from methanol-ether, m.p. 169–171°.

(c) *By* $NaBH_3CN$ *reduction of the nitrone* **13**. To a stirred soln of 0·25 g (0·83 mmol) of **13** and 0·5 g $NaBH_3CN$ in 10 ml MeOH was added a methanolic HCl soln at a rate such that the pH was maintained at 4–5. The mixture was stirred at room temp for 3 hr. The MeOH was removed by rotary evaporation, the residue dissolved in 10 ml water, made alkaline (pH = 8) with 5% KOH, saturated with NaCl, and extracted with 4 × 50 ml ether. The ethereal extracts were dried over $MgSO_4$ and concentrated to give 0·15 g (60%) of product, m.p. 103–105°. An oxalate was prepared from this solid, m.p. 167–170°. Mixed m.p. determinations of both the free base and the oxalate with those prepared previously showed no depression.

(d) *By* N-*alkylhydroxylamination of benzaldehyde*. A methanolic soln (40 ml) of **6** (1·05 g, 0·005 mol) and benzaldehyde (0·636 g, 0·006 mol) was adjusted to pH = 6 with dil HCl and 0·6 g $NaBH_3CN$ was added. The mixture was stirred at room temp, the pH being maintained at 6 by addition of dil HCl. After 5 hr, the soln was made strongly acidic (pH = 1) and after the evolution of gas subsided, the MeOH was partially removed by rotary evaporation. The residue was dissolved in 100 ml water, made alkaline (pH = 8) with 5% KOH, saturated with NaCl, and extracted with 4 × 50 ml ether. The ethereal extracts were dried over $MgSO_4$ and concentrated to give 1·27 g (84%) of a tan oil which solidified upon trituration with pet. ether (40–60°). Recrystallisation from disopropyl ether afforded 0·54 g (36%) of the product, m.p. 104–106°.

Table 1. Structures of the N-oxygenated and other probable metabolic products of 2-substituted-1-(3',4'-dimethoxyphenyl) propane



Compound No.	R.	Compound No.	R.
2	=O	11	$-N=CHC_6H_5$
3	=NOH	12	$-NHCH_2C_6H_5$
4	$-NH_2$	13	$-\overset{+}{N}(O^-)=CHC_6H_5$
5	-OH		
6	-NHOH		
7	-N=O	14	
8	$-NHCH_3$		
9	$-N(OH)CH_3$	15	
10	$-\overset{+}{N}(O^-)=CH_2$	16	$-N(OH)CH_2C_6H_5$

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REFERENCES

[1a] A. H. Beckett, *Xenobiotica* **1**, 365 (1971); [b] A. H. Beckett, *Frontiers in Catecholamine Research*, (Edited by E. Usdin and S. Snyder) p. 139, Pergamon Press (1973); [c] A. H. Beckett and S. Al-Sarraj, *J. Pharm. Pharmac.* **24**, 916 (1972); [d] A. H. Beckett, J. M. Van Dyk, H. H. Chissick and J. W. Gorrod, *Ibid.* **23**, 809 (1971); [e] B. Lindeke, A. K. Cho, T. L. Thomas and L. Michelson, *Acta Pharm. Suecica* **10**, 493 (1973).

[2a] A. H. Beckett and S. Al-Sarraj, *J. Pharm. Pharmac.* **24**, 174 (1972); [b] A. H. Beckett and K. K. Midha, *Xenobiotica* **4**, 297 (1974).

[3a] A. H. Beckett and S. Al-Sarraj, *J. Pharm. Pharmac.* **25**, 335 (1973); [b] A. H. Beckett and E. E. Essien, *Ibid.* **25**, 188 (1973).

[4] A. H. Beckett, R. T. Coutts and F. A. Ogunbona, *Ibid.* **25**, 190 (1973).

[5a] A. H. Beckett and P. M. Belanger, *Ibid.* **26**, 205 (1974); [b] A. H. Beckett and P. M. Belanger, *Xenobiotica* **4**, 509 (1974); [c] A. K. Cho, B. Lindeke and C. Y. Sum, *Drug Metab. Disp.* **2**, 1 (1974); [d] U. Koster, J. Caldwell and R. L. Smith, *Biochem. Soc. Transactions* **2**, 881 (1974).

[6a] C. F. Barfknecht and D. E. Nichols, *J. Med. Chem.* **15**, 109 (1972); [b] C. F. Barfknecht, J. M. Miles and J. L. Leseney, *J. Pharm. Sci.* **59**, 1842 (1970); [c] F. Benington and R. D. Morin, *J. Med. Chem.* **11**, 896 (1968); [d] J. R. Smythies, V. S. Johnston, R. J. Bradley, F. Benington, R. D. Morin and L. C. Clark, Jr., *Nature London*, **216**, 128 (1967).

[7] E. R. Shepard, J. F. Noth, H. D. Porter and C. K. Simmons, *J. Am. Chem. Soc.* **74**, 4611 (1952).

[8] J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 2248 (1951).

[9] R. F. Borch, M. D. Bernstein and H. D. Hurst, *J. Am. Chem. Soc.* **93**, 2897 (1971).

[10] E. Schmidt, A. Ascherl and L. Mayer, *Ber. Dtsch. Chem. Ges.* **58B**, 2430 (1925).

[11] H. Feuer, R. S. Bartlett, B. F. Vincent, Jr. and R. S. Andersen, *J. Org. Chem.* **30**, 2880 (1965).

[12] R. T. Gilsdorf and F. F. Nord, *J. Am. Chem. Soc.* **74**, 1837 (1952).

[13] R. T. Coutts and J. L. Malicky, *Can. J. Chem.* **52**, 395 (1974).

[14a] F. Benington, R. D. Morin and L. C. Clark, Jr., *J. Med. Chem.* **8**, 100 (1965); [b] G. Vavon and N. Krajcinovic, *Bull. Soc. Chim. Fr.* **43**, 231 (1928).

[15] H. Feuer, B. F. Vincent, Jr. and R. S. Bartlett, *J. Org. Chem.* **30**, 2877 (1965).

[16] F. Hodesan and V. Ciurdaru, *Tetrahedron Letters*, 1997 (1971).

[17] T. Kawaguchi, T. Matsubara and H. Kato, *Jap. Pat.* 19495 (1966). *Chem. Abstr.* **66**, 85529q (1967).

[18a] W. D. Emmons, *J. Am. Chem. Soc.* **79**, 5739 (1957); [b] A. R. Butler and B. C. Challis, *J. Chem. Soc.* (B), 778 (1971); [c] M. Ohno, H. Iinuma, N. Yagisawa, S. Shibahara, S. Kondo, K. Maeda, and J. Umezawa, *J. Chem. Soc. Chem. Comm.* 147 (1973); [d] A. H. Beckett, K. Haya, G. R. Jones and P. H. Morgan, *Tetrahedron* **31**, 1531 (1975).

[19] J. Hamer and A. Macaluso, *Chem. Rev.* **64**, 473 (1964); and Refs therein.

[20] M. A. T. Rodgers, *J. Chem. Soc.* 769 (1955).

[21] Y. Isowa and H. Kurita, *Bull. Chem. Soc. Japan* **47**, 720 (1974).

[22] A. H. Beckett, R. T. Coutts and F. A. Ogunbona, *Tetrahedron* **29**, 4189 (1973).

[23] C. Vavon and N. Krajcinovic, *C.R. Acad. Sci. Paris* **187**, 420 (1928).

[24] W. R. Dunstan and E. Goulding, *J. Chem. Soc.* **75**, 792 (1899).

[25] D. B. Denny and D. Z. Denny, *J. Am. Chem. Soc.* **82**, 1389 (1960).

[26] W. Rundel, *Methoden zur Herstellung und Umwandlung von Nitronen.* In *Methoden der Organischen Chemie* (Houben-Weyl), Vol. X/4, p. 309, 4th Edn. Georg Thieme, Stutgart, (1968) and Refs therein.

[27] G. E. Utzinger and F. A. Regeness, *Helv. Chim. Acta* **37**, 1892 (1954).

[28] C. Runti and F. Collino, *Ann. Chim. Rome* **49**, 1472 (1959).

[29] G. Zinner and W. Kliegel, *Chem. Ber.* **99**, 2686 (1966).

[30] J. E. Baldwin, A. K. Qureshi and B. Sklarz, *J. Chem. Soc.* (C), 1073 (1969).

[31] A. H. Beckett, G. R. Jones and R. T. Coutts, unpublished results, Chelsea College, London, U.K.

[32] S. F. Nelsen, *Free Radicals* (Edited by J. K. Kochi), Vol. II, p. 545. Wiley, New York (1973).

[33] R. G. Pews, *J. Org. Chem.* **32**, 1628 (1967).

[34] F. A. Bovey, *Nuclear Magnetic Resonance Spectroscopy*, pp. 159–168. Academic Press, New York (1965).

[35] L. Bilbiano and V. Paolini, *Gazz. Chim. Ital.* **36**, I, 291 (1905). Beilstein, **8**, 281.

[36] B. T. Ho, W. M. McIsaac, R. An, L. W. Tansey, K. E. Walker, L. F. Englert and M. B. Noel, *J. Med. Chem.* **13**, 26 (1970).

[37] G. R. Clemo and J. H. Turnbull, *J. Chem. Soc.*, 124 (1947).

[38] R. J. Borgman, M. R. Baylor, J. J. McPhillips and R. E. Stitzel, *J. Med. Chem.* **17**, 427 (1974).