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Synthesis and Spectral Properties of 2,5-Dimethoxy-4-Ethoxyamphetamine and Its Precursors

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ABSTRACT: 2,5-Dimethoxy-4-ethoxyamphetamine (MEM) was synthesized by two routes. The gas liquid chromatographic data and ultraviolet, infrared, proton magnetic resonance, carbon-13 magnetic resonance, and mass spectra are presented for this amphetamine as well as its precursors. This amphetamine was found to be identical to the sample submitted by the police.

KEYWORDS: toxicology, 2,5-dimethoxy-4-ethoxyamphetamine (MEM), chromatographic analysis, precursors, chemical analysis, gas liquid chromatographic, ultraviolet, infrared, mass spectroscopic, proton magnetic resonance, and carbon-13 magnetic resonance spectral data

Three years ago, 2,5-dimethoxy-4-ethoxyamphetamine (I) was detected as a street drug in Canada; at the time it was not an illegal substance. Subsequently, on 8 Aug. 1986, it was added to Schedule H of Canada's Food and Drugs Act and Regulations. There was a need therefore to prepare a supply of the substance for use as a reference standard. Examination of the literature revealed that Shulgin [*1*] had made the amphetamine via the correspondingly substituted benzaldehyde IV and nitroethane (Fig. 1). The literature, however, is very deficient in spectral and chromatographic data for this amphetamine and its precursors. Dawson and Avdovich [*2*] had performed a proton magnetic resonance (^{1}H-NMR) shift reagent study to identify a street sample as 2,5-dimethoxy-4-ethoxyamphetamine. Following success in these laboratories [*3*] with side-chain nitration of substituted 1-phenyl-1-propenes using nitryl iodide prepared in situ, it was decided to try this approach again on 1-(2,5-dimethoxy-4-ethoxyphenyl)-1-propene (X).

This paper describes the synthesis, purification, and characterization of 2,5-dimethoxy-4-ethoxyamphetamine hydrochloride and precursors for both above routes (Fig. 1).

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Materials and Apparatus

3-Ethoxy-4-methoxyphenol was purchased from Aldrich Chemical Company, Inc.; distilled-in-glass grade methanol from Caledon Laboratories Ltd.; column silica gel from J. T. Baker Chemical Co.; thin-layer chromatographic silica gel from Analtech, Inc.; and proadifen hydrochloride (SKF 525A) from Smith, Kline and French Ltd. The ultraviolet (UV) spectra were run in methanol using a Varian DMS90 UV/VIS spectrophotometer. The infrared (IR) spectra were determined as 0.3% KBr pellets, unless otherwise stated, on a Nicolet Fourier transform model 60SX instrument. Melting points were taken on a Kofler hot-stage apparatus and are reported uncorrected. The electron ionization (45-eV) mass spectra (MS) were obtained in the split mode (1:30) from a Finnigan MAT 4610B gas liquid chromatographic/mass spectroscopic (GLC/MS) instrument on a 15-m, 0.25-mm inside diameter (ID) capillary column (from J. and W. Scientific, Inc.) having a chemically bonded, 0.25-μm DB-5 film. The proton magnetic resonance (^{1}H-NMR) spectra were determined at 80 MHz with a Bruker WP80 instrument using deuterochloroform ($CDCl_3$) as the solvent with tetramethylsilane (TMS) as the internal reference, unless otherwise stated. Most of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were also run on the Bruker WP80 using $CDCl_3$ with TMS as the internal reference, but at 20.1 MHz. A Bruker AM400 instrument at 100.6 MHz was used for the ^{13}C-NMR spectra of III, V, I, and I hydrochloride. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as the internal standard for the deuterium oxide (D_2O) solutions, unless otherwise stated.

Gas Liquid Chromatography

The relative retention times (Rel. R_t) of the various components in Fig. 1 against that of proadifen are listed in Table 1. The GLC conditions were as follows: oven, 150°C for

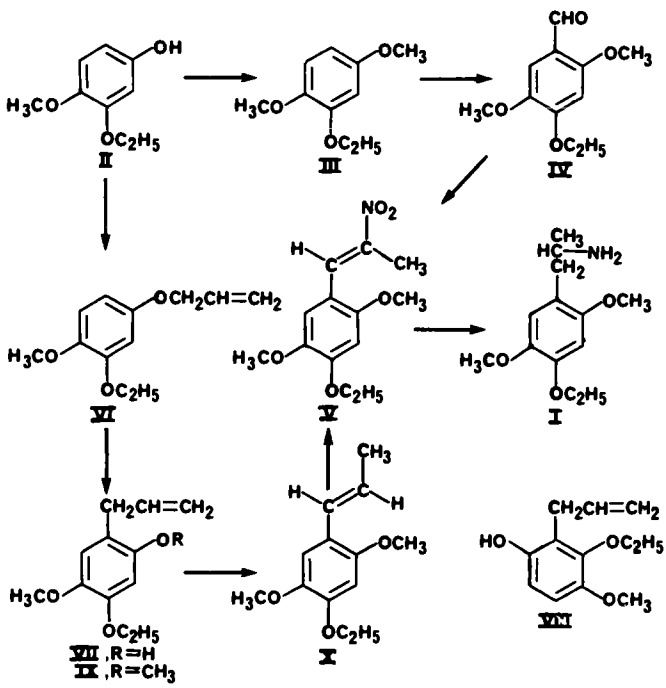

FIG. 1—*2,5-Dimethoxy-4-ethoxyamphetamine (I) made via two different routes.*

TABLE 1—*Relative retention times of the components in Fig. 1 against that of proadifen.*

Compound	Relative R_t
III	217
II	229
VI	292
VIII	327
IX	348
cis X	388
VII	400
X	436
IV	472
I	494
V	848
Proadifen 1000 (7 min)	

1 min, 15°C/min rise to 260°C; carrier gas, helium, 30 cm/s; and injector temperature, 250°C.

Infrared Spectra

The infrared spectra are depicted in Figs. 2 through 12. The free base I was prepared from I hydrochloride by partitioning it between 20% aqueous sodium carbonate (Na_2CO_3) and methylene chloride (CH_2Cl_2), passing the CH_2Cl_2 solution through a small column of anhydrous sodium sulfate (Na_2SO_4), and evaporating the solvent with a stream of dry nitrogen.

Proton Magnetic Resonance Spectra

The ^{1}H-NMR spectra of Fig. 1 compounds are shown in Figs. 13 through 23. The sample for Fig. 23, the free base I, was prepared in situ from a D_2O solution of I

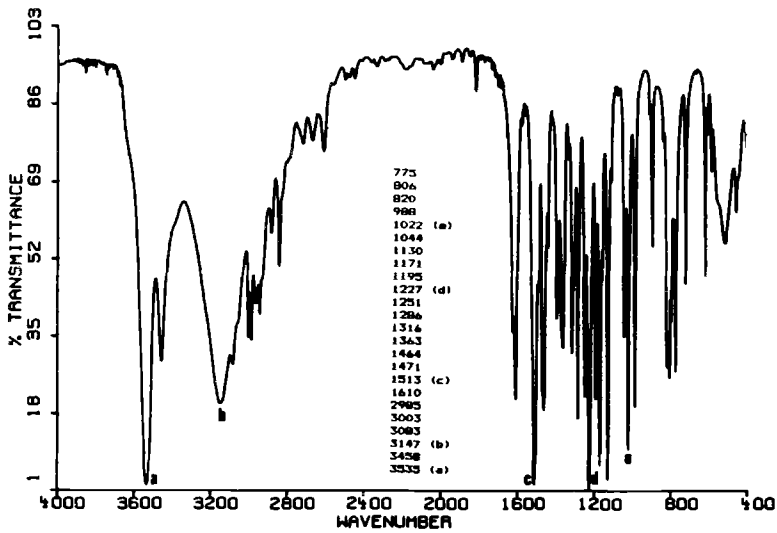

FIG. 2—*IR spectrum of 3-ethoxy-4-methoxyphenol (II).*

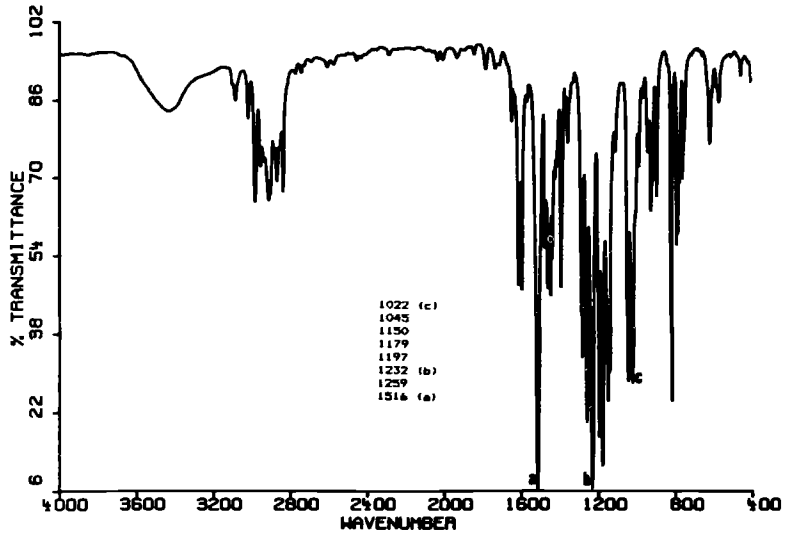

FIG. 3—*IR spectrum of 4-allyloxy-2-ethoxy-1-methoxybenzene (VI).*

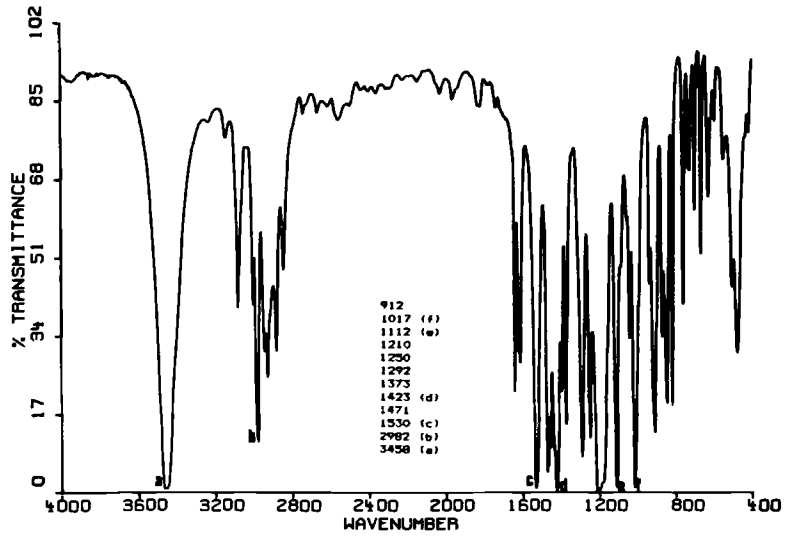

FIG. 4—*IR spectrum of 2-allyl-5-ethoxy-4-methoxyphenol (VII).*

hydrochloride in a 5-mm NMR tube by adding $CDCl_3$ and potassium carbonate (K_2CO_3) and shaking.

Mass Spectra

The mass spectra are reproduced in Figs. 24 through 27. The spectrum of the *N*-acetyl derivative of I was included because it may be of use to toxicologists.

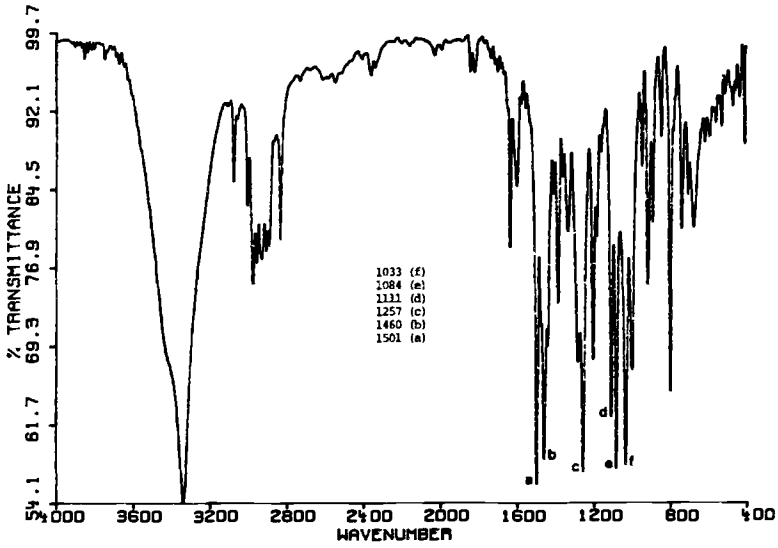

FIG. 5—*IR spectrum of 2-allyl-3-ethoxy-4-methoxyphenol (VIII).*

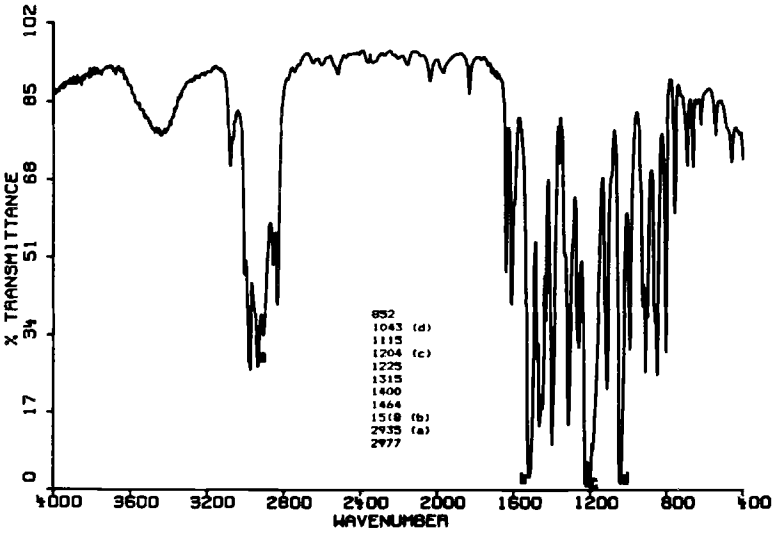

FIG. 6—*IR spectrum of 1-allyl-2,5-dimethoxy-4-ethoxybenzene (IX).*

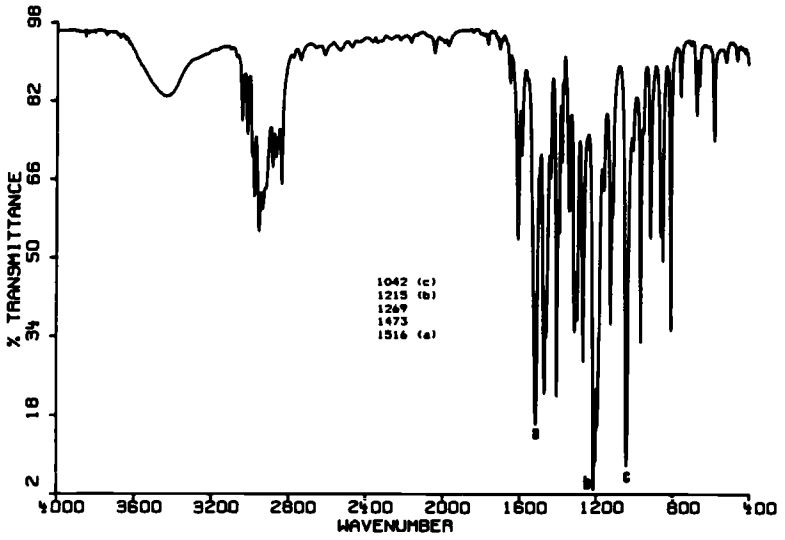

FIG. 7—*IR spectrum of* trans-*1-(2,5-dimethoxy-4-ethoxyphenyl)-1-propene (X).*

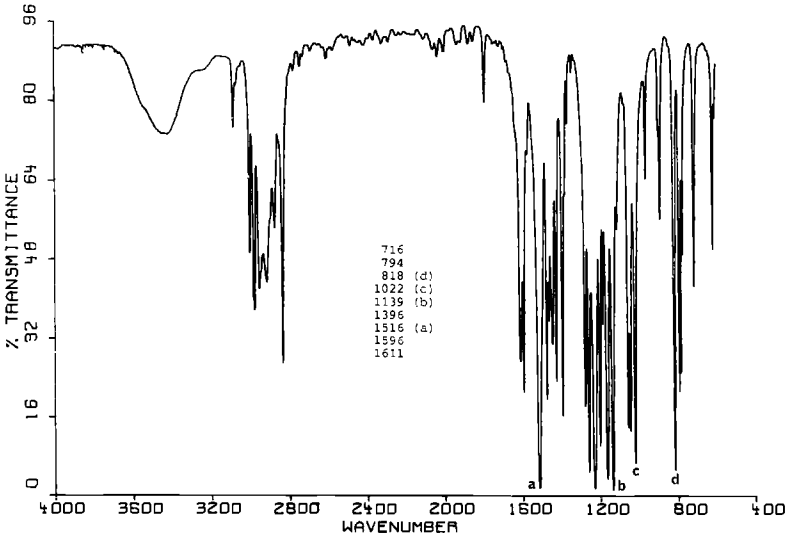

FIG. 8—*IR spectrum of 1,4-dimethoxy-2-ethoxybenzene (III).*

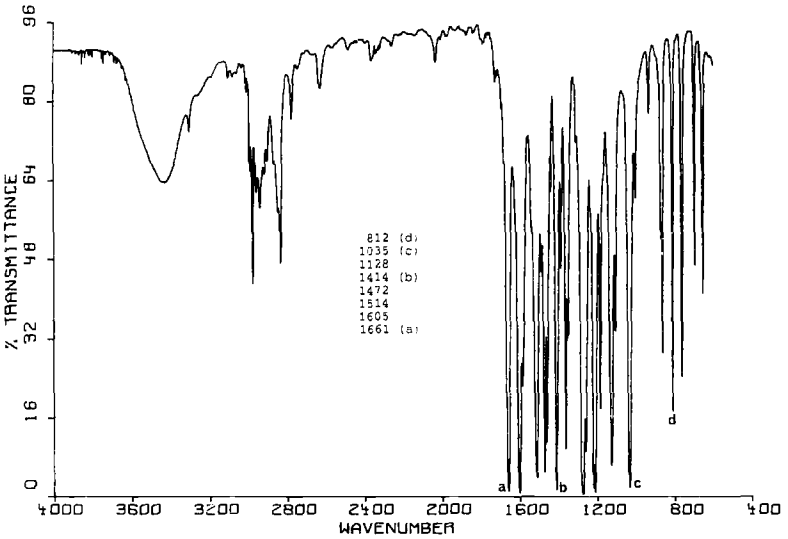

FIG. 9—*IR spectrum of 2,5-dimethoxy-4-ethoxybenzaldehyde (IV).*

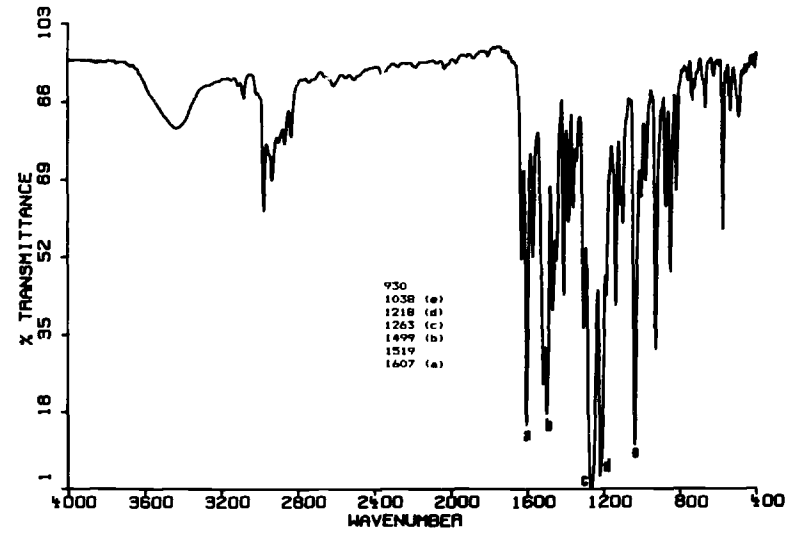

FIG. 10—*IR spectrum of* trans*-1-(2,5-dimethoxy-4-ethoxyphenyl)-1-(2-nitro)propene (V).*

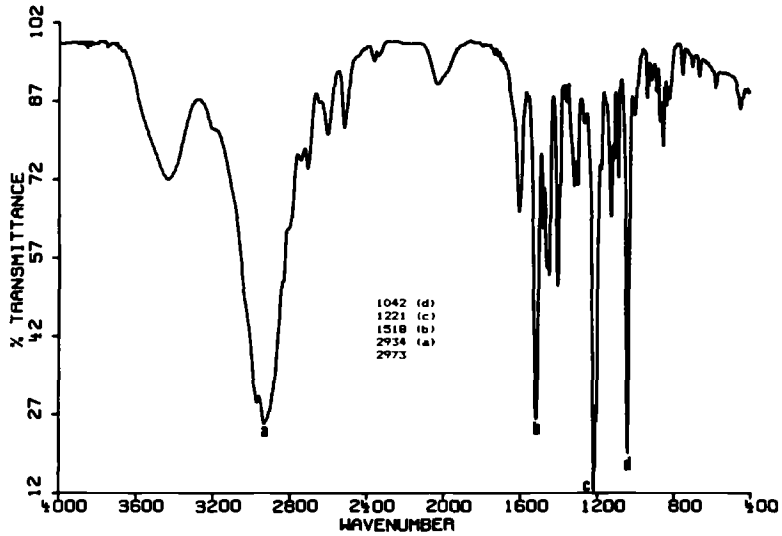

FIG. 11—*IR spectrum of 2,5-dimethoxy-4-ethoxyamphetamine (I) HCl.*

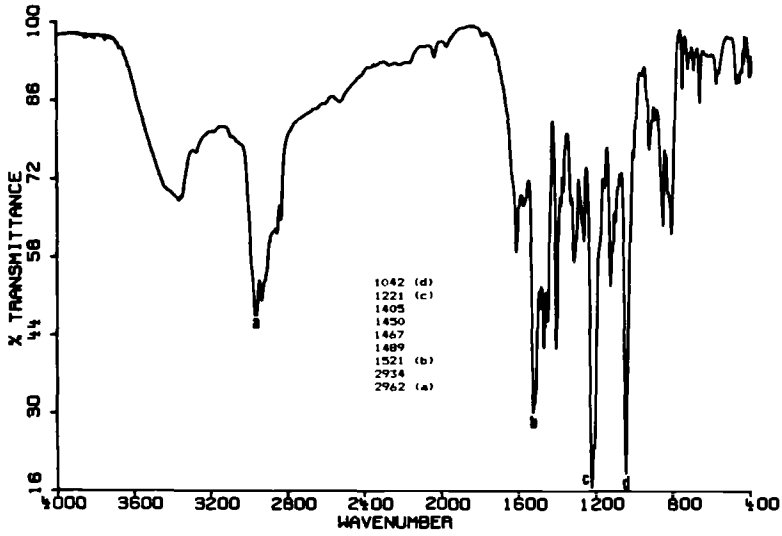

FIG. 12—*IR spectrum of 2,5-dimethoxy-4-ethoxyamphetamine (I).*

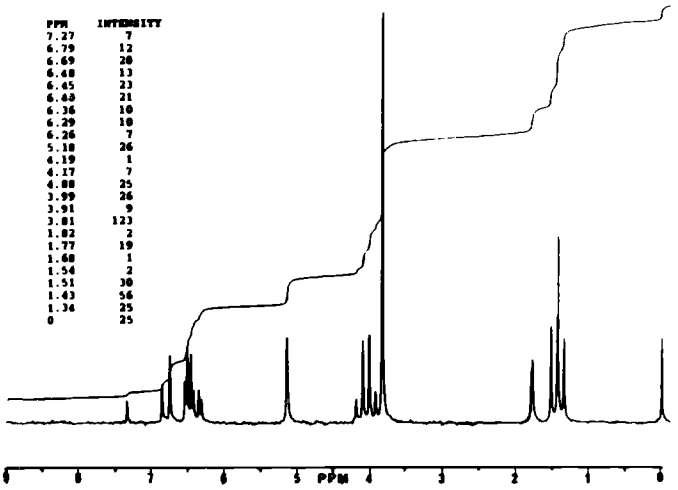

FIG. 13—^{1}*H-NMR spectrum of 3-ethoxy-4-methoxyphenol (II).*

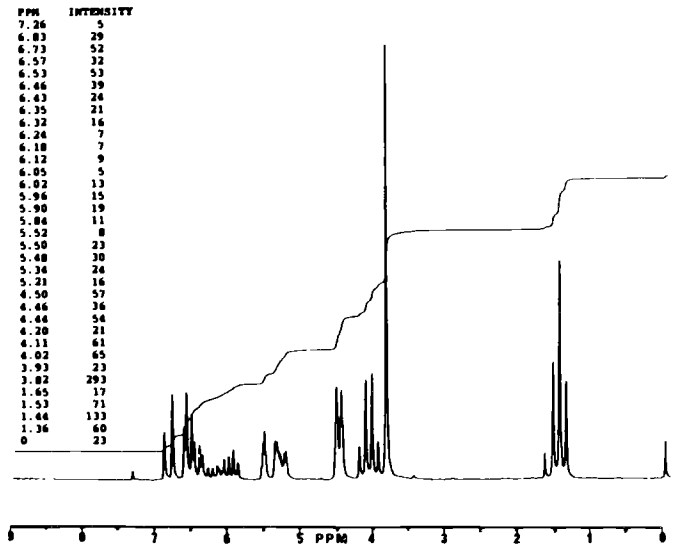

FIG. 14—^{1}*H-NMR spectrum of 4-allyloxy-2-ethoxy-1-methoxybenzene (VI).*

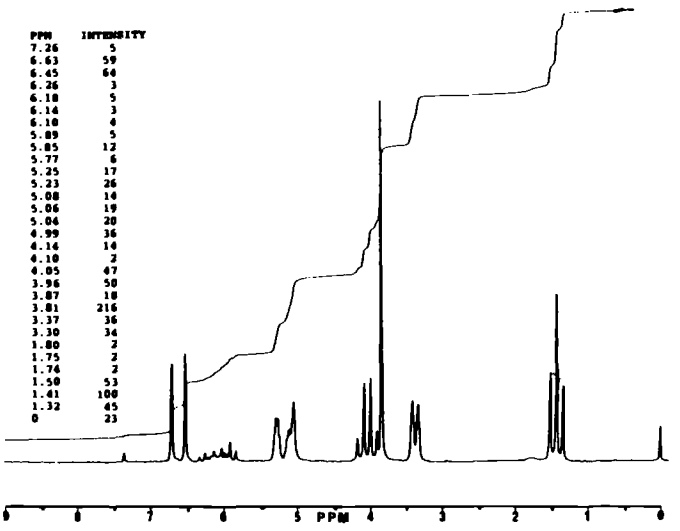

FIG. 15—^{1}*H-NMR spectrum of 2-allyl-5-ethoxy-4-methoxyphenol (VII).*

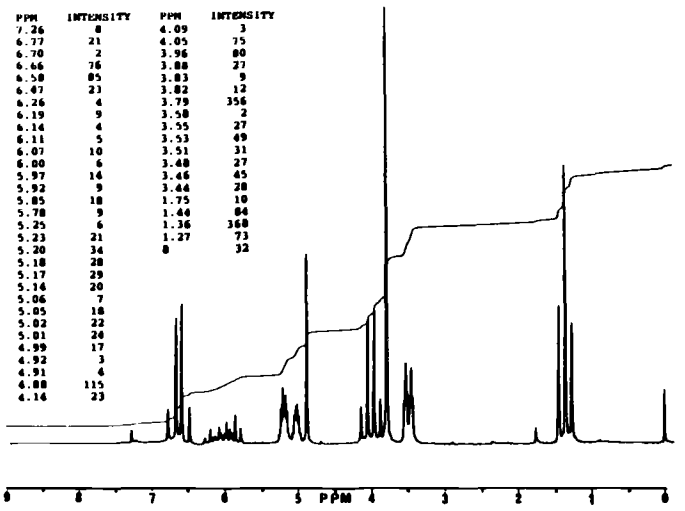

FIG. 16—^{1}*H-NMR spectrum of 2-allyl-3-ethoxy-4-methoxyphenol (VIII).*

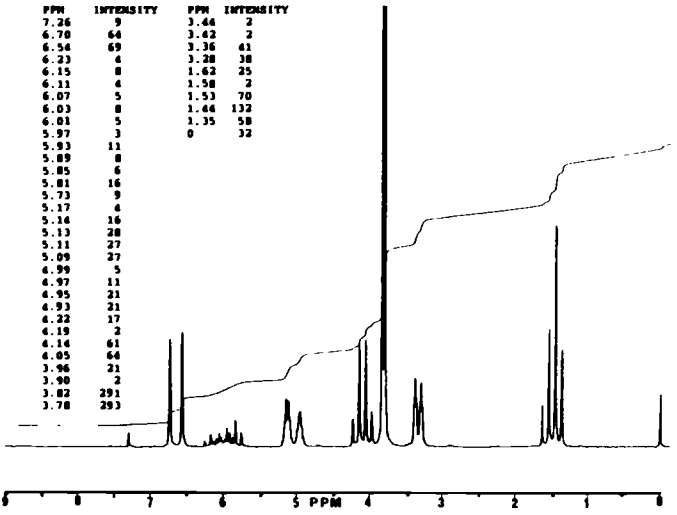

FIG. 17—^{1}*H-NMR spectrum of 1-allyl-2,5-dimethoxy-4-ethoxybenzene (IX).*

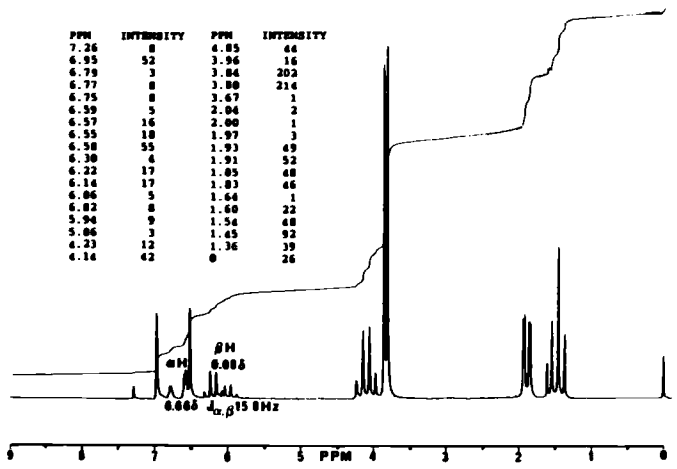

FIG. 18—^{1}*H-NMR spectrum of* trans*-1-(2,5-dimethoxy-4-ethoxyphenyl)-1-propene (X).*

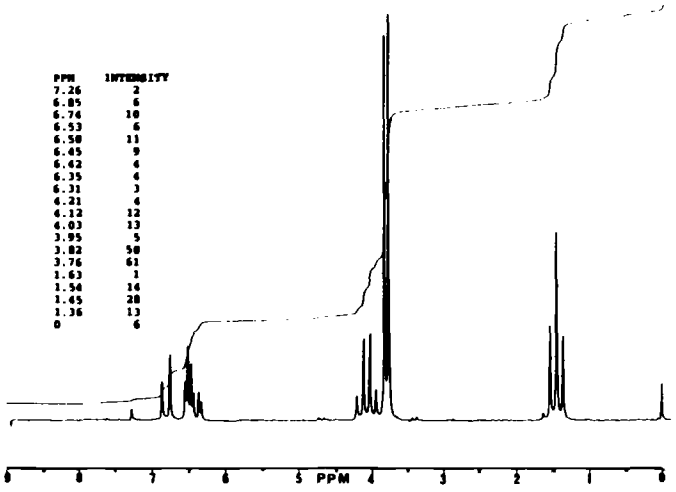

FIG. 19—^{1}*H-NMR spectrum of 1,4-dimethoxy-2-ethoxybenzene (III).*

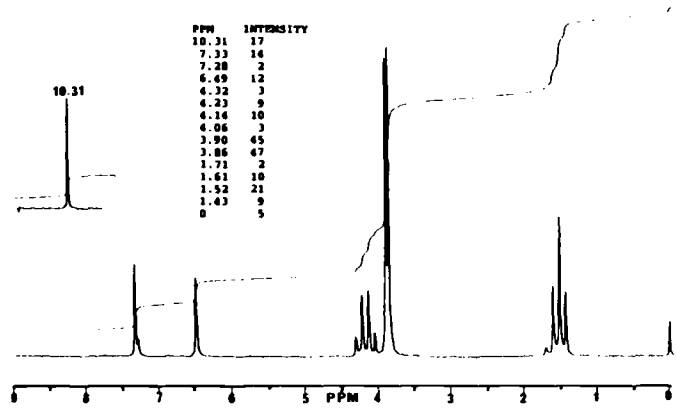

FIG. 20—^{1}*H-NMR spectrum of 2,5-dimethoxy-4-ethoxybenzaldehyde (IV).*

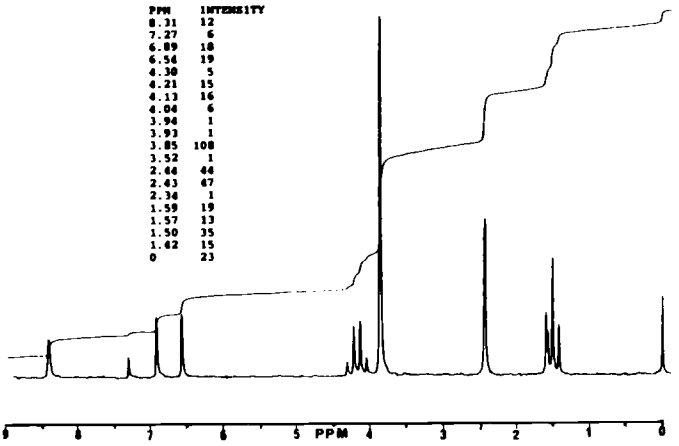

FIG. 21—^{1}*H-NMR spectrum of* trans*-1-(2,5-dimethoxy-4-ethoxyphenyl)-1-(2-nitro)propene (V).*

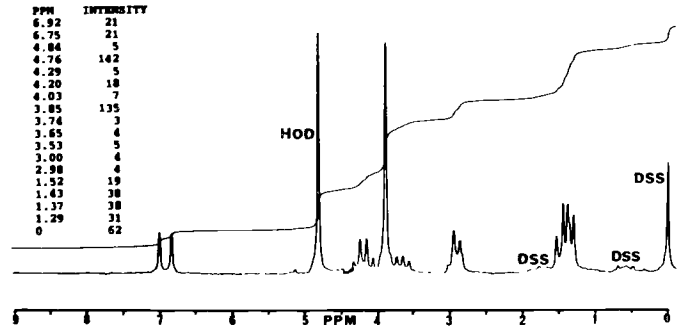

FIG. 22—^{1}*H-NMR spectrum of 2,5-dimethoxy-4-ethoxyamphetamine (I) HCl in* D_2O.

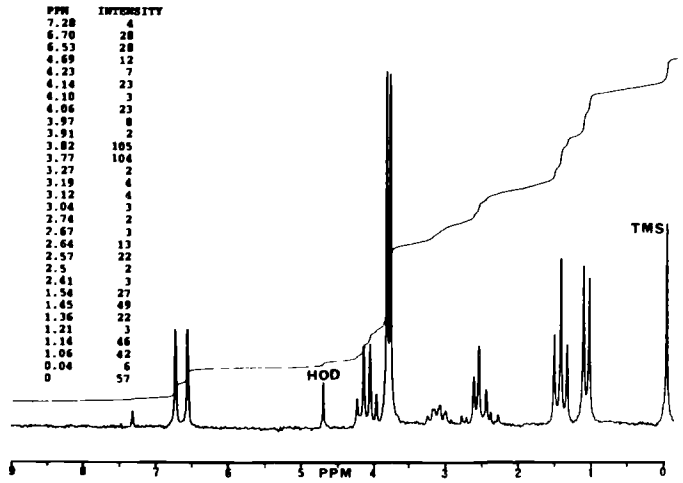

FIG. 23—^{1}*H-NMR spectrum of 2,5-dimethoxy-4-ethoxyamphetamine (I).*

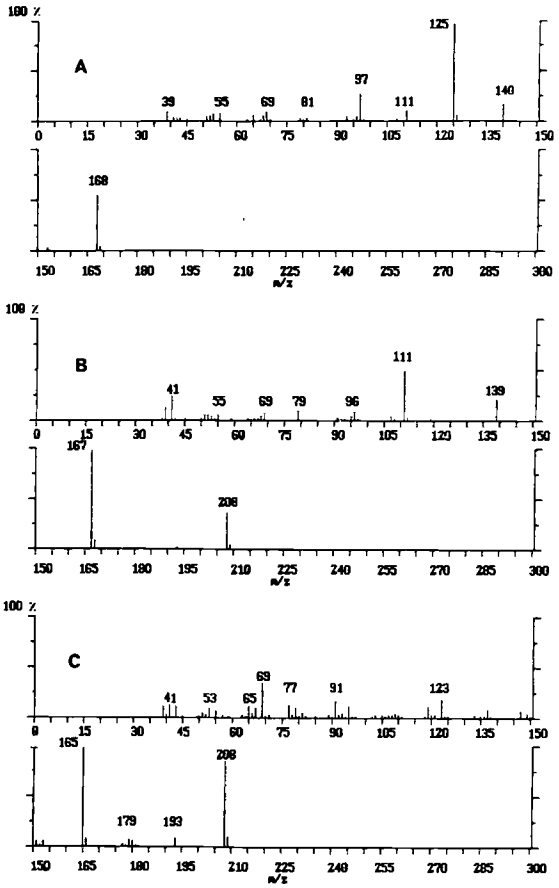

FIG. 24—*Mass spectrum of:* (a) *II,* (b) *VI, and* (c) *VII.*

Syntheses

Preparation of 4-Allyloxy-2-Ethoxy-1-Methoxybenzene (VI)

3-Ethoxy-4-methoxyphenol (II, 5 g, 0.030 mole) was refluxed under nitrogen for 7 h with allyl bromide (5.2 mL, 0.060 mole), anhydrous K_2CO_3 (8.08 g, 0.058 mole), and acetone (65 mL) [*4*]. Then a further amount of allyl bromide (2.6 mL, 0.030 mole) was added and refluxing continued overnight (16.4 h). After being cooled, the solution was filtered; the residue was washed with CH_2Cl_2, and the filtrate was evaporated in vacuo to dryness. The residue easily crystallized to give a pale yellow solid (6.2 g). The crude product was chromatographed on silica gel (90 g, 40–140 mesh) using chloroform ($CHCl_3$). The product was recrystallized first from hexane and then from acetone to obtain VI as fine, white needles (melting point [mp] 56 to 56.5°C). UV: λ_{max} 225 nm (ϵ 7400), 286 (3670); λ_{min} 219 nm (ϵ 7210), 253 (360). ^{13}C-NMR: 153.68(*s*), 149.70(*s*), 144.42(*s*), 133.94(*d*), 117.61(*t*), 112.99(*d*), 104.88(*d*), 102.91(*d*), 69.63(*t*), 64.53(*t*), 56.84(*q*), and 14.82(*q*) ppm. The letters in parentheses pertain to the multiplicity observed in the single frequency off-resonance decoupling spectrum: *s*, singlet; *d*, doublet; *t*, triplet; and *q*, quartet.

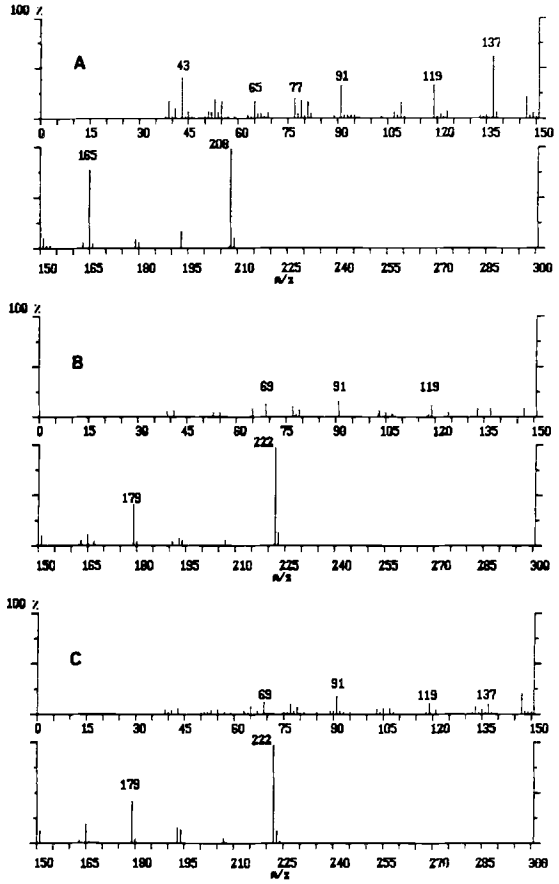

FIG. 25—*Mass spectrum of:* (a) *VIII,* (b) *IX, and* (c) *X.*

Preparation of 2-Allyl-5-Ethoxy-4-Methoxyphenol (VII)

Two batches of 4-allyloxy-2-ethoxy-1-methoxybenzene (VI, 21.9 g, 0.105 mole and 26.9 g, 0.129 mole) were each heated for 45 min under nitrogen using a 240°C silicone oil bath. The combined product was chromatographed on silica gel (800 g, 60–200 mesh) starting with toluene. The minor byproduct, 2-allyl-3-ethoxy-4-methoxyphenol (VIII), was eluted first with toluene. After further chromatography and crystallization from toluene-hexane, VIII gave a mp of 77.5 to 79°C. UV: λ_{max} 288 nm (ϵ 3290); λ_{min} 252 (180). ^{13}C-NMR: 149.29(*s*), 147.61(*s*), 147.46(*s*), 136.77(*d*), 120.76(*s*), 115.94(*t*), 122.02(*d*), 110.71(*d*), 69.23(*t*), 56.66(*q*), 28.70(*t*), and 15.67(*q*) ppm. The desired product VII (27.4 g) was later eluted mainly with 25:1 toluene-ethyl acetate. After the second crystallization from toluene-hexane, pure VII (22.6 g, mp 77.5 to 78°C) was obtained. UV: λ_{max} 292 nm (ϵ 4790); λ_{min} 257 (370). ^{13}C-NMR: 148.55(*s*), 148.34(*s*), 143.90(*s*), 136.98(*d*), 116.60(*s*), 116.36(*t*), 115.18(*d*), 103.21(*d*), 64.77(*t*), 57.09(*q*), 34.80(*t*), and 14.85(*q*) ppm. Thin-layer chromatography on silica gel GHLF (0.25 mm thick) using 4 :1 hexane-ethyl acetate gave an R_f of 0.35 for VII and an R_f of 0.47 for VIII.

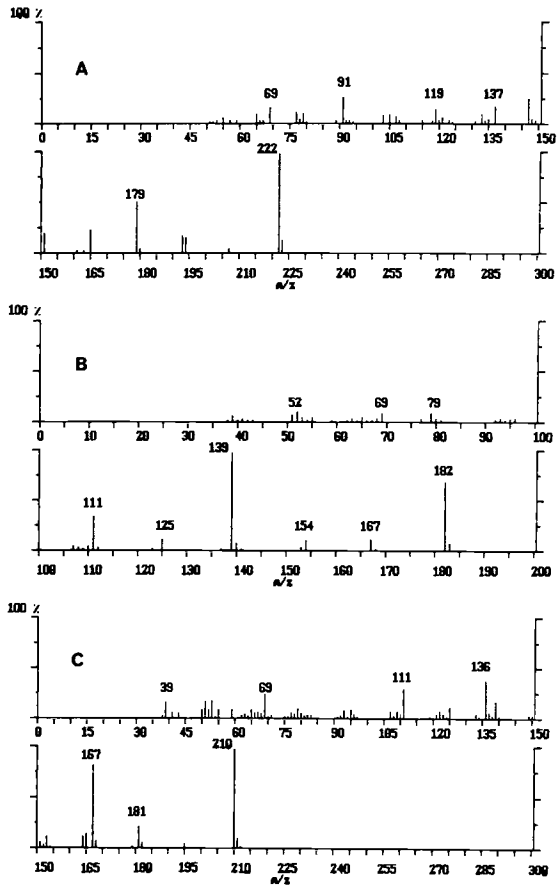

FIG. 26—*Mass spectrum of:* (a) cis *isomer of X,* (b) *III, and* (c) *IV.*

Preparation of 1-Allyl-2,5-Dimethoxy-4-Ethoxybenzene (IX)

2-Allyl-5-ethoxy-4-methoxyphenol (VII, 20.55 g, 0.099 mole) was refluxed under nitrogen with acetone (300 mL), anhydrous K_2CO_3 (28.0 g, 0.203 mole), and iodomethane (13 mL, 0.209 mole) for 3 h with stirring. More iodomethane (13 mL) was then added and refluxing continued for a further 4 h. Then an additional 13 mL of iodomethane was added and refluxing continued overnight (17 h) after which the solution was cooled and evaporated in vacuo. To the residue was added toluene (200 mL). The flask was shaken, and the residue was filtered and washed with toluene (3 × 50 mL). Upon evaporation of the combined toluene solution, an easily crystallizable product (21.4 g) was obtained. A fast column chromatography was carried out using silica gel (100 g, 60–200 mesh) and toluene, whereupon IX (20.4 g) was obtained. Two crystallizations from hexane gave pure IX (mp 31 to 32°C). UV: λ_{max} 231 nm (ϵ 8430), 290 (4760); λ_{min} 221 nm (ϵ 7640), 257 (400). ^{13}C-NMR: 151.89(*s*), 147.79(*s*), 144.18(*s*), 137.65(*d*), 121.01(*s*), 115.36(*d*), 115.36(*t*), 100.66(*d*), 65.35(*t*), 57.12(*q*), 56.72(*q*), 33.80(*t*), and 15.06(*q*) ppm.

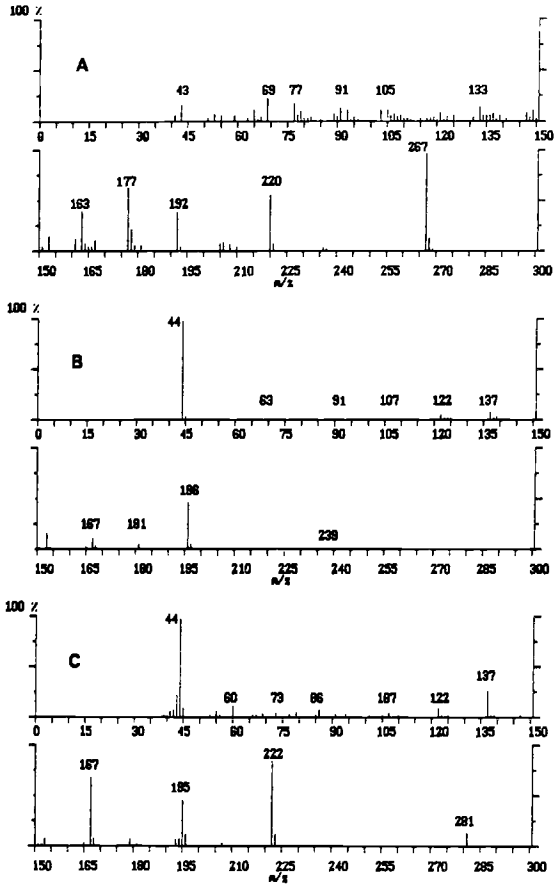

FIG. 27—*Mass spectrum of:* (a) *V,* (b) *I, and* (c) N-*acetyl I.*

Preparation of Trans-*1-(2,5-Dimethoxy-4-Ethoxyphenyl)-1-Propene (X)*

1-Allyl-2,5-dimethoxy-4-ethoxybenzene (IX, 19.8 g, 0.089 mole) was dissolved in absolute ethanol (30 mL) to which potassium hydroxide (KOH) pellets (25 g) were added. The mixture was refluxed with stirring over 40 min. After cooling the mixture in ice water, some ice water and ether were then added to it. The aqueous layer was extracted three times with ether. The combined ether extracts were washed three times with water and once with saturated aqueous sodium chloride (NaCl) solution. The ether layer was dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and evaporated in vacuo to dryness to obtain a light brown solid (19.2 g), which after two recrystallizations from ethyl acetate gave the pure *trans* isomer X (mp 108.5 to 109°C). UV: λ_{max} 230 nm (ϵ 25 320), 275 (17 170), inflexion 282 (14 830), 330 (8310); λ_{min} 256 nm (ϵ 10 270), 298 (1710). ^{13}C-NMR: 151.22(*s*), 148.61(*s*), 144.42(*s*), 125.56(*d*), 124.56(*d*), 119.88(*s*), 111.17(*d*), 100.45(*d*), 65.13(*t*), 56.97(*q*), 56.88(*q*), 18.77(*q*), and 14.97(*q*) ppm.

The unavailability of a proper preparative gas liquid chromatograph meant that the minor (about 10% of X) *cis* isomer of X could not be isolated and characterized by spectra other than the mass spectrum (Fig. 26*a*). As noted in Table 1, the *cis* compound is eluted off GLC before the *trans* one.

Preparation of 1,4-Dimethoxy-2-Ethoxybenzene (III)

3-Ethoxy-4-methoxyphenol (II, 15 g, 0.089 mole) was refluxed 2.5 h with iodomethane (30 mL, 0.482 mole), anhydrous K_2CO_3 (25 g, 0.181 mole), and acetone (225 mL). Then a further 10 mL (0.161 mole) of iodomethane was added with refluxing continued overnight (18 h). After having cooled the solution, it was filtered and evaporated in vacuo. The residue was partitioned between water and CH_2Cl_2, the CH_2Cl_2 solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. Crystallization from aqueous methanol gave 11.23 g, then a further crop of 3.11 g. A portion was recrystallized from the same solvent to give a mp of 44.0 to 44.5°C. UV: λ_{max} 228 nm (ϵ 6980), 289 (3550); λ_{min} 221 nm (ϵ 6660), 255 (235). ^{13}C-NMR: 154.29(*s*), 149.30(*s*), 143.83(*s*), 112.41(*d*), 103.11(*d*), 101.63(*d*), 64.29(*t*), 56.65(*q*), 55.66(*q*), and 14.77(*q*) ppm.

Preparation of 2,5-Dimethoxy-4-Ethoxybenzaldehyde (IV)

The Vilsmeier reaction was conducted according to the procedure described by Shulgin [*1*] using 1,4-dimethoxy-2-ethoxybenzene (III, 9.2 g, 0.061 mole), phosphorus oxychloride ($POCl_3$) (11.9 mL, 0.128 mole), and *N*-methylformanilide (15.8 mL, 0.128 mole). The reaction yielded 8.6 g of IV [mp 108.5 to 110°C (mp 109°C, [*1*])] after crystallization from aqueous methanol. UV: λ_{max} 236 nm (ϵ 15 450), 275 (11 360), 341 (9120); λ_{min} 219 nm (ϵ 7560), 252 (2800), 299 (2080). ^{13}C-NMR: 188.24(*d*), 158.93(*s*), 155.72(*s*), 144.30(*s*), 117.78(*s*), 109.89(*d*), 97.47(*d*), 64.98(*t*), 56.48(*q*), and 14.64(*q*) ppm.

Preparation of Trans*-1-(2,5-Dimethoxy-4-Ethoxyphenyl)-1-(2-Nitro)Propene (V)*

Method A—In a procedure similar to that of Shulgin [*1*], 2,5-dimethoxy-4-ethoxybenzaldehyde (IV, 5.85 g, 0.0278 mole) was gently refluxed over 3 h together with anhydrous ammonium acetate (1.8 g, 0.0234 mole), nitroethane (2.9 g, 0.0386 mole), and glacial acetic acid (22 mL) using a heating mantle and magnetic stirring bar. After the usual work-up, the crude product was chromatographed on silica gel (180 g, 40–140 mesh) using 3:1 toluene-$CHCl_3$. Crystallization of the early fractions from $CHCl_3$-hexane gave V [1.85 g, dark orange crystals, mp 130 to 131°C (mp 129°C, [*1*])]. UV: λ_{max} 240 nm (ϵ 9510), 266 (8780), 319 (4420), 387 (10 390); λ_{min} 226 nm (ϵ 8490), 256 (8340), 293 (3610), 321 (4400). ^{13}C-NMR: 154.09(*s*), 151.73(*s*), 145.40(*s*), 143.06(*s*), 129.57(*d*), 113.74(*d*), 112.46(*s*), 97.76(*d*), 64.63(*t*), 56.86(*q*), 56.23(*q*), 14.64(*q*), and 14.30(*q*) ppm.

Method A is capable of producing the *cis* isomer of V but in very low yield. The *cis* isomer generally comes out of the GLC ahead of the *trans* one, but the former very often is partially converted on the injector to the latter. The photoisomerization of *trans* propenes like V is being investigated at present.

Method B—Iodine (0.508 g, 0.002 mole) and silver nitrite ($AgNO_2$) (0.308 g, 0.002 mole) were stirred in anhydrous tetrahydrofuran (10 mL) at room temperature under nitrogen for 45 min. *Trans*-1-(2,5-dimethoxy-4-ethoxyphenyl)-1-propene (X, 0.222 g, 0.002 mole) and pyridine (0.320 g, 0.004 mole) in anhydrous tetrahydrofuran (3 mL) were added and the mixture was stirred at room temperature for 5 h. After this time, the yellow solid was removed by filtration. The filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed successively with 5% aqueous sodium bisulfite ($NaHSO_3$), 5% aqueous hydrochloric acid (HCl), saturated aqueous sodium bicarbonate ($NaHCO_3$), and water, then dried over Na_2SO_4 after which the solvents were removed under reduced pressure to obtain a brown product. This material was chromatographed on silica gel and eluted with $CHCl_3$ to give V (0.093 g, 34.8% yield, mp 130.5 to 131°C [CH_2Cl_2-ether]).

Methods A and B gave IR spectra (0.3% KBr) of V which were identical.

Preparation of 2,5-Dimethoxy-4-Ethoxyamphetamine (I)

A mixture of 1-(2,5-dimethoxy-4-ethoxyphenyl)-1-(2-nitro)propene (V, 15.84 g, 0.0593 mole), lithium aluminum hydride ($LiAlH_4$) (9.28 g, 0.245 mole) and anhydrous tetrahydrofuran (500 mL) was refluxed for 4 h under dry nitrogen with stirring. The mixture was cooled with ice water, then water (25 mL) was added dropwise. The inorganic salts were filtered out and washed three times with absolute ether (100 mL). The combined filtrate was dried over anhydrous $MgSO_4$ and filtered. The filtrate was brought up to a volume of 700 mL with absolute ether, cooled to 10°C, and gaseous HCl bubbled into it, whereupon the HCl salt of I precipitated. The resultant slurry was cooled to 7°C and filtered. The crystals (9.11 g, 56% yield) were washed with absolute ether and twice recrystallized from absolute ethanol-anhydrous ether to produce I hydrochloride [7.38 g, mp 176.5 to 179°C ([*1*], 172°C)]. UV: λ_{max} 232 nm (ϵ 8710), 271 (5060); λ_{min} 219 nm (ϵ 6870), 257 (370). ^{13}C-NMR (D_2O, external DSS): 154.29 (*s*), 149.78(*s*), 144.68(*s*), 118.18(*s*), 117.80(*d*), 101.71(*d*), 67.56(*t*), 58.73(*q*), 58.61(*q*), 50.95 (*d*), 36.82(*t*), 20.04(*q*), and 16.40(*q*) ppm.

The free base I was generated from the HCl salt using K_2CO_3. ^{13}C-NMR: 151.87(*s*), 147.35(*s*), 143.20(*s*), 119.84(*s*), 115.65(*d*), 99.50(*d*), 64.90(*t*), 56.80(*q*), 56.18(*q*), 47.14(*d*), 40.48(*t*), 23.47(*q*), and 14.96(*q*) ppm.

The *N*-acetyl derivative of I was prepared by adding one drop of acetic anhydride to a small amount of I in ethyl acetate before injection into the GLC/MS instrument. The *N*-acetylation was instantaneous and went to completion.

Discussion

Initially, the route of synthesis of the police sample was unknown. At the same time, the nitration of 1-phenyl-1-propenes with nitryl iodide was being examined in our laboratories and it was thought that it would be interesting to research the feasibility of this approach to the synthesis of I and its 2,4,5-trisubstituted isomers. It was quickly observed that the propene X was not very soluble in anhydrous ether, which could not therefore be used as a solvent in the nitration reaction. Also, this particular reaction proved much more difficult to undertake in reasonable yield than expected. Later, when it was known that Shulgin's route [*1*] was being used for the preparation of the police sample, his method was reproduced.

Conclusion

The synthetically prepared 2,5-dimethoxy-4-ethoxyamphetamine hydrochloride gave identical molecular spectra (UV, MS, IR, ^{1}H-NMR, and ^{13}C-NMR) to those obtained from the street sample originally submitted by the police.

Nitration of substituted 1-phenyl-1-propenes with nitryl iodide appears to be difficult to predict at the present time. Further research in this area is continuing to try to answer some of the questions, such as what intermediates and byproducts are formed.

Detailed spectral analyses of these and related compounds are being performed and will be published separately.

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