249–250°. Further recrystallization afforded an analytical sample: mp 251–252.5°; λ_{max}^{Nujol} (μ) 3.00 or 3.05 (NH), 6.03 or 6.09 (C=O, urea), 8.05 and 9.8 (O-phenyl), 12.2 (*p*-C_6H_4), 13.4 and 14.4 (C_6H_5); λ_{max}^{EtOH} 260 mμ (ϵ 6800).

Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.4; H, 5.70; N, 6.60. Found: C, 76.5; H, 6.01; N, 6.44.

Hydrogenolysis at 1 atm with 5% palladium–carbon catalyst in dimethylformamide afforded 88% of **4,4′-dihydroxycarbanilide (II)**, mp 269–275° dec (lit.[5,6] 240° dec, 280° dec, prepared less conveniently by other methods).

The toluene mother liquor from the initial filtration (above) contained crude ***p*-benzyloxyphenyl isocyanate**[7] **(III)**; this could be prepared in 39% yield, mp 51–55° (recrystallized from petroleum ether, bp 30–60°), if only 1 molar equiv of triethylamine was used in the above reaction.

O-(*p*-Nitrophenyl)-N-(*p*-benzyloxyphenyl)urethan (IV).—A solution of 9.9 g (0.044 mole) of *p*-benzyloxyphenyl isocyanate (III) and 6.25 g (0.045 mole) of *p*-nitrophenol in 200 ml of benzene was treated with 10 drops of triethylamine, refluxed for 10 min, and stored overnight at 25°. The mixture was chilled and 13.3 g of a solid, mp 140–158°, was collected on a filter and washed with ether. Recrystallized from $CHCl_3$–petroleum ether (170: 15 ml) afforded 11.7 g (73%) in 2 crops: mp 159–162°; λ_{max}^{EtOH} 238 mμ (ϵ 22,400), 310 (broad, 10,000); infrared data, λ_{max}^{Nujol} (μ) 3.00 or 3.05 (NH), 5.75 or 5.82 (C=O, urethan), *ca.* 6.5 and 7.4 (NO_2), 8.0–8.3 (O-phenyl plus urethan), 12.2 (*p*-C_6H_4), 13.4–13.6 and 14.4 (C_6H_5). The compound was homogeneous on chromatography in butanol–acetic acid–water (5:2:3) on Whatman No.1 paper, R_f 0.92, detected under ultraviolet light.

Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.9; H, 4.43; N, 7.69. Found: C, 65.5; H, 4.28; N, 7.80.

This urethan in the presence of bases was easily dissociated to *p*-nitrophenol and, presumably, the isocyanate III. Upon solution of the urethan in dimethyl sulfoxide, formation of some urea I was noted, presumably *via* the intermediate isocyanate.

O-(*p*-Aminophenyl)-N-(*p*-hydroxyphenyl)urethan (V).—A suspension of 7.63 g (0.021 mole) of the urethan IV and 0.8 g of palladium black (100%) in 75 ml of glacial acetic acid at 45° was hydrogenated at 1 atm for 24 hr. The turbid white supernatant was decanted from the catalyst, the catalyst was washed with acetic acid, and the liquids were concentrated *in vacuo* to form 5.23 g of residual solid. Recrystallization from 200 ml of ethanol afforded 3.6 g (70%), chromatographically homogeneous with R_f 0.84; λ_{max}^{EtOH} 245 mμ (ϵ 29,300), 288 (3540); λ_{max}^{Nujol} (μ) 3.0 (NH), 5.80 (C=O, urethan), 8.3 (broad, O-phenyl plus urethan), 12.1 (*p*-C_6H_4). Bands of weak–medium intensity were also present in the infrared at 13.6 and 14.4 μ, but it could be established (*e.g.*, from paper chromatography) that these were not due to unremoved O-benzyl; in various samples the NH or the C=O bands were resolved into 2 peaks or a broad band appeared at 11 μ. The compound decomposed gradually on heating from 200–260°.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.95; N, 11.5. Found: C, 63.7; H, 4.92; N, 11.4.

1-[*p*-(Benzyloxyl)phenyl]-3-butylurea (VI).—A solution of 0.50 g (1.4 mmoles) of the urethan IV in 25 ml of chloroform was treated with 0.25 ml (2.5 mmoles) of *n*-butylamine. After 5 min the resultant yellow solution was concentrated *in vacuo* to form a solid residue (0.70 g), which was triturated with water and then extracted, in $CHCl_3$ solution, with water to remove yellow color. The solid, recovered from the chloroform layer, was recrystallized from aqueous methanol to form 0.36 g (88% yield); mp 140–141°; λ_{max}^{Nujol} (μ) 3.02 (NH), 6.10 (C=O, urea), 8.0–8.1 (O-phenyl), 12.1 (*p*-C_6H_4), 13.5–13.6 and 14.4 (C_6H_5); λ_{max}^{EtOH} 245 mμ (ϵ 24,100), 293 (1960). The compound was identical with a sample prepared from equimolar quantities of benzyloxyaniline and *n*-butyl isocyanate in benzene–CH_2Cl_2 solution and recrystallized (78% yield), mp 142–143°.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.4; H, 7.43; N, 9.39. Found: C, 72.5; H, 7.53; N, 9.28.

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The Six Trimethoxyphenylisopropylamines (Trimethoxyamphetamines)

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In view of the well-known *vic*-trimethoxy arrangement found in reserpine, colchicine, podophyllotoxin, and mescaline, many other trimethoxy compounds have been prepared and tested, especially in the psychotomimetic area.[1] Of the six possible position isomers of trimethoxyamphetamine, syntheses of the 3,4,5,[2] 2,4,5,[3] and 2,4,6[4] isomers have been published. The synthetic route to a fourth, the 2,3,4 isomer, has been outlined but with no experimental detail.[1d]

The particulars of this latter preparation and of the syntheses of the two remaining isomers (2,3,5 and 2,3,6) are reported here. Table I compiles the properties of these six possible trimethoxyamphetamines, of the corresponding nitropropene precursors, and of the related benzaldehydes along with their characterizing malononitrile and dinitrophenylhydrazone derivatives. The psychotomimetic efficacies of the first three isomers listed have been compared.[1d] The evaluation of the remaining three isomers is not yet complete.

Experimental Section

The three phenylisopropylamines described are all prepared from the corresponding nitropropenes by a modification of the procedure described by Ramirez and Burger,[5] for which a single illustration will suffice. Different routes have been employed to each of the nitropropenes, and each is described: procedure A, the appropriate benzaldehyde is treated with nitroethane, yielding the nitropropene; procedure B, the allyl ether of an appropriate phenol is allowed to undergo the Claisen rearrangement, and a phenylpropene is prepared by methylation of the intermediate allyl phenol, followed by base-catalyzed isomerization; the propene is then nitrated with tetranitromethane to yield the nitropropene; procedure C, the appropriate aromatic ether is lithiated with butyllithium; reaction with propionaldehyde followed by dehydration provides the phenylpropene which is nitrated as above.

All compounds listed in Table I carried acceptable microanalyses. Melting points were determined on a Kofler Heizbank and are corrected.

Procedure A. 1-(2,3,4-Trimethoxyphenyl)-2-nitropropene.—To a solution of 2,3,4-trimethoxybenzaldehyde (12.4 g, prepared as described by Papadakis and Boand[6]) in glacial acetic acid (45 g), there was added ammonium acetate (4.1 g) and nitroethane (7.0 ml). The mixture was held at reflux for 1.5 hr and cooled, and water was added to induce crystallization. The sticky product was removed by filtration, washed with 50% acetic acid, and recrystallized from boiling methanol. The yield was 6.5 g of fine yellow needles, The two parallel syntheses were similar, employing 3,4,5-trimethoxybenzaldehyde obtained from Aldrich Chemical Co. and 2,4,6-trimethoxybenzaldehyde prepared as described by Benington, *et al.*[4]

2,3,4-Trimethoxyamphetamine.—The above nitropropene was reduced by the Soxhlet technique described by Ramirez and Burger.[5] Rather than using the picrate as a means of isolation, the crude acidic reaction mixture was treated with potassium sodium tartrate (10 g/g of nitropropene employed) and 25% NaOH solution was then added to raise the pH above 9. The mixture was then extracted with CH_2Cl_2. The oil remaining upon evaporation was dissolved in anhydrous ether, and this

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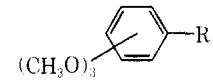
TABLE 1



Orientation	R = CHO: Mp, °C	R = CHO: 2,4-DNPH[a] mp, °C	R = CHO: MN[b] mp, °C	R = CH=C(CH3)NO2: Mp, °C	R = CH=C(CH3)NO2: Yield,[c] %	R = CH2CH(CH3)NH2·HCl: Mp, °C	R = CH2CH(CH3)NH2·HCl: Yield,[d] %
3, 4, 5	75	246[e]	143[f]	94[g]	50 (A)	209[g]	62
2, 4, 5	113	261	168	102[h]	83[i] (B)	181[j]	92
2, 3, 4	30	193[k]	102	57	41 (A)	149[l]	77
2, 3, 5	64	225	102	88	13[m] (B)	119	68
2, 3, 6	20[n]	203	108	74	38[m] (C)	125	90
2, 4, 6	116	262	175	148	20[o] (A)	214	74[p]

[a] 2,4-Dinitrophenylhydrazone derivative; see Experimental Section. [b] Ylidinemalononitrile derivative; see Experimental Section. [c] Procedure for synthesis of nitrostyrene indicated parenthetically; see Experimental Section. [d] All trimethoxyamphetamines reported here are in the racemic form. [e] M. Milletti [*Ann. Chem.*, **45**, 1211 (1955)] reported mp 242–246° dec. [f] At this temperature there is polymorphic behavior, resolidification occurring with refusion at 149°. [g] See ref 1c. [h] Lit.[3] mp 101°. [i] This yield was from the pure *trans*-propenyl isomer. A similar yield resulted (87%) if the *cis* isomer was employed. [j] Lit.[3] mp 187°. [k] Lit.[6] mp 191°. [l] See ref 1d. [m] The crude nitropropene was contaminated with the corresponding benzaldehyde; see Experimental Section. [n] The single report of this aldehyde [J. R. Merchant, R. M. Naik, and A. J. Mountwalla, *J. Chem. Soc.*, 4142 (1957)] describes it as an oil, with a dinitrophenylhydrazone mp 221°. [o] Lit.[4] mp 148°, yield 88%. [p] Lit.[4] mp 215°, yield 78%.

solution was saturated with dry HCl. The crude hydrochloride thus obtained may be recrystallized from boiling isopropyl alcohol. The cogent physical data are included in Table I.

Procedure B. 1-(2,3,5-Trimethoxyphenyl)-2-nitropropene.—A solution of *trans*-2,3,5-trimethoxyphenylpropene (7.2 g, mp 45°, prepared as described[7]) in a mixture of pyridine (3.3 g) and dry acetone (41 g) was cooled to 0° with vigorous stirring. Tetranitromethane (6.9 g) was added over a period of about 1 min and stirring was continued for another 2 min, at which time the reaction was quenched by the addition of aqueous KOH (2.2 g in 40 ml). An additional quantity of water was added, and the product was removed by extraction with methylene chloride and distilled *in vacuo*. The fraction with bp 160–170° (2 mm) (3.0 g) crystallized spontaneously, and yielded, after recrystallization from methanol, fine yellow crystals (1.15 g, mp 88°). The earlier cuts yielded the corresponding benzaldehyde which was recrystallized from methanol.

This nitropropene was reduced with $LiAlH_4$ as described above.

Procedure C. Ethyl-2,3,6-trimethoxyphenylcarbinol.—A solution of 1,2,4-trimethoxybenzene (100 g) in 1 l. of anhydrous hexane was cooled to about 15° and treated with a 15% solution of butyllithium in hexane (400 ml). There was an immediate white precipitate. After a 2-hr period of stirring at room temperature, there was added, in hexane, a solution of freshly distilled propionaldehyde (bp 49°, 40 g) in hexane. Heat was evolved and the precipitate gradually was dissolved as the reaction mixture was stirred at room temperature. After standing overnight, the yellow solution was flooded with water and acidified. The hexane layer was removed and the remaining aqueous phase was extracted first with hexane, then with ether. From the hexane extracts there was obtained, after distillation, pure carbinol (60 g, $n^{26}D$ 1.5192).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.69; H, 8.02. Found: C, 63.91; H, 8.13.

From the ether extracts was obtained 26 g of additional product containing a small amount of the starting ether, for a total yield of over 60%. The location of the aliphatic chain was established with certainty both by an unambiguous *ortho* splitting of the two aromatic protons (by nmr) and by the successful carbonation of an identically prepared lithio derivative of 1,2,4-trimethoxybenzene, to the previously described 2,3,6-trimethoxybenzoic acid, mp 150°.[8]

1-Bromo-1-(2,3,6-trimethoxyphenyl)propane.—The above carbinol (60 g) was cooled externally with ice, and PBr_3 (80 g) was added at a rate that prevented the temperature of the stirred reaction mixture from exceeding 60°. After about 2 min, the reaction was quenched with chipped ice and, after the addition of more water, extracted with ether. The product resulting from the removal of the solvent (60 g, $n^{26}D$ 1.5449) was converted to the conjugated olefin without further purification.

1-(2,3,6-Trimethoxyphenyl)-1-propene.—The above halide was dissolved in an equal weight of ethanol (60 g) and treated with flaked KOH (120 g). The ensuing exothermic reaction was not cooled but the mixture was allowed to stir overnight. After treatment with water and extraction with CH_2Cl_2, the isolated product displayed by glpc analysis (on a 5-ft 20 M column at 180°) no presence of starting bromide. The desired product was contaminated with a new material, however, which proved to be the ethoxy analog resulting by replacement. Brief treatment (2 min) with 50% H_2SO_4 (w/w) at 80° achieved satisfactory conversion of this ether to the expected olefin without noticeable demethylation. Distillation yielded 7.0 g (about 13% from the carbinol) of a clear oil identical with the material reported earlier.[7]

1-(2,3,6-Trimethoxyphenyl)-2-nitropropene.—The above 2,3,6-trimethoxyphenylpropene was nitrated as described for the 2,4,5 isomer. The crude nitro product, as with 2,3,5-trimethoxyphenylnitropropene, was admixed with the benzaldehyde expected from oxidative cleavage of the chain. Distillation of the 5.3-g product yielded substantially two fractions: the first distilled at 150–170° (2 mm) and was predominantly 2,3,6-trimethoxybenzaldehyde; the second distilled at 170–200° (2 mm) and spontaneously crystallized to yield, after recrystallization from methanol, the title compound (see the table for properties). From the earlier fraction, small but pure samples of the aromatic aldehyde could be obtained from a preparative glpc separation (SE-30, 5 ft, 180°). The microderivative techniques employed are shown below. Reduction of this nitropropene to the amine was achieved following the directions above.

Microscale Synthesis of 2,4-Dinitrophenylhydrazones.—A solution was prepared by dissolving 2,4-dinitrophenylhydrazine (0.2 g) in H_2SO_4 (1.85 g) and diluting this slowly with first water (1.5 g) and then 95% ethanol (4.0 g). A sample of the aldehyde (2 mg is adequate) was brought to the fold of a Petri dish (in which it may be caught directly from the preparative glpc column) with a drop or two of ethanol, which was removed by brief heating on a steam bath. With a Hamilton microsyringe the above hydrazine solution was added directly to the test sample (30 μl/mg), and the resulting hydrazone was pressed on a porous plate. Acetic acid serves as a general recrystallization solvent.

Microscale Synthesis of Malononitrile Derivatives.—A fresh solution is prepared, containing 0.75 g of malononitrile and 0.075 g of triethylamine in 10 ml of ethanol. This solution was added as above (10 μl/mg) to the test aldehyde which was first melted by heat. Yellow crystals of the ylidine derivative appeared within 1 min, often immediately. Recrystallization was best performed from toluene.

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