The Six Trimethoxyphenylisopropylamines (Trimethoxyamphetamine)

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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 psychomimetic area. 1 Of the six possible position isomers of trimethoxyamphetamine, syntheses of the 3,5,4', 2,4,5', and 2,4,6' isomers have been published. The synthetic route to a fourth, the 2,5,4 isomer, has been outlined with no experimental detail. 12

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 trimethoxy-amphetamines, of the corresponding nitropropene precursors, and of the related benzaldehydes along with their characteristic malonitrile and dinitrophenylhydrazine derivatives. The psychomimetic efficacies of the first three isomers listed have been compared. 14 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, 2 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 propionylaldehyde followed by dehydration provides the phenylpropene which is nitrated as above.

All compounds listed in Table I entered 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 Bond) 3 in glacial acetic acid (45 g), there was added ammonium acetate (4.1 g) and nitroethane (7.0 g). 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 2,4,6-trimethoxybenzaldehyde obtained from Aldrich Chemical Co. and 2,4,6-trimethoxybenzylalcohol prepared as described by Benington, et al. 14

2,3,4-Trimethoxyamphetamine.—The above nitropropene was reduced by the Soxhlet technique described by Ramirez and Burger. 2 Rather than using the picrate as a means of isolation, the crude acidic reaction mixture was treated with potassium sodium tartrate (10 g/kg of nitropropene employed) and 25% NaOH solution was then added to raise the pH above 9. The mixture was then extracted with CH2Cl2. The oil remaining upon evaporation was dissolved in anhydrous ether, and this

(2) F. Rey, Quart. J. Pharm. Pharmacol., 30, 129 (1947).

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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-(2,3,5,6-Tetramethoxyphenyl)-2-nitropropane.—A solution of trans-2,3,5,6-tetramethoxyphenylpropene (7.2 g, mp 45°, prepared as described) 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, which was washed with water and dried (anhydrous sodium sulfate) to remove the excess reagent. The crude hydrochloride which was precipitated from methanol (1.15 g, 57% yield) was recrystallized from boiling isopropyl alcohol, fine yellow crystals (1.15 g, mp 148°) no presence of starting ether, for a total yield of 63.9%.

The earlier fraction, bismarck brown in color, was collected. Heating the crude hydrochloride mp 148° no presence of starting ether, for a total yield of 63.9%.

The earlier fraction, bismarck brown in color, was collected. Heating the crude hydrochloride mp 148° was brought to the fold of a Petri dish (it) and spontaneously crystallized to yield, after recrystallization, fine yellow crystals (1.15 g, mp 148°) no presence of starting ether, for a total yield of 63.9%.

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This nitropropane was reduced with LiAlH₄ as described above.

Procedure C. Ethyl-2,3,5,6-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 dissolved as the reaction mixture was stirred at room temperature. After standing overnight, the yellow solution was flocculated 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 (80 g, 64%; lit. 51%.

Anal. Caled for C₃₇H₄₆O₂: C, 63.69; H, 8.02. Found: C, 63.91; H, 8.13.

From the ether extracts there 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°.

1-Bromo-1-(2,3,5-trimethoxy) propane.—The above carbinol (60 g) was cooled externally with ice, and PBr₃ (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 chilled ice and, after the addition of more water, extracted with ether. The product resulting from the removal of the solvent (60 g, 66%; lit. 51%) was isolated, washed with water and dried (anhydrous sodium sulfate) to remove the excess reagent. Distillation yielded 7.0 g (about 13% from the carbinol) of a clear oil identical with the material reported earlier.

1-(2,3,6-Tetramethoxyphenyl)-2-nitropropane.—The above 2,3,6-trimethoxyphenylpropane was nitrated as described for the 2,4,5 isomer. The crude nitro product, as with 2,3,5-trimethoxyphenyl-2-nitropropane, was obtained by heat. Yellow crystals of the ylidine derivative appeared (2 mg is adequate) were brought to the fold of a Petri dish (it) and spontaneously crystallized to yield, after recrystallization from methanol, the title compound (see the table for properties).

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Microscale Synthesis of 2,4-Dinitrophenylhydrazones.—A solution was prepared by dissolving 2,4-dinitrophenylhydrazine (0.2 g) in H₂SO₄ (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 preparing gloop 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. Acetyl 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.