idea and showed that the release of histamine from guinea pig lung was prevented by chymotrypsin substrates and inhibitors but not by trypsin, carboxypeptidase, or leucine amino peptidase substrates or by soy bean trypsin inhibitor. They concluded that the activation of a chymotrypsin-like enzyme was a necessary condition for anaphylactic release of histamine. Becker and Austen[2c,16] found that a similar enzyme was required for release of histamine from rat mast cells.

The dibenzodiazepine compounds were found to show varying degrees of inhibition of chymotrypsin activity, and there was a definite trend in the correlation between chymotrypsin inhibition and antianaphylactic activity. Of the compounds protecting at lease 2 species against anaphylaxis in doses of 30 mg/kg or less (1–X), all those tested inhibited chymotrypsin activity, *i.e.*, 9/9 (X was not available). Of the remaining compounds which were tested 7/16 inhibited. It is unfortunate that so many of the compounds in the second group could not be tested either because they were not available or they formed precipitates in the buffer.

The dibenzodiazepines caused little change in the behavior of mice[17] in the doses tested for antianaphylactic activity. A few showed some CNS effects at higher doses, *e.g.*, I at 30, II at 30, and VII at 10 mg/kg caused CNS stimulation; IV at 100, VIII at 30, XVI at 100, and XXIV at 100 mg/kg caused clonic convulsions; V at 100, XIX at 10, XXI at 30, and XXII at 100 mg/kg caused depression.

The most active compounds (I and II) were superior to tripelennamine in protecting mice against fatal anaphylaxis and were comparable to cyproheptadine in this species. Compound I was comparable to cyproheptadine in protecting rats against anaphylaxis and was superior to this compound in guinea pigs. In guinea pigs exposed to a histamine aerosol, I was active in doses as low as 1 mg/kg ip; tripelennamine was active in slightly lower doses.

(16) E. L. Becker and K. F. Austen, *J. Exp. Med.*, **124**, 379 (1966).

(17) W. Veldkamp, personal communication (1967).

Analogs of Amphetamine. 4. Synthesis of Metabolites of 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM)[1,2]

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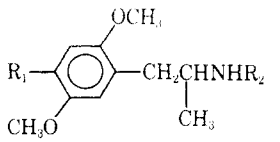
Received July 29, 1970

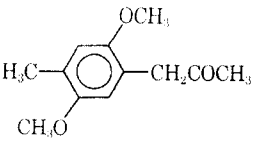
Three amphetamine derivatives and one substituted 1-phenyl-2-propanone, which are possible metabolites of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM or STP, **1**), were synthesized. A formyl group was introduced to the ring C_4 of 1-(2,5-dimethoxyphenyl)-2-aminopropane (**6**) while the amino function was protected by a phthaloyl group. The resulting compound **8** was oxidized by Ag_2O–NaOH to the acid **3**. Reduction of **8** by $Al(O\text{-}i\text{-}Pr)_3$ followed by removal of the phthaloyl group gave the hydroxymethyl compound **2**. 1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone (**5**) was prepared by the Fe–HCl reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene, and the *N*-acetyl derivative **4** was obtained by acetylation of **1**.

During the course of investigation on structures and actions of some hallucinogens the metabolic study of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM or STP, **1**) was undertaken. This compound has multifunctional groups and is structurally related to amphetamine and to a lesser extent to mescaline, whose metabolic fates in a number of species have been well documented. In particular, the 4-CH_3 group of **1** is vulnerable to biotransformation. Gillette[3] reported the oxidation of the CH_3 group of *p*-nitrotoluene by liver microsomal system to a CH_2OH group which was oxidized further by dehydrogenases in the soluble fraction to a COOH group. In a similar fashion 4-hydroxymethylacetanilide was formed from 4-methylacetanilide.[4] By analogy, the conversion of the 4-CH_3 group of **1** in animals or human to CH_2OH was expected to give 1-(2,5-dimethoxy-4-hydroxymethylphenyl)-2-aminopropane (**2**). Further oxidation of **2** to 2,5-dimethoxy-4-(2-aminopropyl)benzoic acid (**3**) occurred as predicted. Other metabolites of **1** might be the *N*-acetyl DOM (**4**) and/or 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone (**5**) resulting from the oxidative deamination of **1**.

Chemistry.—Compounds **2** and **3** were prepared from 1-(2,5-dimethoxyphenyl)-2-aminopropane (**6**).[2a] A previous attempt to prepare **3** from the $KMnO_4$ oxidation of *N*-acetyl DOM (**4**) was unsuccessful; the isolated acidic product showed no NH absorption in its ir spectrum and was, therefore, not characterized further. The amine function of **6** was protected by a phthaloyl



1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = CH_2OH$; $R_2 = H$
3, $R_1 = COOH$; $R_2 = H$
4, $R_1 = CH_3$; $R_2 = Ac$
6, $R_1 = H$; $R_2 = H$
7, $R_1 = H$; R_2H = phthaloyl
8, $R_1 = CHO$; R_2H = phthaloyl
9, $R_1 = CH_2OH$; R_2H = phthaloyl



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(1) This work was supported in part by Grant MH-12959, U. S. Public Health Service, Bethesda, Md., and by the Britton Fund.

(2) Previous papers in the series: (a) 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); (b) B. T. Ho, L. W. Tansey, R. L. Balster, R. An, W. M. McIsaac, and R. T. Harris, *ibid.*, **13**, 134 (1970); (c) B. T. Ho, L. W. Tansey, and W. M. McIsaac, *ibid.*, **13**, 1022 (1970).

(3) J. R. Gillette, *J. Biol. Chem.*, **234**, 139 (1959).

(4) J. W. Daly, G. Guroff, S. Udenfriend, and B. Witkop, *Biochem. Pharmacol.*, **17**, 31 (1968).

group. When the phthaloyl compound **7** was heated with *N*-methylformanilide and $POCl_3$, a formyl group was introduced in the 4 position yielding **8**. Oxidation of **8** with Ag_2O and NaOH converted the 4-formyl into a 4-carboxyl group. The product **3** isolated from the reaction was free of the phthaloyl group which was apparently hydrolyzed in the presence of NaOH. Characterization of **3** was achieved by its benzoyl derivative.

Reduction of **8** with $Al(O\text{-}i\text{-}Pr)_3$ gave the 4-hydroxymethyl compound **9**; the phthaloyl group was then removed with NH_2NH_2. The position of the CH_2OH group in **2** was proved by both nmr and ir analyses. The presence of two singlets (τ 3.05 and 3.26) in its nmr spectrum was attributed to the C_6 and C_3 protons, and in its ir spectrum two absorption peaks at 5.58 and 5.80 μ were both due to aromatic 1,2,4,5 substitution. Substitution of the formyl group for C_6-H of **6** was excluded because of the absence of 2 doublets in the nmr which would be due to the C_3 and C_4 protons. Observation of the ir spectrum of **2** also excluded the possible formation of the 3-formyl compound in the preceding step.

The preparation of **5** was achieved by Fe–HCl reduction of the 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene. Treatment of **1** with Ac_2O yielded *N*-acetyl DOM (**4**).

Biological Results.—Our preliminary studies revealed that the major metabolic fate for DOM (**1**) in rats (5 mg/kg, ip) was the oxidation of the 4-Me group; in 24-hr urine samples the 4-hydroxymethyl compound **2**, free and conjugated, accounted for 50%. The 4-carboxy compound **3** amounted to 28% of the urinary metabolites. Unchanged DOM (**1**) was found to be 8%. Details on the metabolism will be reported in the following paper.[5]

Experimental Section[6]

***N*-Phthaloyl-1-(2,5-dimethoxyphenyl)-2-aminopropane (7).**—A mixture of 16.0 g (82 mmoles) of 2,5-dimethoxyamphetamine (**6**),[2a] 13.2 g (89 mmoles) of phthalic anhydride, 9.1 g (90 mmoles) of Et_3N, and 100 ml of PhMe was refluxed for 4 hr, with continuous removal of H_2O into a Dean–Stark tube. After cooling, the resulting soln was washed successively with 2 *N* NaOH (two 25-ml portions), H_2O (two 50-ml portions), 10% HCl (two 25-ml portions), and H_2O (two 25-ml portions). The washed PhMe soln was dried (Na_2SO_4) and evapd *in vacuo* leaving an oil which slowly solidified to yield 21.4 g (80%) of white material, mp 103–105°. Recrystn from EtOH gave an analytical sample, mp 105–106°. *Anal.* ($C_{19}H_{19}NO_4$) C, H, N.

***N*-Phthaloyl-1-(2,5-dimethoxy-4-formylphenyl)-2-aminopropane (8).**—Compound **7** (18.0 g, 55 mmoles) was added to a mixture of *N*-methylformanilide and $POCl_3$, prepared by mixing 100 mmoles of each substance and allowing to stand for 1 hr. The mixture was heated on a steam bath for 4 hr (during which time evoln of HCl was very prominent), and then poured over 1 l. of crushed ice. The product which separated as a very viscous oil was decanted and dissolved in hot EtOH. Cooling of the EtOH soln gave 12.0 g (62%) of solid, mp 130–132°. Two recrystns from EtOH gave 6.4 g (33%), mp 141–143°. *Anal.* ($C_{20}H_{19}NO_5$) C, H, N.

2,5-Dimethoxy-4-(2-aminopropyl)benzoic Acid (3).—A mixture of 2.9 g (8 mmoles) of **8**, 3.7 g of Ag_2O, and 1.6 g (40 mmoles) of NaOH in 50 ml of H_2O was stirred overnight at room temp and then filtered. The filtrate was washed with $CHCl_3$ (three 25-ml portions), and, upon acidification of the aq soln with 10% HCl, an oil formed which was extd into 25 ml of $CHCl_3$. A white solid pptd from the $CHCl_3$ within a few min; yield, 700 mg, mp 172–174°. When the filtrate was stirred with 10% HCl for 48 hr, an addl 800 mg (mp 168–171°) of tan solid was obtained. Recrystn of these two fractions from H_2O gave in each case 350 mg of solid, mp 176–177°; total yield 36%.

2,5-Dimethoxy-4-(2-benzamidopropyl)benzoic Acid.—A mixture of 350 mg (1.5 mmoles) of **3**, 412 mg (3 mmoles) of BzCl, and 236 mg (6 mmoles) of NaOH was stirred with 15 ml of H_2O for 4 hr. After acidification with 2 *N* HCl the ppt which formed was collected on a filter and washed with 400 ml of pet ether to remove any BzOH; yield, 300 mg (58%), mp 173–178°. Recrystn from EtOH gave 200 mg, mp 182–182.5°. A second recrystn from the same solvent gave 80 mg (16%), mp 185–186°. *Anal.* ($C_{19}H_{21}NO_5$) C, H, N.

***N*-Phthaloyl-1-(2,5-dimethoxy-4-hydroxymethylphenyl)-2-aminopropane (9).**—The reduction of 3.5 g (10 mmoles) of **8** with 0.33 g (1.6 mmoles) of $Al(O\text{-}i\text{-}Pr)_3$ in 100 ml of *i*-PrOH was achieved by the slow distn of the *i*-PrOH and produced Me_2CO over a period of 4 hr. The reaction was followed by analyzing for Me_2CO in the distillate with 2,4-dinitrophenylhydrazine. The remaining soln was concd to about 10 ml, 25 ml of 10% HCl was added, and the product was extd with $CHCl_3$ (two 25-ml portions). The $CHCl_3$ exts were combined, dried (Na_2SO_4), and evapd *in vacuo* to yield a viscous oil which solidified upon trituration with Et_2O and drying *in vacuo;* yield, 2.8 g (79%), mp 80–84°. Recrystn from C_6H_6–C_6H_{14} gave 2.1 g (59%), mp 83–84°. *Anal.* ($C_{20}H_{21}NO_5$) C, H, N.

1-(2,5-Dimethoxy-4-hydroxymethylphenyl)-2-aminopropane (2).—A mixture of 4.8 g (13.5 mmoles) of **9**, 4 ml of anhyd NH_2NH_2, and 50 ml of abs EtOH was refluxed for 90 min, during which period a very flocculent ppt formed. The solid was removed by filtration and the EtOH was evapd *in vacuo*. The residue was dissolved in 10 ml of $CHCl_3$. After washing with H_2O (three 25-ml portions) and drying (Na_2SO_4), the $CHCl_3$ was evapd, and the solid was dried *in vacuo;* yield, 2.0 g (66%), mp 71–74°. Recrystn from 50 ml of C_7H_{16} gave 1.4 g, mp 83–88°. A second recrystn gave 1.2 g (39%), mp 92–95°: ir (CCl_4) 5.68 and 5.76 μ (aromatic 1,2,4,5 substn); nmr ($CDCl_3$) τ 3.05, 3.26 (singlet, C_6-H or C_3-H). *Anal.* ($C_{12}H_{19}NO_3$) C, H, N.

1-(2,5-Dimethoxy-4-methylphenyl)-2-acetamidopropane (4).—A soln of 4.5 g (22 mmoles) of **1** in 100 ml of 10% HCl was treated with 6 *N* NaOH until a ppt just began to form. The amine was brought back into soln by the addition of HCl. To the soln were added 20 ml of Ac_2O, 5 g of NaOAc in 25 ml of H_2O, and 100 ml of C_6H_6. The mixture was stirred overnight at room temp. The C_6H_6 phase was sepd, and the aq phase extd with C_6H_6 (two 50-ml portions). The combined C_6H_6 solns were washed successively with satd $NaHCO_3$ (three 50-ml portions) and H_2O (two 50-ml portions), dried (Na_2SO_4), and evapd *in vacuo*, leaving 3.0 g (55%) of solid, mp 139–140°. Recrystn from C_6H_{14}–C_6H_6 gave 2.5 g (46%), mp 144–145°. *Anal.* ($C_{14}H_{20}NO_3$) C, H, N.

1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone (5).—A mixture of 9.5 g (40 mmoles) of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene[2a] in 50 ml of PhMe, 7.8 g (140 mmoles) of Fe filings, 4.0 g of $FeCl_3$, and 50 ml of H_2O was rapidly stirred and heated to reflux (approx 90°). Concd HCl (20 ml) was added, and the heating was contd for 7 hr. The cooled mixture was filtered; the two phases of the filtrate were sepd. The aq phase was extd with PhMe (two 100-ml portions), and the combined PhMe exts were washed with a satd soln of $NaHCO_3$ (two 100-ml portions) and then H_2O (100 ml). After drying (Na_2SO_4) the PhMe was evapd *in vacuo* leaving a liquid. When this product was distd, 4.1 g (49%) of liquid, bp 126–129° (0.4 mm) was obtained. After a second distn the liquid, bp 105–109° (0.05 mm), solidified to yield 2.9 g (35%), mp 43–46°. Recrystn of the solid from C_6H_{14} gave 2.6 g (31%), mp 49–51°. *Anal.* ($C_{12}H_{16}O_3$) C, H.

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(6) Melting points were taken on a Mel-Temp apparatus and are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Ir spectra of all the compounds were compatible with the assigned structures.