

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<sup>20,16</sup> 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 least 2 species against anaphylaxis in doses of 30 mg/kg or less (I-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

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

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<sup>17</sup> 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 tripeleminamine 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; tripeleminamine was active in slightly lower doses.

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

## Analogs of Amphetamine. 4. Synthesis of Metabolites of 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM)<sup>1,2</sup>

BENG T. HO\* AND L. WAYNE TANSEY

Texas Research Institute of Mental Sciences, Houston, Texas 77025

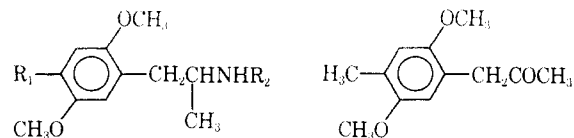
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Three amphetamine derivatives and one substituted 1-phenyl-2-propanone, which are possible metabolites of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM or STP, **1**), were synthesized. A formyl group was introduced to the ring C<sub>4</sub> 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<sub>2</sub>O-NaOH to the acid **3**. Reduction of **8** by Al(*i*-Pr)<sub>3</sub> 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<sub>3</sub> group of **1** is vulnerable to biotransformation. Gillette<sup>3</sup> reported the oxidation of the CH<sub>3</sub> group of *p*-nitrotoluene by liver microsomal system to a CH<sub>2</sub>OH 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.<sup>4</sup> By analogy, the conversion of the 4-CH<sub>3</sub> group of **1** in animals or human to CH<sub>2</sub>OH was expected to give 1-(2,5-dimethoxy-4-hydroxymethylphenyl)-2-aminopropane (**2**). Further oxidation of **2** to 2,5-dime-

thoxy-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**).<sup>2a</sup> A previous attempt to prepare **3** from the KMnO<sub>4</sub> oxidation of *N*-acetyl DOM (**4**) was unsuccessful; the isolated



- 1, R<sub>1</sub> = CH<sub>3</sub>; R<sub>2</sub> = H
- 2, R<sub>1</sub> = CH<sub>2</sub>OH; R<sub>2</sub> = H
- 3, R<sub>1</sub> = COOH; R<sub>2</sub> = H
- 4, R<sub>1</sub> = CH<sub>3</sub>; R<sub>2</sub> = Ac
- 6, R<sub>1</sub> = H; R<sub>2</sub> = H
- 7, R<sub>1</sub> = H; R<sub>2</sub>H = phthaloyl
- 8, R<sub>1</sub> = CHO; R<sub>2</sub>H = phthaloyl
- 9, R<sub>1</sub> = CH<sub>2</sub>OH; R<sub>2</sub>H = phthaloyl

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

\* To whom correspondence should be addressed.

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(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  $\text{POCl}_3$ , a formyl group was introduced in the 4 position yielding **8**. Oxidation of **8** with  $\text{Ag}_2\text{O}$  and  $\text{NaOH}$  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  $\text{NaOH}$ . Characterization of **3** was achieved by its benzoyl derivative.

Reduction of **8** with  $\text{Al}(\text{O}-i\text{-Pr})_3$  gave the 4-hydroxymethyl compound **9**; the phthaloyl group was then removed with  $\text{NH}_2\text{NH}_2$ . The position of the  $\text{CH}_2\text{OH}$  group in **2** was proved by both nmr and ir analyses. The presence of two singlets ( $\tau$  3.05 and 3.26) in its nmr spectrum was attributed to the  $\text{C}_6$  and  $\text{C}_3$  protons, and in its ir spectrum two absorption peaks at 5.58 and 5.80  $\mu$  were both due to aromatic 1,2,4,5 substitution. Substitution of the formyl group for  $\text{C}_6\text{-H}$  of **6** was excluded because of the absence of 2 doublets in the nmr which would be due to the  $\text{C}_3$  and  $\text{C}_4$  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  $\text{Fe-HCl}$  reduction of the 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene. Treatment of **1** with  $\text{Ac}_2\text{O}$  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.<sup>5</sup>

### Experimental Section<sup>6</sup>

***N*-Phthaloyl-1-(2,5-dimethoxyphenyl)-2-aminopropane (7).**—A mixture of 16.0 g (82 mmoles) of 2,5-dimethoxyamphetamine (**6**),<sup>2a</sup> 13.2 g (89 mmoles) of phthalic anhydride, 9.1 g (90 mmoles) of  $\text{Et}_3\text{N}$ , and 100 ml of PhMe was refluxed for 4 hr, with continuous removal of  $\text{H}_2\text{O}$  into a Dean-Stark tube. After cooling, the resulting soln was washed successively with 2 *N*  $\text{NaOH}$  (two 25-ml portions),  $\text{H}_2\text{O}$  (two 50-ml portions), 10%  $\text{HCl}$  (two 25-ml portions), and  $\text{H}_2\text{O}$  (two 25-ml portions). The washed PhMe soln was dried ( $\text{Na}_2\text{SO}_4$ ) 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.* ( $\text{C}_{19}\text{H}_{19}\text{NO}_4$ ) 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  $\text{POCl}_3$ , 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 evolv of  $\text{HCl}$  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.* ( $\text{C}_{20}\text{H}_{19}\text{NO}_5$ ) 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  $\text{Ag}_2\text{O}$ , and 1.6 g (40 mmoles) of  $\text{NaOH}$  in 50 ml of  $\text{H}_2\text{O}$  was stirred overnight at room temp and then filtered. The filtrate was washed with  $\text{CHCl}_3$  (three 25-ml portions), and, upon acidification of the aq soln with 10%  $\text{HCl}$ , an oil formed which was extd into 25 ml of  $\text{CHCl}_3$ . A white solid pptd from the  $\text{CHCl}_3$  within a few min; yield, 700 mg, mp 172–174°. When the filtrate was stirred with 10%  $\text{HCl}$  for 48 hr, an addl 800 mg (mp 168–171°) of tan solid was obtained. Recrystn of these two fractions from  $\text{H}_2\text{O}$  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  $\text{BzCl}$ , and 236 mg (6 mmoles) of  $\text{NaOH}$  was stirred with 15 ml of  $\text{H}_2\text{O}$  for 4 hr. After acidification with 2 *N*  $\text{HCl}$  the ppt which formed was collected on a filter and washed with 400 ml of pet ether to remove any  $\text{BzOH}$ ; 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.* ( $\text{C}_{19}\text{H}_{21}\text{NO}_5$ ) 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  $\text{Al}(\text{O}-i\text{-Pr})_3$  in 100 ml of *i*-PrOH was achieved by the slow distn of the *i*-PrOH and produced  $\text{Me}_2\text{CO}$  over a period of 4 hr. The reaction was followed by analyzing for  $\text{Me}_2\text{CO}$  in the distillate with 2,4-dinitrophenylhydrazine. The remaining soln was coned to about 10 ml, 25 ml of 10%  $\text{HCl}$  was added, and the product was extd with  $\text{CHCl}_3$  (two 25-ml portions). The  $\text{CHCl}_3$  exts were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and evapd *in vacuo* to yield a viscous oil which solidified upon trituration with  $\text{Et}_2\text{O}$  and drying *in vacuo*; yield, 2.8 g (79%), mp 80–84°. Recrystn from  $\text{C}_6\text{H}_6\text{-C}_6\text{H}_{14}$  gave 2.1 g (59%), mp 83–84°. *Anal.* ( $\text{C}_{20}\text{H}_{21}\text{NO}_5$ ) 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  $\text{NH}_2\text{-NH}_2$ , 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  $\text{CHCl}_3$ . After washing with  $\text{H}_2\text{O}$  (three 25-ml portions) and drying ( $\text{Na}_2\text{SO}_4$ ), the  $\text{CHCl}_3$  was evapd, and the solid was dried *in vacuo*; yield, 2.0 g (66%), mp 71–74°. Recrystn from 50 ml of  $\text{C}_7\text{H}_{16}$  gave 1.4 g, mp 83–88°. A second recrystn gave 1.2 g (39%), mp 92–95°; ir ( $\text{CCl}_4$ ) 5.68 and 5.76  $\mu$  (aromatic 1,2,4,5 substn); nmr ( $\text{CDCl}_3$ )  $\tau$  3.05, 3.26 (singlet,  $\text{C}_6\text{-H}$  or  $\text{C}_3\text{-H}$ ). *Anal.* ( $\text{C}_{12}\text{H}_{15}\text{NO}_3$ ) 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%  $\text{HCl}$  was treated with 6 *N*  $\text{NaOH}$  until a ppt just began to form. The amine was brought back into soln by the addition of  $\text{HCl}$ . To the soln were added 20 ml of  $\text{Ac}_2\text{O}$ , 5 g of  $\text{NaOAc}$  in 25 ml of  $\text{H}_2\text{O}$ , and 100 ml of  $\text{C}_6\text{H}_6$ . The mixture was stirred overnight at room temp. The  $\text{C}_6\text{H}_6$  phase was sepd, and the aq phase extd with  $\text{C}_6\text{H}_6$  (two 50-ml portions). The combined  $\text{C}_6\text{H}_6$  solns were washed successively with satd  $\text{NaHCO}_3$  (three 50-ml portions) and  $\text{H}_2\text{O}$  (two 50-ml portions), dried ( $\text{Na}_2\text{SO}_4$ ), and evapd *in vacuo*, leaving 3.0 g (55%) of solid, mp 139–140°. Recrystn from  $\text{C}_6\text{H}_{14}\text{-C}_6\text{H}_6$  gave 2.5 g (46%), mp 144–145°. *Anal.* ( $\text{C}_{14}\text{H}_{20}\text{NO}_3$ ) 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<sup>2a</sup> in 50 ml of PhMe, 7.8 g (140 mmoles) of  $\text{Fe}$  filings, 4.0 g of  $\text{FeCl}_3$ , and 50 ml of  $\text{H}_2\text{O}$  was rapidly stirred and heated to reflux (approx 90°). Concd  $\text{HCl}$  (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  $\text{NaHCO}_3$  (two 100-ml portions) and then  $\text{H}_2\text{O}$  (100 ml). After drying ( $\text{Na}_2\text{SO}_4$ ) 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  $\text{C}_6\text{H}_{14}$  gave 2.6 g (31%), mp 49–51°. *Anal.* ( $\text{C}_{12}\text{H}_{16}\text{O}_3$ ) C, H.

(5) B. T. Ho, V. Estevez, L. W. Tansey, L. F. Englert, P. J. Creaven, and W. M. McIsaac, *J. Med. Chem.*, **14**, 158 (1971).

(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  $\pm 0.4\%$  of the theoretical values. Ir spectra of all the compounds were compatible with the assigned structures.