

was removed and recrystallized from a mixture of benzene and methanol, wt. 4.32 g., m.p. 176–177° dec.

*Anal.* Calcd. for  $C_{17}H_{16}N_2O_2$ : C, 72.84; H, 5.75; N, 9.99. Found: C, 72.64; H, 5.73; N, 9.86.

2-(*p*-Bromophenyl)-6-phenyl-3-pyridazinone (VI). **A.** From 2,6-Diphenyl-4,5-dihydro-3-pyridazinone.<sup>11</sup>—A 1.52-g. (0.006 mole) sample of the dihydropyridazinone in 2.7 ml. of anhyd. glacial acetic acid was treated dropwise with 1.7 g. (0.010 mole) of bromine. A flocculent, yellow colored solid formed rapidly in the cooled solution and hydrogen bromide was evolved. This solid redissolved in two hours. The reaction mixture was allowed to stand at room temperature for 24 hr. and then 10 ml. of ether was added to precipitate a colorless crystalline solid. This was refluxed with 1.72 g. of anhyd. sodium acetate in 20 ml. of anhyd. glacial acetic acid. The solvent was removed under reduced pressure and the residue extracted with chloroform. Evaporation of the chloroform solution produced a colorless product which was recrystallized from benzene and 95% ethanol; wt. 1.20 g. (80% yield); m.p. 175–177°.

*Anal.* Calcd. for  $C_{16}H_{11}N_2OBr$ : C, 58.75; H, 3.39; N, 8.56. Found: C, 59.03; H, 3.48; N, 8.60.

**B.** From 2,6-Diphenyl-3-pyridazinone (III).—A 1.0-g. sample of the pyridazinone was dissolved in the minimum

amount of hot anhyd. glacial acetic acid. The cooled solution was treated with 0.645 g. (one equiv.) of bromine and allowed to stand at room temperature for 24 hr. The reaction mixture was worked up as described above to give 0.5 g. of unchanged starting material and 0.21 g. of the expected product VI, m.p. 174–176°.

**C.** From  $\beta$ -Benzoylacrylic Acid *p*-Bromophenylhydrazone.—The *p*-bromophenylhydrazone (VII) of  $\beta$ -benzoylacrylic acid was obtained from  $\beta$ -benzoylacrylic acid and *p*-bromophenylhydrazine in glacial acetic acid in a 90% yield by allowing the reaction mixture to stand at room temperature for ten hours; recrystallized from 95% ethanol, yellow crystals, m.p. 201–203° dec.

*Anal.* Calcd. for  $C_{16}H_{13}N_2O_2Br$ : C, 55.66; H, 3.79; N, 8.12. Found: C, 55.99; H, 4.04; N, 8.30.

A 0.4-g. sample of the hydrazone VII was refluxed in 8 ml. of acetic anhydride for 40 minutes, cooled and poured into cold water. This mixture precipitated a tan colored solid after standing for 12 hr., which was recrystallized from ethanol and benzene to give 0.22 g. of colorless crystals, m.p. 174–176°, mixed with VI as prepared under A, m.p. 175–176°.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

## Nuclear Substituted 3,4-Dihydroxyphenethylamines and Related Derivatives

BY ALFRED BURGER AND RICHARD D. FOGGIO<sup>1</sup>

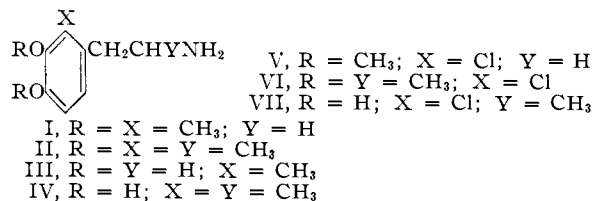
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The synthesis of several 2-methyl- and 2-chloro-3,4-dihydroxyphenethylalkyl- and alkanolamines, and of 5-methylpapaveraldine is described. This study includes observations on the cleavage of the methoxyl groups in the dimethyl ethers of some of these compounds and synthetic intermediates, and evidence for the structure of partially cleaved ether derivatives.

In continuation of a study of nuclear substitution in norepinephrine and related pharmacodynamic drugs,<sup>2</sup> several 2-chloro- and 2-methyl-3,4-dihydroxyphenethylamine and  $\beta$ -aminophenylpropane derivatives have been prepared. The corresponding 3,4-dimethoxy compounds may be regarded as structural analogs of 2,3,4-trimethoxyphenethylamine, a hallucinogenically interesting isomer<sup>3</sup> of the alkaloid mescaline. Replacement of all three methoxyl groups in mescaline by chlorine gives, in 3,4,5-trichlorophenethylamine, a compound which exhibits the sympathomimetic but not the psychogenic properties of the model alkaloid.<sup>4</sup> A comparison of methyl and chlorine substituted compounds in this series appeared especially interesting since approximative calculations based on accurately constructed models<sup>5–7</sup> indicate that the volumes of the chlorine atom (14.087 Å.<sup>3</sup>) and the methyl group (14.126 Å.<sup>3</sup>) are almost the same, and biological differences between such isosteres must be due to electronic effects only.

2-Methylveratraldehyde, previously obtained by a Gattermann reaction from 3-methylveratrole,<sup>8</sup>

was prepared conveniently by a Sommelet reaction on 3-methyl-4-chloromethylveratrole,<sup>2</sup> and condensed with nitromethane and nitroethane, respectively. The resulting  $\alpha,\beta$ -unsaturated nitro compounds were reduced with lithium aluminum hydride, and the ether groups of 2-methyl-3,4-dimethoxyphenethylamine (I) and 1-(2-methyl-3,4-dimethoxyphenyl)-2-aminopropane (II) were cleaved with hydrobromic acid. The catecholic amines III and IV were isolated as the stable hydrobromide salts.



Starting with 2-chloroveratraldehyde,<sup>2</sup> the amines V and VI were prepared by a similar synthetic sequence. The two ether groups of VI were cleaved with hydrobromic acid, and 1-(2-chloro-3,4-dihydroxyphenyl)-2-aminopropane (VII) was isolated as the hydrobromide. Treatment of V with hydrobromic acid in an atmosphere of nitrogen gave only dark uncrystallizable gums. Therefore, attempts were renewed to demethylate 2-chloroveratraldehyde to 2-chloroprocatechuic aldehyde, and to use this compound in the synthesis of 2-chloro-3,4-dihydroxyphenethylamine. However, as observed previously<sup>2</sup> 2-chloroveratraldehyde could be only monodemethylated; the re-

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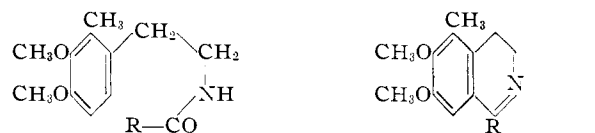
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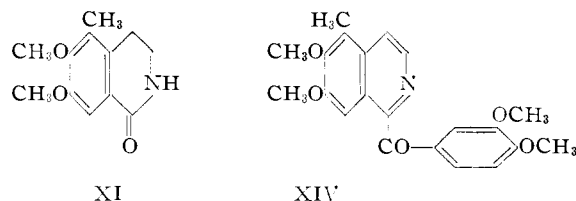
action product differs from 2-chlorovanillin,<sup>9</sup> and the oximes of the two isomers are also different. Our monophenolic aldehyde must, therefore, be 2-chloroisovanillin.

When 2-methylveratraldehyde was heated with hydrobromic acid for longer periods, the material decomposed; brief heating gave 2-methylisovanillin in good yield. This compound had been described by Perkin without structural proof.<sup>10</sup> The position of the hydroxyl group has now been ascertained by ethylation to the known 2-methyl-3-ethoxy-4-methoxybenzaldehyde<sup>11</sup> and oxidation of this substance to 2-methyl-3-ethoxy-4-methoxybenzoic acid for which adequate structural proof is at hand.<sup>11</sup> It had appeared likely initially that a comparison of the ultraviolet absorption spectra of 2-methylisovanillin, isovanillin and vanillin would lend support for the position of the phenolic hydroxyl group in 2-methylisovanillin, but the absorption maxima of these three compounds are too close to each other to furnish this information.

The availability of the amine I suggested a study of related isoquinoline derivatives. Its isobutyramide VIII was cyclized to 1-isopropyl-5-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IX).



VIII, R = CH(CH<sub>3</sub>)<sub>2</sub>  
 X, R = CH(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>  
 XII, R = CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(OCH<sub>3</sub>)<sub>2-3,4</sub>  
 IX, R = CH(CH<sub>3</sub>)<sub>2</sub>  
 XIII, R = COC<sub>6</sub>H<sub>4</sub>(OCH<sub>3</sub>)<sub>2-3,4</sub>



XI

XIV

Reduction furnished 1-isopropyl-5-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. The ether groups of this substance were extremely resistant to cleavage. Boiling with 48% hydrobromic acid for 327 hours, or with 48% hydriodic acid for 88 hours, produced only a small amount of monophenolic compounds, much of the starting material being recovered.

N-(2-Methyl-3,4-dimethoxyphenethyl)-diphenylacetamide (X) lost its benzhydryl group on cyclization with phosphorus oxychloride. The reaction product exhibited analytical values and properties expected of 5-methyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolone (XI). 2-Methyl-3,4-dimethoxyphenethylhomoveratramide (XII), obtained from I and homoveratryl chloride, gave on cyclization 1-(3,4-dimethoxybenzoyl)-3,4-dihydro-5-methyl-6,7-dimethoxyisoquinoline (XIII) in a yield of 37% instead of the expected 3,4-dihydro-5-methylpapaverine. Similar oxidative isoquinoline ring

closures have been observed in analogous cases.<sup>12,13</sup> The compound could be dehydrogenated to 5-methylpapaveraldine (XIV) with methanolic potassium hydroxide.<sup>14</sup>

In addition to the dihydroxy amines III, IV and VII, we have also prepared 2-methyl-3,4-dihydroxy- $\alpha$ -piperidino- and - $\alpha$ -morpholinoacetophenone. For this purpose, 2-methyl-3,4-dimethoxyphenacyl chloride<sup>2</sup> was condensed with piperidine, and the corresponding iodide<sup>2</sup> with morpholine. The methoxyl groups of the amino ketones were cleaved with hydrobromic acid. 2-Methyl-3,4-dihydroxy- $\alpha$ -piperidinoacetophenone was hydrogenated to 1-(2-methyl-3,4-dihydroxyphenyl)-2-piperidinoethanol.

### Experimental<sup>15</sup>

**2-Methyl-3,4-dimethoxybenzaldehyde.**—A solution of 120.0 g. (0.6 mole) of 3-methyl-4-chloromethylveratrole and 92.4 g. (0.66 mole) of hexamethylenetetramine in 600 ml. of chloroform was refluxed for three hours. The solid which soon precipitated was filtered, air-dried (200 g., 98%), and refluxed for five hours with 1 l. of 50% acetic acid. Hydrochloric acid (210 ml.) was added, the cooled solution was stirred into 500 ml. of ice-water, and the precipitate filtered. It weighed 73.0 g. (68%) and melted at 47–49°. The reported melting point<sup>8</sup> of material prepared by a Gattermann synthesis is 50°. The oxime melted at 95–97°. The recorded melting point is 98–99°.

**2-Methylisovanillin.**—A mixture of 3.0 g. (0.017 mole) of 2-methylveratraldehyde and 20 ml. of 48% hydrobromic acid was refluxed for ten minutes, poured into 50 ml. of water, the gray precipitate was filtered and recrystallized from dilute methanol. The alkali-soluble colorless plates melted at 134.5–136.5°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>: C, 65.05; H, 6.07. Found: C, 65.30; H, 6.14.

A comparison of the ultraviolet absorption spectra showed that in comparable concentrations (1.5 to 2.7  $\times 10^{-6}$  M) in ethanol, vanillin had absorption maxima at 230 and 280 m $\mu$ , isovanillin at 235 and 275 m $\mu$ , and 2-methylisovanillin at 230 and 275 m $\mu$ , respectively.

**2-Methyl-3-ethoxy-4-methoxybenzaldehyde.**—The dry potassium salt (3.5 g.) obtained by evaporating a solution of 2.7 g. (0.0162 mole) of 2-methylisovanillin and 0.91 g. (0.0162 mole) of potassium hydroxide in 30 ml. of warm ethanol under reduced pressure, was refluxed with 20 ml. of ethyl iodide in 20 ml. of dry ethanol for three hours. The filtrate from the precipitated 1.6 g. of potassium iodide was evaporated under reduced pressure, the residue was treated with water, the oil was extracted into ether, and the solvent was removed. The alkali-insoluble oil (2.85 g., 90%) furnished an oxime which melted at 88–89°. The reported melting point<sup>11</sup> is 88°.

Diazoethane did not ethylate 2-methylisovanillin.

**2-Methyl-3-ethoxy-4-methoxybenzoic Acid.**—A solution of 0.55 g. (3.5 millimoles) of potassium permanganate in 11 ml. of water was added dropwise to a stirred solution of 0.5 g. (2.6 millimoles) of 2-methyl-3-ethoxy-4-methoxybenzaldehyde in 10 ml. of acetone at 45°. The mixture was stirred for an additional 15 minutes, filtered and the filtrate acidified. The precipitated acid was filtered. It weighed 0.45 g. (82%) and crystallized from dilute acetone, m.p. 175–177°, reported m.p.<sup>11</sup> 176°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>14</sub>O<sub>4</sub>: C, 62.84; H, 6.71. Found: C, 62.76; H, 6.59.

**2-Chloroisovanillin Oxime.**—This derivative, obtained from the aldehyde<sup>2</sup> with hydroxylamine hydrochloride and

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TABLE I  
 SUBSTITUTED DIHYDROXY- AND DIMETHOXYPHENYL NITROALKENES, AMINOALKANES, AMINOALKANONES AND AMINOALKANOLS

Name of compound	R	X	Z	Yield, %	M.p., °C. corr.	Crystn. solvent	Composition	Analyses, %			
								C	Calcd. H	C	Found H
2-Methyl-3,4-dimethoxy-β-nitrostyrene	CH <sub>3</sub>	CH <sub>3</sub>	CH=CHNO <sub>2</sub>	86	91.5-92.5	EtOH	C <sub>11</sub> H <sub>13</sub> NO <sub>4</sub>	59.18	5.87	59.15	5.80
1-(2-Methyl-3,4-dimethoxyphenyl)-2-nitropropene	CH <sub>3</sub>	CH <sub>3</sub>	CH=C(CH <sub>3</sub> )NO <sub>2</sub>	65	101-102	EtOH	C <sub>12</sub> H <sub>15</sub> NO <sub>4</sub>	60.75	6.37	60.63	6.21
2-Chloro-3,4-dimethoxy-β-nitrostyrene	CH <sub>3</sub>	Cl	CH=CHNO <sub>2</sub>	89	94.5-96.5	EtOH	C <sub>10</sub> H <sub>10</sub> ClNO <sub>4</sub>	49.29	4.14	49.45	4.16
1-(2-Chloro-3,4-dimethoxyphenyl)-2-nitropropene	CH <sub>3</sub>	Cl	CH=C(CH <sub>3</sub> )NO <sub>2</sub>	82	118.5-120	EtOH	C <sub>11</sub> H <sub>12</sub> ClNO <sub>4</sub>	51.27	4.69	51.16	4.71
2-Methyl-3,4-dimethoxyphenethylamine·HCl	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> ·HCl	60	175-177	Dioxane	C <sub>11</sub> H <sub>17</sub> NO <sub>2</sub> ·HCl	57.01	7.83	56.97	7.89
1-(2-Methyl-3,4-dimethoxyphenyl)-2-aminopropane·HCl	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> CHNH <sub>2</sub> CH <sub>3</sub> ·HCl	53	171-173	MeOH-Et <sub>2</sub> O	C <sub>12</sub> H <sub>19</sub> NO <sub>2</sub> ·HCl	N, 5.70		N, 5.51	
2-Methyl-3,4-dihydroxyphenethylamine·HBr	H	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> ·HBr	75	165.5-167.5	EtOH-Et <sub>2</sub> O	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub> ·HBr	43.56	5.69	43.90	5.48
1-(2-Methyl-3,4-dihydroxyphenyl)-2-aminopropane·HBr	H	CH <sub>3</sub>	CH <sub>2</sub> CHNH <sub>2</sub> CH <sub>3</sub> ·HBr	66	210-212	EtOAc, MeOH	C <sub>10</sub> H <sub>15</sub> NO <sub>2</sub> ·HBr	N, 5.65	6.15	N, 5.56	6.07
2-Chloro-3,4-dimethoxyphenethylamine succinate	CH <sub>3</sub>	Cl	CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> ·1/2C <sub>4</sub> H <sub>6</sub> O <sub>4</sub>	46	171-172.5	EtOH-Et <sub>2</sub> O	C <sub>24</sub> H <sub>34</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>8</sub>	52.46	6.24	52.06	6.12
1-(2-Chloro-3,4-dimethoxyphenyl)-2-aminopropane·HCl	CH <sub>3</sub>	Cl	CH <sub>2</sub> CHNH <sub>2</sub> CH <sub>3</sub> ·HCl	58	203.5-205.5	MeOH-Et <sub>2</sub> O	C <sub>11</sub> H <sub>16</sub> ClNO <sub>2</sub> ·HCl	N, 5.10	6.44	N, 5.19	6.81
1-(2-Chloro-3,4-dihydroxyphenyl)-2-aminopropane·HBr	H	Cl	CH <sub>2</sub> CHNH <sub>2</sub> CH <sub>3</sub> ·HBr	64	194.5-196.5	EtOAc, MeOH	C <sub>9</sub> H <sub>12</sub> ClNO <sub>2</sub> ·HBr	N, 5.26	4.64	N, 5.27	4.46
2-Methyl-3,4-dimethoxy-α-piperidinoacetophenone·CH <sub>3</sub> I	CH <sub>3</sub>	CH <sub>3</sub>	COCH <sub>2</sub> NC <sub>4</sub> H <sub>10</sub> ·CH <sub>3</sub> I	94	193.5-194.5	EtOAc, EtOH	C <sub>17</sub> H <sub>26</sub> I NO <sub>3</sub>	38.25	6.25	38.39	6.15
2-Methyl-3,4-dimethoxy-α-morpholinoacetophenone·HCl	CH <sub>3</sub>	CH <sub>3</sub>	COCH <sub>2</sub> NC <sub>4</sub> H <sub>8</sub> O·HCl	73	201-203	MeOH-Et <sub>2</sub> O	C <sub>15</sub> H <sub>21</sub> NO <sub>4</sub> ·HCl	48.69	4.44	48.79	4.39
2-Methyl-3,4-dihydroxy-α-piperidinoacetophenone·HBr	H	CH <sub>3</sub>	COCH <sub>2</sub> NC <sub>4</sub> H <sub>10</sub> ·HBr	61	278-280	H <sub>2</sub> O	C <sub>14</sub> H <sub>19</sub> NO <sub>3</sub> ·HBr	50.92	6.10	50.99	6.03
2-Methyl-3,4-dihydroxy-α-morpholinoacetophenone·HBr	H	CH <sub>3</sub>	COCH <sub>2</sub> NC <sub>4</sub> H <sub>8</sub> O·HBr	38	268-270	MeOH-Et <sub>2</sub> O	C <sub>13</sub> H <sub>17</sub> NO <sub>4</sub> ·HBr	47.00	5.46	47.00	5.47
1-(2-Methyl-3,4-dihydroxyphenyl)-2-piperidinoethanol·HBr	H	CH <sub>3</sub>	CHOHCH <sub>2</sub> NC <sub>4</sub> H <sub>10</sub> ·HBr	60	187-189	MeOH-Et <sub>2</sub> O	C <sub>14</sub> H <sub>21</sub> NO <sub>3</sub> ·HBr	50.61	6.67	50.85	6.21
								N, 4.22		N, 4.34	

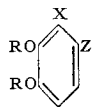


TABLE II  
N-(2-METHYL-3,4-DIMETHOXYPHENETHYLAMIDES) AND 1-SUBSTITUTED 5-METHYL-6,7-DIMETHOXYISOQUINOLINE DERIVATIVES

Name of compound	Yield, %	M.p., °C., corr.	Crystn. solvent	Composition	Analyses, %			
					Calcd. C	H	Found C	H
N-(2-Methyl-3,4-dimethoxyphenethyl)-isobutyramide	58	104-105.5	Cyclohexane	C <sub>15</sub> H <sub>23</sub> NO <sub>2</sub>	67.89	8.73	67.80	8.87
N-(2-Methyl-3,4-dimethoxyphenethyl)-diphenylacetamide	71	133-134	Cyclohexane	C <sub>25</sub> H <sub>27</sub> NO <sub>2</sub>	77.09	6.99	77.16	7.07
N-(2-Methyl-3,4-dimethoxyphenethyl)-3,4-dimethoxyphenylacetamide	63	118.5-120.5	Cyclohexane	C <sub>21</sub> H <sub>27</sub> NO <sub>5</sub>	N, 3.75		N, 3.86	
1-Isopropyl-5-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline picrate	73	198-200	EtOH	C <sub>21</sub> H <sub>24</sub> N <sub>4</sub> O <sub>9</sub>	52.93	5.08	53.23	5.09
1-Isopropyl-5-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline·HCl	90	231-233	EtOH-Et <sub>2</sub> O	C <sub>15</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl	63.03	8.46	62.80	8.63
1-Oxo-5-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline <sup>a</sup>	36	154.5-156.5	Cyclohexane	C <sub>17</sub> H <sub>15</sub> NO <sub>3</sub>	65.14	6.83	65.10	6.94
1-(3,4-Dimethoxybenzoyl)-5-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline·Picrate	37	154.5-156.5	Cyclohexane	C <sub>21</sub> H <sub>23</sub> NO <sub>5</sub>	68.27	6.27	68.13	6.12
					N, 3.79		N, 4.01	
1-(3,4-Dimethoxybenzoyl)-5-methyl-6,7-dimethoxyisoquinoline·Picrate	56	186-188	EtOH	C <sub>27</sub> H <sub>26</sub> N <sub>4</sub> O <sub>12</sub>	54.18	4.38	54.13	4.49
		174-176	MeOH	C <sub>21</sub> H <sub>21</sub> NO <sub>5</sub>	68.65	5.76	68.20	5.65
1-(3,4-Dimethoxybenzoyl)-5-methyl-6,7-dimethoxyisoquinoline; [5-Methylpapaveraldine]·Picrate		205-207	EtOH, Me <sub>2</sub> CO	C <sub>27</sub> H <sub>24</sub> N <sub>4</sub> O <sub>12</sub>	54.36	4.05	54.12	4.03

<sup>a</sup> Insoluble in dilute sodium hydroxide solution, sparingly soluble in dilute mineral acids.

sodium acetate solution, crystallized from dilute methanol, m.p. 184-186°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>9</sub>ClNO<sub>2</sub>: C, 47.66; H, 4.00. Found: C, 47.94; H, 3.87.

**General Directions.**—Yields and physical and analytical data for substances covered by these directions may be found in Tables I and II.

**Nitrostyrene Derivatives.**—A mixture of 0.25 mole of the aldehyde, 0.32 to 0.38 mole of the nitroalkane, 0.15 to 0.18 mole of ammonium acetate, and 200-240 ml. of glacial acetic acid was refluxed for two to three hours, cooled, poured into an equal volume of ice-water, and the yellow or orange reaction product was filtered.

**3,4-Dimethoxyphenylalkylamines.**—To a mixture of 0.8 mole of lithium aluminum hydride and 200 ml. of absolute ether which had been stirred for 0.5 hour, a solution of 0.2 mole of the nitrostyrene derivative in about 800 ml. of absolute ether was added dropwise. After the addition was complete, the suspension was stirred and refluxed for five to six hours, cooled, and decomposed by dropwise addition of water. The inorganic salts were filtered, washed with ether and the combined ether solutions were extracted with three small portions of 10% hydrochloric acid. The aqueous extracts were made alkaline with 10% sodium hydroxide solution, and the amine was extracted into ether. The oily base was converted to the respective salt in ether solution.

Cleavage of the methoxyl groups was accomplished by refluxing the amines, or their hydrochloride salts, with seven to eight volumes of 48% hydrobromic acid for ten hours. The hydrobromides of the dihydroxyphenylalkylamines crystallized on cooling.

**N-(2-Methyl-3,4-dimethoxyphenethyl)-amides.**—A mixture of equimolar quantities of 2-methyl-3,4-dimethoxyphenethylamine, anhydrous sodium carbonate, and the

respective acyl chloride<sup>16</sup> in 25 volumes of dry benzene was refluxed for one hour, cooled and decomposed with 5% hydrochloric acid. The benzene layer was washed with 5% hydrochloric acid, 5% sodium bicarbonate solution and water, and then diluted with an equal volume of petroleum ether. The amide crystallized on cooling.

**Isoquinoline Ring Closures.**—A solution of the respective amide (0.5-2.5 g.) in 15-40 ml. of dry benzene was refluxed with equimolar amounts of phosphorus oxychloride for two hours, cooled, made basic with 5% potassium hydroxide solution and extracted twice with 5% hydrochloric acid. The bases were liberated from the acid solution, and extracted into benzene and ether. The residue, if solid, was recrystallized, or if oily converted to a salt.

**1-Isopropyl-5-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.**—A solution of 5.6 g. (0.0226 mole) of 1-isopropyl-5-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in 135 ml. of absolute ether was added slowly to a stirred mixture of 0.86 g. (0.0226 mole) of lithium aluminum hydride in 40 ml. of ether. Refluxing was continued for 5.5 hours, water was dropped in until a granular precipitate had formed, the ether layer was decanted and the precipitate washed twice with ether. The dried ether solution was evaporated and left 5.1 g. of an oily base which was converted to the hydrochloride.

**1-(3,4-Dimethoxybenzoyl)-5-methyl-6,7-dimethoxyisoquinoline.**—A solution of 0.2 g. of 1-(3,4-dimethoxybenzoyl)-5-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in 5 ml. of 10% methanolic potassium hydroxide was refluxed for 1.5 hours. It deposited, on cooling, 0.11 g. of a solid which was washed with water and recrystallized.

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(16) The homoveratric acid used was donated generously by Dr. Thomas P. Carney, Eli Lilly & Co.