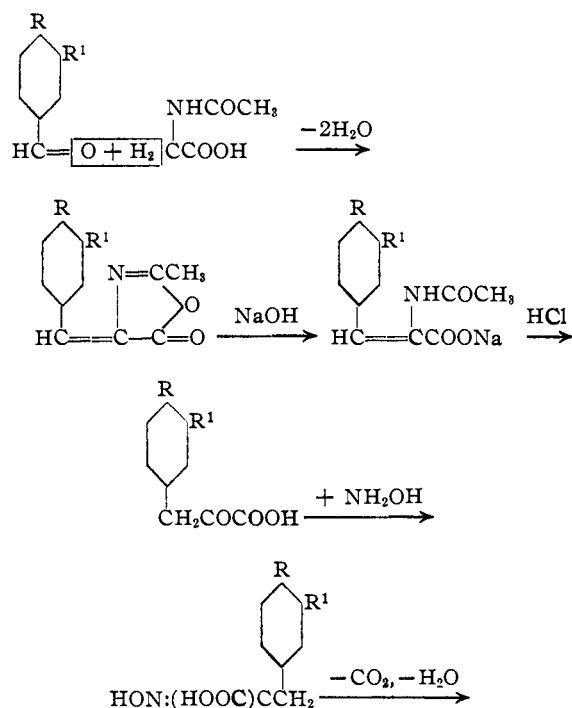


[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

## Unsymmetrical Cyanostilbenes

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The present-day physiological importance of certain stilbene types of compounds<sup>2-7</sup> led to the systematic investigation in unsymmetrical  $\alpha$ -cyanostilbenes presented in this communication. The preparation of these compounds involved the condensation of *p*-methoxy- (I), 3,4-dimethoxy- (II) and 3,4-methylenedioxy-benzyl nitriles (III) with various aromatic aldehydes (benzaldehyde, *o*- and *p*-chloro-, *o*- and *p*-methoxy-, *m*-nitro- and *p*-dimethyl-aminobenzaldehydes, veratric aldehyde and piperonal). The intermediate nitriles were prepared from the respective aldehydes (anisaldehyde, veratric aldehyde and piperonal) by a five-step synthesis as shown below<sup>8-10</sup>



(1) Abstracted from Part I of the thesis presented by A. Ziering to the Faculty of the Graduate School of New York University in partial fulfillment for the degree of Doctor of Philosophy, June, 1942.

(2) Wessely, *Naturwissenschaften*, **27**, 567 (1939).

(3) Novelli, *Ciencia*, **1**, 19 (1940).

(4) Wessely, *Monatsh.*, **73**, 127 (1940).

(5) Noble, *Lancet*, **II**, 142 (1938).

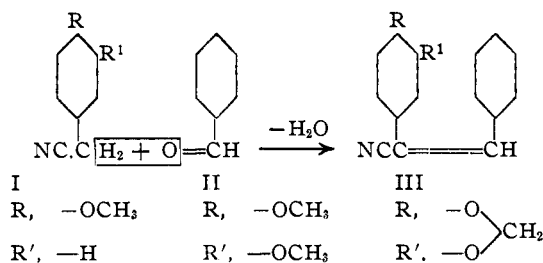
(6) Kerschbaum, *Naturwissenschaften*, **27**, 131 (1939).

(7) Dodds, Goldberg, and Lawson, *Nature*, **141**, 247 (1938); **142**, 34 (1938); **139**, 627 (1937).

(8) Dakin, *J. Biol. Chem.*, **82**, 439 (1929).

(9) Edwards, *J. Chem. Soc.*, 740 (1926).

(10) "Organic Syntheses," Vol. XIX, John Wiley and Sons, New York, N. Y., 1939, p. 4.



All condensation products proved to be crystalline compounds, which were not only properly characterized but were also examined for possible physiological activity.

## Experimental

## Preparation of the Alkoxybenzyl nitriles (I, II, III).—

One and one-tenth moles of acetyl glycine,<sup>10</sup> one mole of the respective alkoxybenzaldehyde, one mole of fused sodium acetate, and 250 cc. of acetic anhydride were placed in a 2-liter Erlenmeyer flask, provided with a calcium chloride drying tube, and heated on a steam-bath for seven hours.<sup>8,9</sup> The azlactone usually began to precipitate from the reaction mixture after three hours of heating. After the heating period was over, the flask was permitted to stand overnight at room temperature. The contents of the flask, colored deep brown, were then treated with 400 cc. of warm water, the lumps were broken up with a spatula and the mixture filtered through a fritted glass filter. The azlactone was then washed three times with 300 cc. of water and finally with 200 cc. of alcohol. The yields usually were between 30–40% of the theoretical; m. p. of the azlactones: anisaldehyde, 114° (uncor.); veratric aldehyde, 167° (uncor.); piperonal, 181° (uncor.).

Three hundred grams of the respective azlactone was hydrolyzed by adding the lactone to a solution of 60 g. of sodium hydroxide in 1200 cc. of water and heating on a steam-bath until most of it had dissolved. The solution was cooled and then filtered through fluted filter paper into a 5-liter round-bottomed flask. Acidification with dilute hydrochloric acid to congo red precipitated the respective alkoxy- $\alpha$ -acetaminocinnamic acid; m. p. of the alkoxy- $\alpha$ -acetamino acids: *p*-methoxy-, 216° (uncor.); 3,4-dimethoxy-, 208° (uncor.); 3,4-methylenedioxy-, 219° (uncor.).

To the filtrate contained in the above-mentioned 5-liter round-bottomed flask which was now provided with a reflux condenser, was added 250 cc. more of concentrated hydrochloric acid and enough water to make the volume about 2000 cc. The mixture was then refluxed. To control frothing, a few drops of octyl alcohol were added. The acetamino-cinnamic acid gradually dissolved and, on continued boiling, the phenylpyruvic acid separated out. After three hours of refluxing, the solution was cooled and filtered. The filtrate was refluxed again for one hour and then cooled in an ice-bath when an additional amount of reaction prod-

TABLE I

Reactants	$\alpha$ -Cyanostilbenes	Formula	M. p., °C. (uncor.)	Analyses, % N Calcd.	% N Found
<i>p</i> -Methoxybenzyl nitrile (I):					
Benzaldehyde	4-Methoxy-	C <sub>16</sub> H <sub>15</sub> NO <sub>2</sub>	94	5.96	5.99
<i>o</i> -chloro-	-2'-chloro-	C <sub>16</sub> H <sub>12</sub> NCIO	129	5.19	5.24
<i>p</i> -chloro-	-4'-chloro-	C <sub>16</sub> H <sub>12</sub> NCIO	110	5.19	5.00
<i>m</i> -nitro-	-3'-nitro-	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	159	10.00	10.17
<i>p</i> -methyl-	-4'-methyl-	C <sub>17</sub> H <sub>16</sub> NO	97	5.62	5.81
<i>o</i> -methoxy-	-2'-methoxy-	C <sub>17</sub> H <sub>16</sub> NO <sub>2</sub>	98	5.28	5.40
<i>p</i> -methoxy-	-4'-methoxy-	C <sub>17</sub> H <sub>16</sub> NO <sub>2</sub>	108	5.28	5.25
3,4-dimethoxy-	-3',4'-dimethoxy-	C <sub>18</sub> H <sub>17</sub> NO <sub>3</sub>	105	4.74	4.84
3,4-methylenedioxy-	-3',4'-methylenedioxy-	C <sub>17</sub> H <sub>13</sub> NO <sub>3</sub>	129	5.02	5.14
<i>p</i> -dimethylamino-	-4'-dimethylamino-	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O	149	10.02	10.27
3,4-Dimethoxybenzyl nitrile (II):					
Benzaldehyde	3,4-Dimethoxy-	C <sub>17</sub> H <sub>15</sub> NO <sub>2</sub>	87	5.28	5.08
<i>o</i> -chloro-	-2'-chloro-	C <sub>17</sub> H <sub>14</sub> NCIO <sub>2</sub>	113	4.67	4.55
<i>p</i> -chloro-	-4'-chloro-	C <sub>17</sub> H <sub>14</sub> NCIO <sub>2</sub>	115	4.67	4.49
<i>m</i> -nitro-	-3'-nitro-	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	166	9.03	8.92
<i>p</i> -methyl-	-4'-methyl-	C <sub>18</sub> H <sub>17</sub> NO <sub>2</sub>	112	5.01	4.95
<i>o</i> -methoxy-	-2'-methoxy-	C <sub>18</sub> H <sub>17</sub> NO <sub>3</sub>	87	4.74	4.80
<i>p</i> -methoxy-	-4'-methoxy-	C <sub>18</sub> H <sub>17</sub> NO <sub>3</sub>	129	4.74	4.91
3,4-dimethoxy-	-3',4'-dimethoxy-	C <sub>19</sub> H <sub>19</sub> NO <sub>4</sub>	155	4.31	4.46
3,4-methylenedioxy-	-3',4'-methylenedioxy-	C <sub>18</sub> H <sub>15</sub> NO <sub>4</sub>	150	4.53	4.72
<i>p</i> -dimethylamino-	-4'-dimethylamino-	C <sub>18</sub> H <sub>20</sub> N <sub>2</sub> O	121	9.09	8.90
3,4-Methylenedioxybenzyl nitrile (III):					
Benzaldehyde	3,4-Methylenedioxy-	C <sub>16</sub> H <sub>11</sub> NO <sub>2</sub>	125	5.62	5.80
<i>o</i> -chloro-	-2'-chloro-	C <sub>16</sub> H <sub>10</sub> NCIO <sub>2</sub>	135	4.93	4.73
<i>p</i> -chloro-	-4'-chloro-	C <sub>16</sub> H <sub>10</sub> NCIO <sub>2</sub>	130	4.93	4.80
<i>m</i> -nitro-	-3'-nitro-	C <sub>16</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub>	195	9.52	9.74
<i>p</i> -methyl-	-4'-methyl-	C <sub>17</sub> H <sub>13</sub> NO <sub>2</sub>	122	5.32	5.30
<i>o</i> -methoxy-	-2'-methoxy-	C <sub>17</sub> H <sub>13</sub> NO <sub>3</sub>	102	5.02	5.12
<i>p</i> -methoxy-	-4'-methoxy-	C <sub>17</sub> H <sub>13</sub> NO <sub>3</sub>	129	5.02	5.16
3,4-dimethoxy-	-3',4'-dimethoxy-	C <sub>18</sub> H <sub>15</sub> NO <sub>4</sub>	144	4.53	4.54
3,4-methylenedioxy-	-3',4'-methylenedioxy-	C <sub>17</sub> H <sub>11</sub> NO <sub>4</sub>	185	4.78	4.88
<i>p</i> -dimethylamino-	-4'-dimethylamino-	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	169	9.58	9.43

uct separated out. The total yield of alkoxyphenylpyruvic acid was about 90%; m. p. of the alkoxyphenylpyruvic acids: *p*-methoxy-, 184° (uncor.); 3,4-dimethoxy-, 185° (uncor.); 3,4-methylenedioxy-, 213° (uncor.).

The oxime was prepared by dissolving the pyruvic acid in 800 cc. of a solution containing 2 mole equivalents of sodium hydroxide and then adding 1.5 mole equivalents of hydroxylamine. After standing for 36 hours, the oxime was precipitated with dilute hydrochloric acid. The yield was 95%, based on the weight of the phenylpyruvic acid; m. p. of the oximes: *p*-methoxy-, 159° (uncor.); 3,4-dimethoxy-, 164° (uncor.); 3,4-methylenedioxy-, 170° (uncor.).

The oxime was dehydrated by refluxing a solution of one part of the oxime in four parts of acetic anhydride.<sup>9</sup> Since the reaction is very violent, it is necessary to add one-third of the oxime at a time to the acetic anhydride, warming gently until the reaction starts, and then letting the reaction subside before adding the next third; yield 50-70% of the theoretical; b. p. of the alkoxybenzyl nitriles: *p*-methoxy (I)-, 120° (4 mm.); 3,4-dimethoxy (II)-, 183° (16 mm.); 3,4-methylenedioxy (III)-, 160° (10 mm.).

**Condensation Procedure.**—Equivalent amounts of the above alkoxybenzyl nitriles (I, II, III) and the respective aromatic aldehydes were dissolved in 10 parts of 95% ethyl alcohol, and to this solution was added an equivalent

amount of sodium in 25 parts of 95% ethyl alcohol. The mixture was warmed over a flame and then allowed to cool. In the case of homopiperonyl and of the veratryl nitriles, the reaction was very rapid, but with homoanisyl nitrile the reaction was slow. The yields were excellent with homopiperonyl and veratryl nitrile, and only fair with homoanisyl nitrile. The final condensation products, the  $\alpha$ -cyanostilbenes, were crystallized from 95% ethyl alcohol, and in a few cases from ethyl acetate.

### Summary

Three series of unsymmetrical cyanostilbenes were prepared, involving the condensation of three representative types of alkoxybenzyl nitriles with various aromatic aldehydes.

Preliminary pharmacological tests on these compounds indicate that most of them exhibit feeble estrogenic activity in the following order:

