

2. Further proof of the structure of Wardner and Lowy's mononitro and monoamino derivatives is presented.

3. A corrected m. p. of 74° for 4-amino-*m*-di-

phenylbenzene is reported. For characterization purposes, the phenylthiourea derivative is also described.

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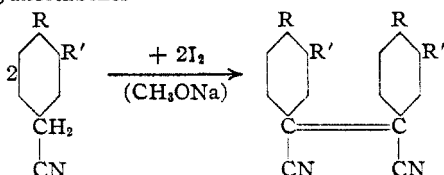
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

## Symmetrical Cyanostilbenes

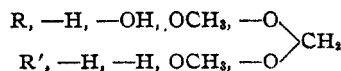
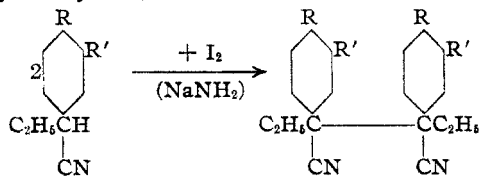
BY JOSEPH B. NIEDERL AND ALBERT ZIERING<sup>1</sup>

In a previous communication<sup>2</sup> the preparation of unsymmetrical cyanostilbenes was presented. The purpose of this communication is to give report on the preparation of symmetrical and variously ring and side-chain substituted cyanostilbenes and dihydrostilbenes related in structure to diethylstilbestrol. The ring substituents included the following: nitro, amino, hydroxy, acetoxy, methoxy, dimethoxy and methylenedioxy groups, while the side-chain substituents comprised either hydrogen or ethyl groups. The method of preparation of these compounds consisted in self-condensation of the respective benzyl nitriles by means of iodine in the presence of sodium methoxide or sodium amide as follows<sup>3</sup>

### Dicyanostilbenes



### Dicyanodihydrostilbenes:



## Experimental

**$\alpha,\alpha'$ -Dicyanostilbenes.**—One-tenth mole of the respective benzyl nitrile (*p*-methoxy-3,4-methylenedioxy-3,4-dimethoxy) was dissolved in 65 cc. of absolute methyl alcohol. To this solution 25.4 g. of iodine, dissolved in 130 cc.

of absolute ether, was added, followed by the dropwise addition of a solution of 4.6 g. of sodium in 70 cc. of absolute methyl alcohol.<sup>3</sup> The precipitated solid was filtered and recrystallized from ethyl acetate. All dicyanostilbenes were colored and gave positive unsaturation tests with potassium permanganate dissolved in acetone; yields, 35% (approx.). The 4,4'-dihydroxy derivative was prepared by diazotizing the corresponding amine,<sup>4</sup> acetylating the resulting solid and then hydrolyzing the acetate with alkali to the phenolic derivative.

**$\alpha,\alpha'$ -Dicyanodihydrostilbenes.**—One-tenth mole of phenylethylacetonitrile was added dropwise to a suspension of sodamide (0.1 mole) in 150 cc. of anhydrous ether. The mixture was refluxed until the evolution of ammonia had ceased. To this was then added slowly 0.05 mole of iodine in 100 cc. of absolute ether.<sup>3</sup> The precipitated solid was filtered, washed with water and recrystallized from ethanol. All dicyanodihydrostilbenes were colorless and the unsaturation tests with potassium permanganate in acetone were negative; yields, 25% (approx.).

Piperonylethylacetonitrile was treated in the same manner and the final reaction product was recrystallized from dioxane; yield, 25%.

The piperonylethylacetonitrile was prepared by first treating 3,4-methylenedioxybenzyl nitrile with diethyl carbonate in the presence of sodium at 60° in benzene to yield the ethyl piperonylcynoacetate (b. p. 161° at 3 mm.). This ester was then ethylated in the usual manner with ethyl iodide and sodium ethoxide in absolute ethanol to give the ethyl piperonylethylcynoacetate (m. p. 72°) which was then hydrolyzed with alkali in the cold to the piperonylethylcynoacetic acid (m. p. 110°). The acid was decarboxylated by heating to 180°. The resulting piperonylethylacetonitrile boiled at 174° at 15 mm.

The corresponding phenolic derivative was prepared by nitrating phenylethylacetonitrile with fuming nitric acid at 0° to yield the *p*-nitrophenylethylacetonitrile (b. p. 165° at 3 mm.). The nitro compound was converted to the dihydrostilbene by means of iodine and sodium methoxide.<sup>3</sup> The resulting dihydrostilbene was then reduced to the amine, which was then diazotized and finally hydrolyzed to the phenolic derivative, which was recrystallized from benzene containing a little alcohol.

**Physiological Tests.**—All compounds were subjected to the Fluhmann<sup>5,6</sup> test for estrogenic activity. Most re-

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

(2) J. B. Niederl and A. Ziering, *THIS JOURNAL*, **64**, 885 (1942).

(3) Knoevenagel and Chalanay, *Ber.*, **25**, 285 (1892).

(4) Heller, *Ann.*, **332**, 280 (1904).

(5) Fluhmann, *Endocrinology*, **18**, 705 (1934).

(6) Deckert, Mulhall and Swiney, *J. Lab. Clin. Med.*, **23**, 85 (1937).

active of all the substances was the  $\alpha,\alpha'$ -dicyanostilbestrol, which exhibited the following degrees of activity:

	Dose, microg.	Reaction
$\alpha,\alpha'$ -Dicyanostilbestrol	6.25	5.0
$\alpha,\alpha'$ -Dicyanostilbestrol	3.12	4.5
$\alpha,\alpha'$ -Dicyanostilbestrol	1.56	4.3
$\alpha,\alpha'$ -Dicyanostilbestrol	0.78	3.5
Stilbestrol	0.02	5.0
Estrone	0.08	5.0

TABLE I  
 $\alpha,\alpha'$ -DICYANOSTILBENES

	Formula	M. p., °C. (uncor.)	Analyses, % N Calcd.	% N Found
4,4'-Dihydroxy	$C_{16}H_{10}N_2O_2$	287	10.7	10.5
4,4'-Diacetoxy	$C_{20}H_{14}N_2O_4$	217	8.09	8.17
4,4'-Dimethoxy	$C_{18}H_{14}N_2O_2$	187	9.65	9.50
3,4,3',4'-Dimethyl-enedioxy	$C_{18}H_{10}N_2O_4$	235	8.81	8.90
3,4,3',4'-Tetra-methoxy	$C_{20}H_{18}N_2O_4$	205	8.00	8.20

$\alpha,\alpha'$ -DIETHYL- $\alpha,\alpha'$ -DICYANODIHYDROSTILBENES

Unsubstituted	$C_{20}H_{20}N_2$	175	9.72	9.51
3,4,3',4'-Dimethyl-enedioxy	$C_{22}H_{20}N_2O_4$	213	7.45	7.26
4,4'-Dinitro	$C_{20}H_{18}N_4O_4$	225	14.8	14.6
4,4'-Diamino	$C_{20}H_{22}N_4$	205	17.6	17.4
4,4'-Dihydroxy	$C_{20}H_{20}N_2O_2$	218	7.95	7.80

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**Summary**

Various substituted symmetrical cyano- and dihydrocyanostilbenes have been prepared, characterized and tested for estrogenic activity.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY AND OF LAFAYETTE COLLEGE]

## Phenylmercapto-thiazolines

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The condensation of allyl- and methallyl mustard oils with phenols yielded thiazolinephenols as shown in previous publications.<sup>1,2</sup> The same condensation procedure has now been applied to the reaction between allyl mustard oil and various thiophenols.

There were obtained excellent yields of hydrochlorides which analyzed correctly for the expected salts of thiazoline-thiophenols. From these, picrates were prepared which also analyzed as expected. However, when an attempt was made to prepare the free bases by neutralization of a solution of the hydrochlorides with sodium carbonate, hydrolysis occurred, one of the products being the thiophenol, and the other, 5-methyl-thiazolidone-2.

From these hydrolysis products it appears that the products of these condensations are the hydrochlorides of 5-methyl-2-phenylmercapto-thiazolines, instead of the expected thiazoline-thiophenols. The hydrochlorides of these thio-ethers are remarkably stable to acid treatment. The compounds, however, are completely hydrolyzed in dilute sodium bicarbonate solution.

(1) Niederl, Hart and Scudi, *THIS JOURNAL*, **58**, 707 (1936).

(2) Hart and Niederl, *ibid.*, **61**, 1145 (1939); **63**, 945 (1941).

## Experimental

**Condensation.**—Allyl mustard oil was condensed with thiophenol, thio-*o*-cresol and thio-*m*-cresol in the manner previously described.<sup>3</sup> Condensation was usually complete within one week. The product was taken up in water, the acid solution extracted several times with ether, and the ether extracts discarded. The acid solution was then evaporated to dryness on a water-bath, yielding the hydrochloride in a quite pure form. The hydrochlorides were washed several times with dry acetone, and then recrystallized from 95% ethyl alcohol several times until the melting point was constant.

The picrates were made by adding a filtered, saturated picric acid solution to an equal volume of filtered aqueous solution of the hydrochloride. The resulting crystalline precipitate was washed several times with water, dried and recrystallized once from 95% ethyl alcohol.

**Hydrolysis.**—Twenty grams of the hydrochloride of the thio-*m*-cresol condensation product was dissolved in water, and the solution was made distinctly alkaline with sodium bicarbonate. A blue oil separated, which was removed by ether extraction and the ether extracts were in turn extracted with 10% hydrochloric acid, which removed the blue color. The ether solution was washed, dried, and the solvent removed by distillation. The residue was an almost quantitative yield of 10.5 g. of thio-*m*-cresol, which was identified by the boiling point, and by oxidation to dim-*m*-cresyl di-sulfide with 3% hydrogen peroxide in acetone solution.

The hydrochloric acid extract was used to acidify the