[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

THE SYNTHESIS OF SULFUR-CONTAINING ANALOGS OF SYNTHETIC ESTROGENS[1]

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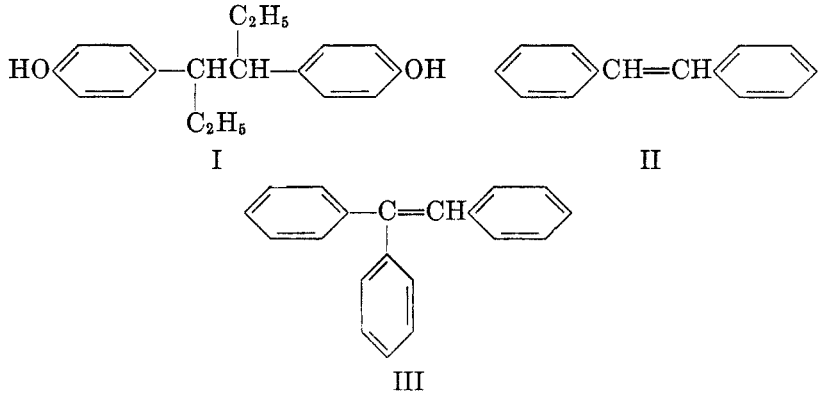
A line of research pursued for a long time in this Institute has been the synthesis of compounds of molecular structures resembling as closely as possible those of natural or synthetic estrogens, but bearing little or no estrogenic activity. Such compounds would be able to replace estrogens in their attachment to specific cellular receptors, resulting possibly in a biological effect similar to the known reduction of the activity of a potent carcinogenic hydrocarbon by a weaker one (1). Apart from their potential antagonistic effects upon estrogens, such substances might also be of interest for use in prostatic cancer, a condition wherein the activity of stilbestrol and other estrogenic substances does not run strictly parallel to their activity in the Allen-Doisy test (2).

A reliable way of reducing or destroying the hormonal activity of a synthetic estrogen has been found in the introduction of sulfur atoms in its molecule, by replacing either one or several benzene rings by thiophene ones (3), or one or several phenol groups by thiophenol ones (4). Thus, 1,2,2-triphenylethylene is active in the Allen-Doisy test in mice at 100 γ, whereas 1,2-diphenyl-2-(2-thienyl)ethylene is far less active, and 1-phenyl-2,2-di(2-thienyl)ethylene is inactive even at 10 mg. Similarly, 1-bromo-1-phenyl-2,2-di(4-methylmercaptophenyl)ethylene (5) is far less active than its corresponding oxygen-containing analog.

This paper describes a continuation of this line of research, with the synthesis of new sulfur-containing compounds related to three key substances: hexestrol (I), stilbene (II), and 1,2,2-triphenylethylene (III).



I

II

III

4-(α-Hydroxypropyl)thioanisole (V), prepared from 4-propionylthioanisole (IV) through the Meerwein-Ponndorf reaction, was converted by hydrogen

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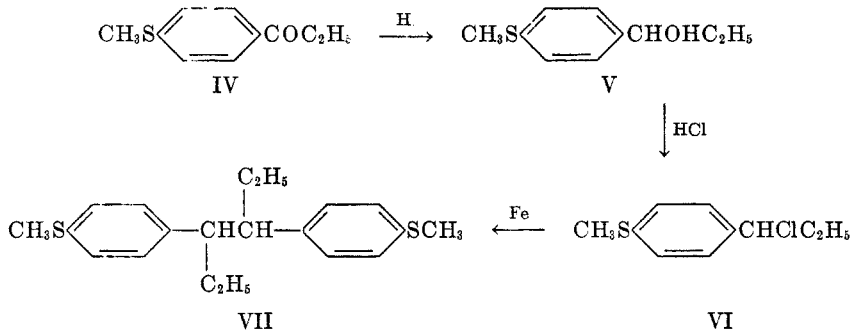
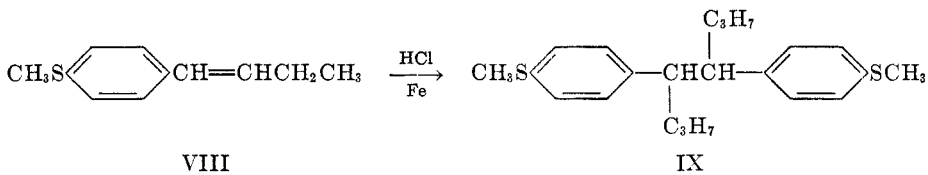
chloride into 4-(α-chloropropyl)thioanisole (VI); this compound readily underwent the known coupling reaction shown by activated iron powder in aqueous medium (6), and gave in good yield a solid 3,4-di(4-methylmercaptophenyl) hexane, inferred by analogy with the synthesis of hexestrol to be the *meso* form (VII). Along with this product was obtained an oily isomer, probably impure *dl*-3,4-di(4-methylmercaptophenyl)hexane.

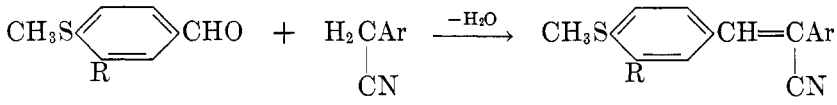


The Meerwein-Ponndorf reduction of 4-*n*-butyrylthioanisole [*p*-$CH_3SC_6H_4CO(CH_2)_2CH_3$] gave a secondary alcohol which was rather unstable towards heat, and was therefore directly dehydrated by anhydrous formic acid to 4-methylmercapto-β-ethylstyrene (VIII); the addition compound from this latter and hydrogen chloride underwent the coupling reaction with iron powder to give a solid 4,5-di(4-methylmercaptophenyl)octane, presumably the *meso* form (IX). Unfortunately, all attempts to demethylate this compound and its



lower homolog (VII) by routine dealkylation agents (pyridine hydrochloride, hydrobromic and hydriodic acids in acetic acid) met with failure. This demonstrates anew the difficulty of cleaving thioethers compared with the corresponding oxygen compounds (7).

In the field of stilbene derivatives bearing thioether groups, the alkali-catalyzed condensation of 4-methylmercaptobenzaldehyde (thioanisaldehyde) (X) with various substituted arylacetonitriles readily yielded a series of 1-aryl-2-(4-methylmercaptophenyl)acrylonitriles of the general formula XII. These compounds are listed in Table I, along with their higher homologs, the 1-aryl-2-(3-methyl-4-methylmercaptophenyl)acrylonitriles (XIII), similarly prepared from 3-methyl-4-methylmercaptobenzaldehyde (XI). The halogen-containing acrylonitriles were of special interest to us, in view of the known unfavorable effect of nuclear halogens on estrogenic activity. When 2-thienylacetonitrile was condensed with the aldehydes X and XI, 1-(2-thienyl)-2-(4-methylmercaptophenyl)-acrylonitrile (XIV) and 1-(2-thienyl)-2-(3-methyl-4-methylmercaptophenyl)-



X R = H
XI R = CH_3

XII R = H
XIII R = CH_3

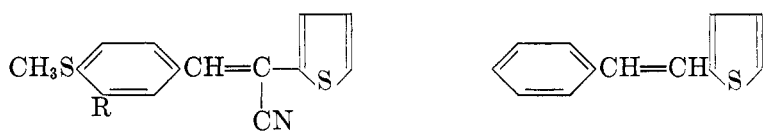
acrylonitrile (XV) were obtained. These are derivatives of 2-styrylthiophene (XVI), a compound already found to be far less estrogenic than *trans*-stilbene.

TABLE I

1,2-DISUBSTITUTED ACRYLONITRILES OF TYPES XII, XIII, XIV, AND XV

SUBSTITUENTS	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
1-Phenyl-2-*p*-methylmercaptophenyl-	$C_{16}H_{13}NS$	96	76.5	5.2	76.4	5.1
1-*p*-Tolyl-2-*p*-methylmercaptophenyl-	$C_{17}H_{15}NS$	113	77.0	5.7	76.8	5.8
1-*p*-Fluorophenyl-2-*p*-methylmercaptophenyl-	$C_{16}H_{12}FNS$	117	71.4	4.5	71.0	4.8
1-*p*-Chlorophenyl-2-*p*-methylmercaptophenyl-	$C_{16}H_{12}ClNS$	100	67.1	4.2	66.8	4.2
1-*p*-Bromophenyl-2-*p*-methylmercaptophenyl-	$C_{16}H_{12}BrNS$	131	58.2	3.6	58.0	3.8
1-*p*-Iodophenyl-2-*p*-methylmercaptophenyl-	$C_{16}H_{12}INS$	135	50.9	3.2	50.6	3.5
1-(2-Thienyl)-2-*p*-methylmercaptophenyl-	$C_{14}H_{11}NS_2$	89	65.4	4.3	65.3	4.3
1-Phenyl-2-(3-methyl-4-methylmercapto-phenyl)-	$C_{17}H_{15}NS$	99	77.0	5.7	77.1	5.9
1-*p*-Tolyl-2-(3-methyl-4-methylmercapto-phenyl)-	$C_{18}H_{17}NS$	96	77.4	6.1	77.2	6.2
1-*p*-Fluorophenyl-2-(3-methyl-4-methyl-mercaptophenyl)-	$C_{17}H_{14}FNS$	123	72.1	4.9	72.0	5.2
1-*p*-Chlorophenyl-2-(3-methyl-4-methyl-mercaptophenyl)-	$C_{17}H_{14}ClNS$	134	68.0	4.7	67.7	4.8
1-*p*-Bromophenyl-2-(3-methyl-4-methyl-mercaptophenyl)-	$C_{17}H_{14}BrNS$	132	59.3	4.1	59.0	4.1
1-*p*-Iodophenyl-2-(3-methyl-4-methyl-mercaptophenyl)-	$C_{17}H_{14}INS$	152	52.2	3.6	51.9	3.8
1-(2-Thienyl)-2-(3-methyl-4-methyl-mercaptophenyl)-	$C_{15}H_{13}NS_2$	98	66.4	4.8	66.6	4.8

4-Methylmercapto- and 3-methyl-4-methylmercapto-benzaldehyde were best prepared, using a Sommelet reaction, from 4-methylmercapto- (XVII) and

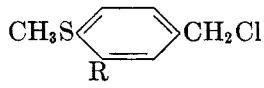


XIV R = H
XV R = CH_3

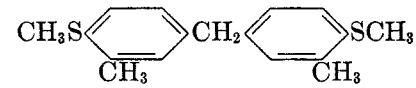
XVI

3-methyl-4-methylmercapto-benzyl chloride (XVIII), obtained conveniently by chloromethylating thioanisole and *o*-thiocresol methylether with chloromethyl

ether. In the chloromethylation of *o*-thiocresol methylether, 3,3′-dimethyl-4,4′-di(methylmercapto)diphenylmethane (XIX) was obtained as a by-product.

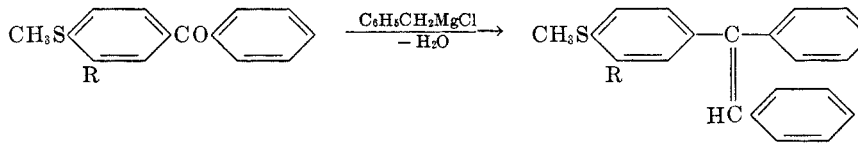


XVII R = H
XVIII R = CH_3



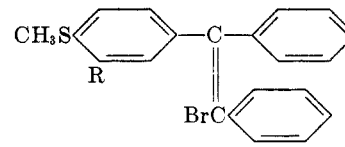
XIX

In the 1,2,2-triphenylethylene series, in which the presence of alkyloxy groups in *para*-positions is known to enhance the estrogenic activity (8), we prepared 1,2-diphenyl-2-*p*-methylmercaptophenylethylene (XXII) by reacting benzylmagnesium chloride with 4-methylmercaptobenzophenone (XX), and dehydrating the intermediary carbinol with anhydrous formic acid (9); bromination of this compound in acetic acid readily yielded 1-bromo-1,2-diphenyl-2-*p*-methylmercaptophenylethylene (XXIV). The same sequence of reactions, applied to 3-methyl-4-methylmercaptobenzophenone (XXI), similarly gave 1-bromo-1,2-phenyl-2-(3-methyl-4-methylmercaptophenyl)ethylene (XXV) *via* 1,2-diphenyl-2-(3-methyl-4-methylmercaptophenyl)ethylene (XXIII).



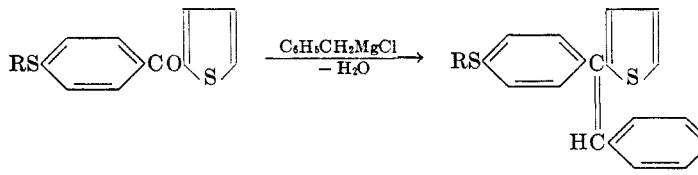
XX R = H
XXI R = CH_3

XXII R = H
XXIII R = CH_3



XXIV R = H
XXV R = CH_3

Similar substances bearing thiophene nuclei in addition to thioether groups have also been synthesized: 1-phenyl-2-*p*-methylmercaptophenyl-2-(2-thienyl) ethylene (XXVIII) and 1-phenyl-2-*p*-ethylmercaptophenyl-2-(2-thienyl)ethylene (XXIX) were prepared by the routine Grignard reaction between benzylmagnesium chloride and 2-*p*-methylmercaptobenzoylthiophene (XXVI) and 2-*p*-ethylmercaptobenzoylthiophene (XXVII) respectively.



XXVI R = CH_3
XXVII R = C_2H_5

XXVIII R = CH_3
XXIX R = C_2H_5

Preliminary biological investigations, to be fully reported elsewhere, show all the substances described herein to be inactive or but feebly active in the Allen-Doisy test; they are now being investigated as possible antagonists of estrogens and as potential inhibitors of the follicle-stimulating pituitary hormone. In bacteriological testings, the thiosemicarbazones of 4-methylmercaptobenzaldehyde and 3-methyl-4-methylmercaptobenzaldehyde have proved to be strongly tuberculostatic *in vitro*; detailed results will be reported elsewhere.

EXPERIMENTAL

4-(α-Hydroxypropyl)thioanisole (V). The starting 4-propionylthioanisole was obtained in 80% yield by a Friedel-Crafts reaction between 30 g. of thioanisole, 24 g. of propionyl chloride, and 40 g. of aluminum chloride in carbon disulfide (200 ml.). A mixture of 35 g. of this ketone, 50 g. of aluminum isopropoxide, and 200 ml. of anhydrous 2-propanol was gently refluxed with removal of acetone until the latter could no longer be detected in the distillate. After cooling, the reaction product was treated with cold dilute hydrochloric acid, and extracted with ether; the ether solution was washed with an aqueous solution of sodium carbonate, then with water, dried over sodium sulfate, the solvent removed and the residue vacuum-fractionated. Yield, 98% of a pale yellow, rather viscous oil, boiling at 160–162°/17 mm.

Anal. Calc'd for $C_{10}H_{14}OS$: C, 65.9; H, 7.7.
Found: C, 65.9; H, 7.9.

meso-3,4-Di(4-methylmercaptophenyl)hexane (VII). The alcohol (V, 30 g.) was saturated at 0° with dry hydrogen chloride; the crude oily 4-(α-chloropropyl)thioanisole thus obtained was washed three times with ice-water, and added in small portions to a well-stirred suspension of 12 g. of pure hydrogen-reduced iron powder in 200 ml. of hot water (about 95°). An immediate reaction began, which was visible by the greenish coloration of the water. When the reaction had subsided, the mixture was brought to the boil, and left overnight at room temperature; a partial crystallization of the reaction product resulted. This was taken up in hot benzene, the benzene solution was washed with water and dried over sodium sulfate, and the solvent largely removed. After cooling, the solid obtained was collected, and gave on recrystallization from ethanol, long colorless needles, m.p. 155–156°; yield, 25%.

Anal. Calc'd for $C_{20}H_{26}S_2$: C, 72.7; H, 7.9.
Found: C, 72.5; H, 8.0.

Attempts at demethylation with either redistilled pyridine hydrochloride (6) or HBr and HI in acetic acid, resulted in almost complete recovery of the starting material. The benzene mother-liquors gave on vacuum-fractionation some *4-propenylthioanisole* (thioanethole) in the form of a fluid, colorless liquid, b.p. about 146–148°/17 mm., having an odor reminiscent of anethole, and solidifying in the refrigerator to large prisms which melted at room temperature (23°).

Anal. Calc'd for $C_{10}H_{12}S$: C, 73.2; H, 7.3.
Found: C, 73.0; H, 7.3.

The higher-boiling portions consisted mostly of a pale yellow, viscous oil, b.p. 256–258°/17 mm., which solidified partly, giving some of compound VII, the oily residue probably being the *dl*-isomer.

4-n-Butyrylthioanisole. To an ice-cooled solution of 30 g. of thioanisole and 30 g. of *n*-butyryl chloride in carbon disulfide (200 ml.), 40 g. of powdered aluminum chloride was added in small portions with stirring. After seven hours' standing at room temperature, the mixture was treated in the usual way, giving 45 g. (95% yield) of a ketone, b.p. 187°/17 mm., crystallizing from ligroin in fine colorless prisms, m.p. 66–67°, and giving a brown-yellow color with sulfuric acid.

Anal. Calc'd for $C_{11}H_{14}OS$: C, 68.0; H, 7.2.
Found: C, 67.7; H, 7.2.

p-Methylmercapto-β-ethylstyrene (VIII). The preceding ketone, (30 g.) was reduced by

33 g. of aluminum isopropoxide in 200 ml. of 2-propanol as for the lower homolog. The crude alcohol obtained was dehydrated by ten minutes' boiling with 4 times its weight of 98% formic acid; the resulting ethylene was taken up in benzene, and the benzene solution washed with an aqueous solution of sodium carbonate, then with water, and dried over sodium sulfate. After removal of the solvent, the residue gave on vacuum-distillation a fluid, colorless liquid, b.p. 153°/15 mm., with a less pronounced aniseed odor than the lower homolog.

Anal. Calc'd for $C_{11}H_{14}S$: C, 74.2; H, 7.9.
Found: C, 74.1; H, 8.0.

meso-4,5-Di(4-methylmercaptophenyl)octane (IX). The preceding compound readily absorbed hydrogen chloride, and the crude oily 4-(α-chloro-*n*-butyl)thioanisole was treated with iron powder in the usual way. The coupling product formed fine colorless needles from ethanol, melting at 112°.

Anal. Calc'd for $C_{22}H_{30}S_2$: C, 73.7; H, 8.4.
Found: C, 73.4; H, 8.5.

Chloromethylation of thioanisole. A solution of 40 g. of thioanisole and 23 g. of chloromethyl methyl ether (CH_3OCH_2Cl) in acetic acid was gently heated at 70–80° on a water-bath for two days. After cooling, the reaction product was poured into water, the lower layer taken up in chloroform, the solution dried, the solvent removed, and the residue vacuum-fractionated. Yield, 13 g. of *p*-methylmercaptobenzyl chloride, a colorless, fluid liquid, boiling at 145°/17 mm., irritant to the mucous membranes.

Anal. Calc'd for C_8H_9ClS: Cl, 20.5. Found: Cl, 20.8.

The higher-boiling fraction consisted mainly of 2,4-*bis*-(chloromethyl)thioanisole [a compound previously found to be the sole product from chloromethylation of thioanisole (10)], and of a portion boiling at about 250°/17 mm., which was probably 4,4′-*bis*(methylmercapto)diphenylmethane.

4-Methylmercaptobenzaldehyde (X). A solution of 11 g. of chloromethylthioanisole and 13 g. of hexamethylenetetramine in acetic acid was gently refluxed for three hours, and the orange-colored reaction product then boiled for a further hour with water. The aldehyde formed was taken up in benzene, the benzene solution dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield, 8.5 g. of a pale yellow oil of pronounced aromatic odor, boiling at about 153°/17 mm., and giving with thiosemicarbazide a *thiosemicarbazone* crystallizing from ethanol in yellowish prisms melting at about 177–179°.

Anal. Calc'd for $C_9H_{11}N_3S_2$: N, 18.6. Found: N, 18.4.

Chloromethylation of o-thiocresol methylether. A solution of 40 g. of *o*-thiocresol methylether prepared in almost theoretical yield from *o*-thiocresol and methyl sulfate in alkaline medium) and 23 g. of chloromethyl methyl ether in 200 ml. of acetic acid, was treated as for the lower homolog. Yield, 16 g. of *3-methyl-4-methylmercaptobenzyl chloride* (XVIII), a fluid, pungent, colorless liquid boiling at about 154–155°/17 mm.

Anal. Calc'd for $C_9H_{11}ClS$: Cl, 19.0. Found: Cl, 19.3.

The higher-boiling portion consisted mainly of *3,3′-dimethyl-4,4′-di(methylmercapto)-diphenylmethane* (XIX), b.p. about 260°/17 mm., crystallizing from ligroin in fine colorless needles melting at 74°. Yield, 16 g.

Anal. Calc'd for $C_{17}H_{20}S_2$: C, 70.8; H, 6.9.
Found: C, 70.5; H, 7.0.

3-Methyl-4-methylmercaptobenzaldehyde (XI). A mixture of 15 g. of the preceding chloromethyl compound (XVIII) and 17 g. of hexamethylenetetramine was treated as for the lower homolog in acetic acid medium. Yield, 77% of a pale yellow oil with an aromatic odor, boiling at 166–168°/17 mm.

Anal. Calc'd for $C_9H_{10}OS$: C, 65.0; H, 6.0.
Found: C, 65.1; H, 6.2.

The corresponding *thiosemicarbazone* formed from ethanol or acetic acid pale yellow needles melting at about 208° (dec.).

Anal. Calc'd for $C_{10}H_{13}N_3S_2$: N, 17.6. Found: N, 17.3.

4-Methylmercaptobenzophenone (XX). To an ice-cooled solution of 15 g. of thioanisole

and 18 g. of benzoyl chloride in carbon disulfide (150 ml.), 20 g. of finely powdered aluminum chloride was added in small portions with stirring. After eight hours' standing at room temperature, the reaction product was worked up in the usual way, giving 25 g. (91% yield) of a *ketone* boiling at about 239°/17 mm., and crystallizing from methanol in shiny colorless leaflets, m.p. 76° (22 g.); it gives an orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{14}H_{12}OS$: C, 73.7; H, 5.2.
Found: C, 73.5; H, 5.5.

3-Methyl-4-methylmercaptobenzophenone (XXI) was similarly obtained in 92% yield from *o*-thiocresol methylether, 25 g. of benzoyl chloride, and 25 g. of aluminum chloride in carbon disulfide. The ketone formed from methanol fine colorless leaflets, m.p. 84°, giving with sulfuric acid an orange-yellow coloration.

Anal. Calc'd for $C_{15}H_{14}OS$: C, 74.4; H, 5.8.
Found: C, 74.3; H, 5.9.

1,2-Diphenyl-2-p-methylmercaptophenylethylene (XXII). To an ice-cooled ether solution of a Grignard reagent made from 3 g. of magnesium shavings and 12 g. of benzyl chloride, 15 g. of ketone XX was added in small portions. The mixture was subsequently refluxed for 15 minutes, and was decomposed with a cold dilute aqueous solution of sulfuric acid. The residue, after the evaporation of the solvent from the ether layer, was treated with boiling 98% formic acid to complete the dehydration of the crude carbinol. The reaction product was poured into water, taken up in benzene, and the benzene solution was washed with an aqueous solution of sodium carbonate, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 95% of a thick pale yellow oil, b.p. 272–274°/17 mm., which solidified on prolonged standing in ethanol, and which formed from that solvent after several crystallizations fine colorless needles, m.p. 100°, giving a red halochromic coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{18}S$: C, 83.4; H, 6.0.
Found: C, 83.3; H, 6.2.

1-Bromo-1,2-diphenyl-2-p-methylmercaptophenylethylene (XXIV). To a cooled solution of 8 g. of the preceding compound in acetic acid, 5 g. of bromine (dissolved in some ml. of acetic acid) was added dropwise with stirring. The reaction mixture was poured into water, and the solid obtained collected, washed with water, and recrystallized several times from ethanol. Fine shiny yellowish prisms were obtained, m.p. 131°, giving with sulfuric acid a brown-red coloration.

Anal. Calc'd for $C_{21}H_{17}BrS$: C, 66.1; H, 4.5.
Found: C, 66.0; H, 4.8.

1,2-Diphenyl-2-(3-methyl-4-methylmercaptophenyl)ethylene (XXIII) was obtained from 10 g. of ketone (XXI) and an ether solution of benzylmagnesium chloride (made from 6.5 g. of benzyl chloride and 1.3 g. of magnesium). This ethylene formed a thick pale yellow oil, boiling at 280°/17 mm., which did not solidify, and gave a red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{20}S$: C, 83.5; H, 6.3.
Found: C, 83.6; H, 6.2.

1-Bromo-1,2-phenyl-2-(3-methyl-4-methylmercaptophenyl)ethylene (XXV) was obtained as for the lower homolog from 9.5 g. of the preceding ethylene and 5 g. of bromine in acetic acid. It formed fine colorless prisms, m.p. 124°, from ethanol or acetic acid.

Anal. Calc'd for $C_{22}H_{19}BrS$: C, 66.8; H, 4.8.
Found: C, 66.5; H, 5.0.

1-Phenyl-2-p-methylmercaptophenyl-2-(2-thienyl)ethylene (XXVIII) was prepared in the usual way from 15 g. of 2-*p*-methylmercaptobenzoylthiophene (11), 12 g. of benzyl chloride, and 3 g. of magnesium. The reaction product boiled at about 276–278°/17 mm., and crystallized from acetic acid in large colorless flat prisms, m.p. 118°, giving with sulfuric acid a deep violet coloration.

Anal. Calc'd for $C_{19}H_{16}S_2$: C, 74.0; H, 5.2.
Found: C, 74.2; H, 5.1.

1-Phenyl-2-p-ethylmercaptophenyl-2-(2-thienyl)ethylene (XXIX) was similarly obtained

from 10 g. of 2-*p*-ethylmercaptobenzoylthiophenone (11), 8 g. of benzyl chloride, and 2 g. of magnesium. It crystallized from acetic acid in fine colorless needles, m.p. 60°, boiling at about 285–286°/17 mm., and giving with sulfuric acid a deep violet coloration.

Anal. Calc'd for $C_{20}H_{18}S_2$: C, 74.5; H, 5.6.

Found: C, 74.3; H, 5.8.

Preparation of the 1,2-disubstituted acrylonitriles XII, XIII, XIV, and XV. These were prepared by shaking equimolecular amounts of the aldehyde and arylacetonitrile (or 2-thienylacetonitrile) in warm ethanol with a few drops of 30% aqueous potassium hydroxide. In all cases, there occurred an almost immediate separation of either a solid or of an oil which rapidly solidified. The substances were collected, washed with water, and recrystallized from ethanol; they formed from pale (in the case of the non-halogenated acrylonitriles) to bright yellow shiny needles, giving with sulfuric acid deep halochromic colorations ranging from green to violet.

The *p*-halogenated arylacetonitriles and the 2-thienylacetonitrile were prepared according to the literature (12).

SUMMARY

1. Several new compounds related to the estrogens hexestrol, stilbene, and 1,2,2-triphenylethylene, and bearing either thioether groups or thiophene nuclei or both, have been synthesized for biological investigation.

2. A contribution is offered to the chemistry of the alkylethers of thiophenol and *o*-thiocresol.

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