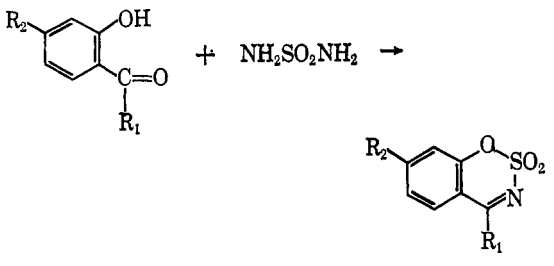

VIIa, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = C_6H_5$; $R_2 = CH_3O$-

dioxides (VII), a previously unreported heterocyclic system.

Experimental Section[5,6]

Procedure A. Preparation of 4-Methyl-1H-2,1,3-benzothiadiazine 2,2-Dioxide.—A mixture of 20.25 g. (0.15 mole) of 2-aminoacetophenone and 74 g. (0.75 mole) of sulfamide was heated at 140° with stirring for 2 hr. An additional 74 g. of sulfamide was added and stirring and heating were continued at 180–190° for 6 hr. After cooling, the mixture, consisting of a hard cake, was stirred thoroughly with 250 ml. of a 3% sodium hydroxide solution. The mixture was filtered and the filtrate was acidified with acetic acid. The precipitate was removed by filtration and purified by recrystallization.

Procedure B. Preparation of 1-Methyl-4-phenyl-2,1,3-benzothiadiazine 2,2-Dioxide (IIIa).—To 5.19 g. (0.02 mole) of 4-phenyl-1H-2,1,3-benzothiadiazine 2,2-dioxide was added 10 ml. of a 10% sodium hydroxide solution and 20 ml. of ethanol. The solution was cooled to 10°, 4 ml. of methyl iodide was added, and the mixture was stirred at room temperature for 24 hr., using an efficient reflux condenser on the reaction flask. Water (25 ml.) was added and the reaction mixture was filtered. There was obtained 3.65 g. of yellow platelets melting at 205–208°. Acidification of the filtrate with acetic acid gave 1.59 g. of recovered starting material.

1-Methyl-4-phenyl-2,1,3-benzothiadiazine 2,2-Dioxide (IIIa).—A mixture of 5.0 g. (0.024 mole) of N-methyl-o-aminobenzophenone[7] and 6.99 (0.72 mole) of sulfamide was heated at 170–180° for 24 hr. An additional 6.9 g. of sulfamide was added and the mixture was again heated at 170–180° for an additional 24 hr. The mixture was stirred with 25 ml. of water, then with 25 ml. of ether and filtered. There was obtained 5.04 g. (77%) of a tan solid melting at 204–206°. This material was identical with the material prepared by procedure B, as shown by a mixture melting point and comparison of infrared spectra.

4-Phenyl-3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-Dioxide (IV).—A solution of 12.9 g. (0.05 mole) of 4-phenyl-1H-2,1,3-benzothiadiazine 2,2-dioxide in 250 ml. of acetic acid was hydrogenated at an initial pressure of 3 atm. using 200 mg. of platinum oxide as catalyst. One mole of hydrogen was absorbed after 3 hr. The mixture was warmed to dissolve all of the organic material and the catalyst was removed by filtration. On cooling the solution, 2.76 g. of starting material precipitated. The acetic acid was removed from the filtrate by concentration *in vacuo* and the residue was recrystallized from ethanol. Filtration gave an additional 1.96 g. of starting material. The filtrate was again concentrated to dryness and the residue was recrystallized from benzene. There was obtained 3.0 g. (36%, based on recovered starting material) of yellow prisms melting at 133–136°. Additional recrystallization raised the melting point to 133.5–135°: λ_{max}^{EtOH} 228 mμ (sh) (ε 9100), 278 (3200), and 355 (710).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 60.51; H, 4.38; N, 11.03; S, 12.13.

4-Methyl-1,2,3-benzoxathiazine 2,2-Dioxide (VIIa).—A mixture of 13.165 g. (0.1 mole) of 2′-hydroxyacetophenone and 24 g. (0.25 mole) of sulfamide was stirred and heated in an oil bath at 130° for 1 hr. An additional 24 g. of sulfamide was added, heating was continued at 130° for 0.5 hr., and then the temperature was raised slowly to 180°. After heating the reaction mixture at this temperature for 3 hr. with stirring, the mixture was allowed to cool and was stirred with a mixture of 150 ml. of water and 150 ml. of methylene chloride. The organic layer was separated and the solvent was removed. There was obtained 8.25 g. (42%) of material melting at 114–118°. Recrystallization from ethanol gave tan prisms melting at 119–121°: λ_{max}^{EtOH} 264 mμ (ε 9950) and 308 mμ (ε 1700).

Anal. Calcd. for $C_8H_7NO_3S$: C, 48.73; H, 3.58; N, 7.10; S, 16.26. Found: C, 48.88; H, 3.62; N, 7.13; S, 15.94.

4-Phenyl-7-methoxy-1,2,3-benzoxathiazine 2,2-Dioxide (VIIb).—Utilizing the procedure described above for 4-methyl-1,2,3-benzoxathiazine 2,2-dioxide with an equivalent amount (22.8 g.) of 2-hydroxy-4-methoxybenzophenone there was obtained, after recrystallization of the crude product from isopropyl alcohol, 8.61 g. (30%) of light yellow prisms melting at 148.5–150°: λ_{max}^{EtOH} 241 mμ (sh) (ε 7800), 246 (7850), 302 (15,100), and 320 (14,700).

Anal. Calcd. for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.84; N, 4.84; S, 11.08. Found: C, 58.51; H, 3.66; N, 4.82; S, 11.37.

(5) All melting points are corrected.

(6) Microanalyses were performed by Mr. Norman Knight and associates and n.m.r. data were obtained by Dr. George Slomp and Mr. Forrest MacKellar of our Physical and Analytical Chemistry Department. The author is indebted also to Miss Lorraine Pschigoda for infrared spectral data, to Miss Betty Zimmer for the ultraviolet spectra data, and to Mr. Albert Lallinger for excellent technical assistance.

(7) L. H. Sternbach, *et al.*, *J. Org. Chem.*, **27**, 3787 (1962).

The Preparation of Mercaptomethyl Hydroquinones, Catechols, and Related Compounds

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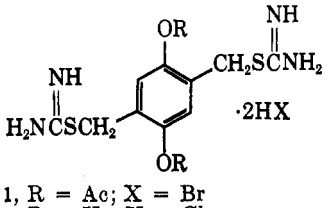
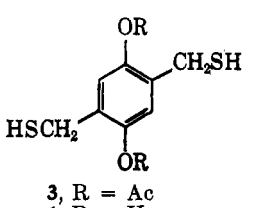
We have recently described[1] a synthesis of acetylated bromomethylphenols which makes mono- and poly(bromomethyl)hydroquinone and catechol diacetates readily available. We wish to report here results of our investigations dealing with the conversions of several of these intermediates into the corresponding mercaptomethyl derivatives.

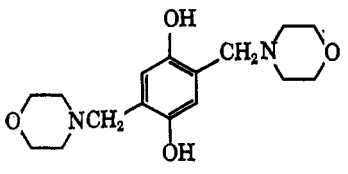
A general thiol synthesis which would appear to be applicable to our starting materials is the base cleavage of S-alkylthiuronium salts.[2] Bisisothiuronium salt **1** was therefore prepared and, in turn, allowed to react with morpholine under conditions known to be ef-



1, R = Ac; X = Br
2, R = H; X = Cl



3, R = Ac
4, R = H



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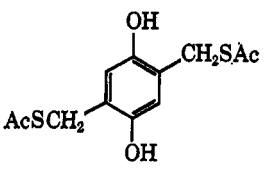
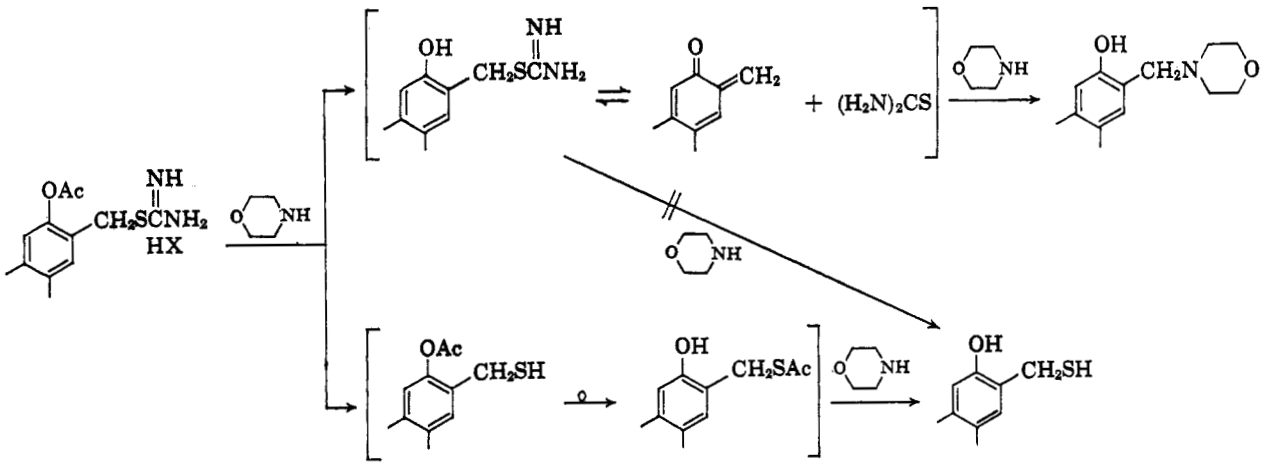


6

(1) D. L. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **29**, 2640 (1964).

(2) Benzyl bromide, for example, has been converted to benzyl mercaptan in 70–75% yield by this procedure: R. L. Frank and P. V. Smith, *J. Am. Chem. Soc.*, **68**, 2103 (1946).

CHART I



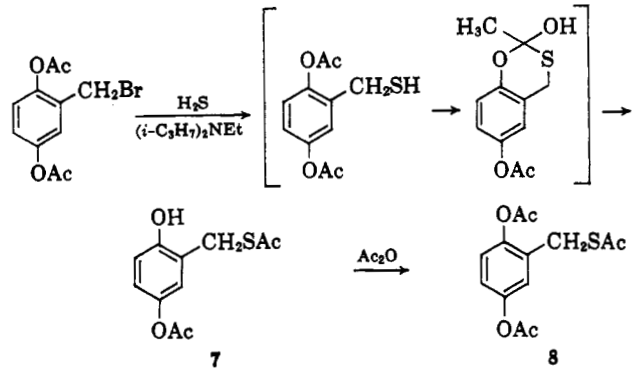
fective for thiol production.[3] A mixture of products resulted from which was isolated a low yield of the desired dithiol **4** and a 26% yield of **5**. It is suggested that these products result from competitive reactions shown in Chart I based on the fact that treatment of **6**[4] with morpholine gave **4** in 79% yield while similar treatment of **2** with morpholine gave **5** in 78% yield. Thus, these results show that neighboring acetoxy group participation need not be invoked to explain the unusual thiourea displacement by morpholine in the formation of **5**, but suggest instead the intermediacy of a quinone methide[5] as shown.

Since the isothiuronium salt route appeared to be impractical, attention was directed toward the synthesis of acetylthiomethyl derivatives which did prove to be satisfactory precursors of the desired mercaptomethyl phenols. These thiolacetates are available by the reaction of the bromomethylphenyl acetate with potassium thiolacetate, and in some instances this is the preferred synthesis. However, a more interesting and expedient route was developed which gave the thiolacetates of Table I in 92–96% yields (Chart II).

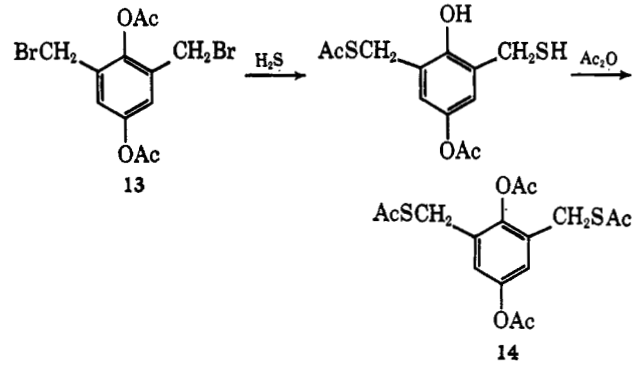
The experimental procedure consisted of adding the halide to a saturated methanolic hydrogen sulfide solution containing ethyl diisopropylamine.[6] After removal of solvent, acetylation of the crude reaction mixture with acetic anhydride afforded the easily isolable thiolacetate.

Typically, sulfide by-products are formed in alkylation reactions of hydrogen sulfide with reactive halides, the extent being governed by the experimental reaction conditions as well as the halide structure. For example, we find that benzyl sulfide is formed in 20 and 70% yields in methanol and methylene chloride, respectively, when this synthesis is applied to benzyl bromide. Interestingly, no detectable amount of sulfide was observed in analogous preparations of the thiolacetates of Table I. This is attributed to the fact that each bromomethyl precursor possesses one neighboring acetate group per bromomethyl group. This structural arrangement permits a rapid O → S acyl migration[4] to occur, thus preventing the thiol

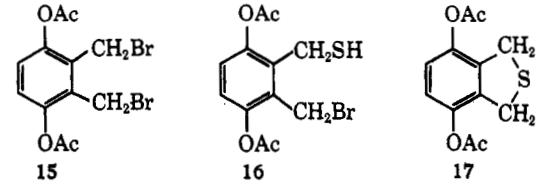
CHART II



from undergoing further reaction with starting halide. A compound not having this structural feature, namely **13**, then behaves like benzyl bromide and gives **14** as one component of an inseparable mixture.



The conversion of 2,3-bis(bromomethyl)hydroquinone diacetate (**15**) to **9** in 93% yield is a particularly interesting example of this synthesis. The 2-mercapto-3-bromomethyl intermediate **16** would seem to be ideally suited for ring closure to **17**.[7] Careful exami-



(3) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5116 (1961).

(4) Thiol **3** is unisolable owing to its rapid rearrangement to **6**. See J. B. Miller, D. L. Fields, and D. D. Reynolds, *ibid.*, **30**, 247 (1965).

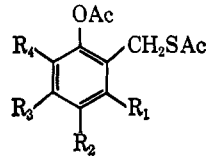
(5) A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

(6) S. Hünig and M. Kiessel, *Ber.*, **91**, 380 (1958).

(7) 1,3-Dihydroisothianaphthene, for example, is prepared from *o*-xylylene bromide and sodium sulfide, presumably *via* an intermediate analogous to **17**: J. v. Braun, *ibid.*, **58B**, 2165 (1925).

TABLE I

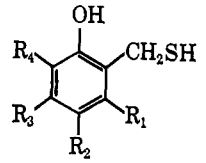
ACETYLTHIOMETHYLHYDROQUINONE AND -CATECHOL DIACETATES



Compd.	R_1	R_2	R_3	R_4	M.p., °C.	% yield	Calcd., % C	Calcd., % H	Calcd., % S	Found, % C	Found, % H	Found, % S
8	H	AcO	H	H	68–70	92	55.3	5.0	11.4	55.1	5.1	11.1
9	$AcSCH_2$	AcO	H	H	98–101	93	51.9	4.9	17.3	51.8	5.1	16.9
10	H	AcO	$AcSCH_2$	H	157–159	95	51.9	4.9	17.3	51.9	5.1	17.4
11	H	H	H	AcO	72–73	96	55.3	5.0	11.4	55.0	5.0	11.0
12	H	H	$AcSCH_2$	AcO	132–134	92	51.9	4.9	17.3	51.6	5.1	17.3

TABLE II

MERCAPTOMETHYLHYDROQUINONES AND -CATECHOLS

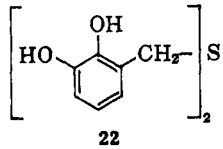


Compd.	R_1	R_2	R_3	R_4	M.p., °C. (b.p., °C.)	Calcd., % C	Calcd., % H	Calcd., % S	Found, % C	Found, % H	Found, % S
18	H	OH	H	H	124–126	53.8	5.1	20.5	54.2	5.4	20.5
19	CH_2SH	OH	H	H	152–155	47.6	5.0	31.7	47.8	5.3	31.6
4	H	OH	CH_2SH	H	192–194	47.6	5.0	31.7	47.9	5.2	31.9
20	H	H	H	OH	(72, 4 μ)[a]	53.8	5.1	20.5	54.2	5.5	20.8
21	H	H	CH_2SH	OH	79–80	47.6	5.0	31.7	47.9	5.1	31.8

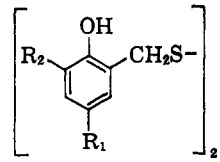
[a] $n^{25}D$ 1.6245.

nation of the crude reaction product by vapor phase chromatography (v.p.c.), however, indicated the presence of **9** uncontaminated by any appreciable amounts of impurity.

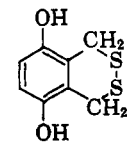
Deacetylation of the thiol acetates of Table I to the corresponding mercaptomethyl derivatives of Table II was readily effected by methanolysis with 1% methanolic hydrogen chloride giving, with the exception of **20**, white crystalline solids. Thiol **20**, a liquid, was isolated and purified by high vacuum distillation which was necessary since **20** was found to readily undergo pyrolysis with loss of hydrogen sulfide at temperatures in excess of 120° to yield **22**, quantitatively. Thiols **18, 19,** and **20** were further characterized as their respective disulfides **23, 25,** and **24.**



22



23, $R_1 = OH$; $R_2 = H$
24, $R_1 = H$; $R_2 = OH$



25

Experimental Section

2,5-Bis(acetoxy)-α,α′-*p*-xylylene Bisisothiuronium Dihydrobromide(1).—A mixture of 2,5-bis(bromomethyl)hydroquinone diacetate[1] (100 g., 0.263 mole) and thiourea (42 g., 0.55 mole) in 400 ml. of dimethylformamide was warmed at 60° for 20 min. The homogeneous solution was cooled, diluted with ether until crystallization commenced, and then refrigerated for 4 hr. at 5°, giving 114 g. (82%) of pure product, m.p. 230–232° dec.

Anal. Calcd. for $C_{14}H_{20}Br_2N_4O_4S_2$: C, 31.6; H, 3.8; N, 10.5; S, 12.0. Found: C, 31.7; H, 3.7; N, 10.3; S, 12.2.

2,5-Dihydroxy-α,α′-*p*-xylylene Bisisothiuronium Dihydrochloride (2).—Compound **2**, m.p. 223° dec., was obtained after refluxing a solution of **1** and 2% methanolic hydrogen chloride for 20 hr.

Anal. Calcd. for $C_{10}H_{16}Cl_2N_4O_2S_2$: C, 33.4; H, 4.5; Cl, 19.8; S, 17.9. Found: C, 33.4; H, 4.6; Cl, 19.6; S, 17.8.

1 with Morpholine.—A mixture of **1** (31.0 g., 0.058 mole) and morpholine (100 g.) was heated on a steam bath for 2 hr. The mixture was concentrated under reduced pressure until relatively free of morpholine and then poured into 1 l. of cold water. The cloudy solution was extracted with two 250-ml. portions of chloroform and the chloroform extract was dried over sodium sulfate and then concentrated free of solvent to yield a partially crystalline residue. After the residue was washed with benzene, the residual crystals (4.6 g., 26%) proved to be **5** by melting point and by a comparison of the infrared spectrum with that of an authentic material.

The benzene filtrate was concentrated to a syrup from which was isolated a small amount of **4**.

2 with Morpholine.—In a similar manner **2** (20.0 g., 0.056 mole) and morpholine (100.0 g.) were heated on a steam bath for 2 hr. The mixture was concentrated to a crystalline mass, which was triturated in 1 l. of cold water. The product collected by filtration was recrystallized from benzene, giving 12.9 g. (78%) of pure **5**, m.p. 204–207°.

6 with Morpholine.—A mixture of **6**[4] (14.3 g., 0.05 mole) and morpholine (100.0 g.) in 100 ml. of ethanol was warmed at 60° for 30 min. The solution was cooled and poured into 500 ml. of cold water. A product (8.0 g., 79%), m.p. 192–194°, crystallized over a 2-hr. period and was shown to be **4** by mixture melting point and a comparison of its infrared spectrum with that of an authentic material.

Acetylthiomethyl Derivatives (See Table I).—An example of the procedure followed in the preparation of the thiol acetates of Table I is illustrated below.

A solution of ethyl diisopropylamine (52.0 g., 0.412 mole) in 400 ml. of methanol was saturated with hydrogen sulfide. As hydrogen sulfide was slowly bubbled into the stirred solution, 2-bromomethylhydroquinone diacetate[1] (57.4 g., 0.2 mole) was added in portions over a 10-min. period. The solvent was removed under reduced pressure.

4-Acetoxy-2-acetylthiomethylphenol (7).—Compound **7**, m.p. 121–123°, could be isolated in 84% yield at this point by washing the solids with 500 ml. of water and recrystallizing the residual crystals from 80% aqueous ethanol.

Anal. Calcd. for $C_{11}H_{12}O_4S$: C, 55.0; H, 5.0; S, 13.3. Found: C, 54.7; H, 5.1; S, 13.0.

Phenol intermediates such as **7**, however, were not usually isolated, but, instead, were acetylated by refluxing the crude mixture of phenol and amine hydrobromide for 1 hr. in 500 ml. of acetic anhydride. The clear solution was concentrated to a syrup which was triturated in 1 l. of cold water. After standing for 1 hr. the crystals were collected, dried, and recrystallized from 80% aqueous ethanol.

When this thiolation procedure was applied to 2,6-bis(bromomethyl)hydroquinone diacetate (**13**), a difficultly separable mixture (m.p. 88–130°) containing **14** (by v.p.c.) was obtained. Authentic **14** was prepared by adding a solution of thiolacetic acid (60.8 g., 0.8 mole) and potassium hydroxide (39 g., 85% pure, 0.59 mole) in 300 ml. of ethanol to **13** (91 g., 0.24 mole) in 300 ml. of warm dimethylformamide. After standing for 30 min., the mixture was poured into 5 l. of cold water. The product crystallized over a 2-hr. period and was collected (76 g., 86%) and recrystallized as yellow plates from benzene–ligroin (b.p. 60–90°), m.p. 91–94°. Repeated recrystallizations from a variety of solvents as well as use of column chromatography failed to rid this material of a small amount of yellow impurity.

Anal. Calcd. for $C_{16}H_{18}O_6S_2$: C, 51.9; H, 4.9; S, 17.3. Found: C, 51.6; H, 5.1; S, 17.3.

Mercaptomethyl Derivatives (See Table II).—A mixture of 0.5 mole of a thiolacetate of Table I and 500 ml. of 1% methanolic hydrogen chloride was heated on a steam bath for 2 hr. With the exception of **20** the crystalline residue obtained after removal of the solvent was dissolved in 1 l. of ether and washed until neutral with 5% aqueous sodium bicarbonate. Concentration of the dried (sodium sulfate) ether layer to *ca.* 200 ml., followed by dilution with ligroin (b.p. 30–60°), yielded the desired crystalline product. Thiol **20** was purified by short-path distillation after the sodium bicarbonate neutralization step.

2,3-Dihydroxybenzyl Sulfide (22).—3-Mercaptomethylcatechol (**20**, 5.0 g., 0.032 mole) was heated in the presence of two crystals of sodium bicarbonate for 5 hr. at 130° under 5-mm. pressure. Sulfide **22** (4.5 g., 100%), m.p. 147–149°, crystallized from the hot melt. A recrystallization from ether–ligroin (b.p. 30–60°) did not change the melting point.

Anal. Calcd. for $C_{14}H_{14}O_4S$: C, 60.5; H, 5.0; S, 11.5. Found: C, 60.4; H, 5.3; S, 11.7.

Authentic **22** was prepared by allowing 3-bromomethylcatechol diacetate (14.35 g., 0.05 mole), **20** (7.8 g., 0.05 mole), and ethyl diisopropylamine (6.3 g., 0.05 mole) in 200 ml. of acetone to react at room temperature for 15 min. The mixture was concentrated to a syrup which, in turn, was placed in 400 ml. of ether and washed with 400 ml. of water. The ether layer was dried over sodium sulfate and concentrated to a syrup which was dissolved in 500 ml. of 1% methanolic hydrogen chloride. The syrup obtained after refluxing the solution for 4 hr., followed by removing the solvent, was dissolved in 500 ml. of ether and washed until neutral with 5% aqueous sodium bicarbonate solution. The desired product (**22**) crystallized after the ether solution was concentrated to 100 ml., followed by dilution with ligroin (b.p. 30–60°), and was identical in every respect with the product from the pyrolysis of **20**.

Disulfides.—Disulfides **23**, **24**, and **25** were prepared by a general procedure involving the iodometric titration (0.1 *N* iodine solution) of the thiol (5.0 g.) dissolved in 200 ml. of ether containing the stoichiometric quantity of pyridine to act as a hydrogen iodide scavenger. The ether layer was separated, washed with 100 ml. of water, and then concentrated to a crystalline residue.

Disulfide **23** was recrystallized from ethanol–ligroin (b.p. 30–60°) and had m.p. 195–197°.

Anal. Calcd. for $C_{14}H_{14}O_4S_2$: C, 54.2; H, 4.5; S, 20.7. Found: C, 54.3; H, 5.0; S, 20.3.

Disulfide **24** from ethyl acetate–ligroin had m.p. 115–119°.

Anal. Calcd. for $C_{14}H_{14}O_4S_2$: C, 54.2; H, 4.5; S, 20.7. Found: C, 54.0; H, 4.7; S, 20.7.

Disulfide **25**, m.p. 171–173°, was recrystallized twice from ether–ligroin

Anal. Calcd. for $C_8H_8O_2S_2$: C, 48.0; H, 4.0. Found: C, 48.7; H, 4.4.

The diacetate of **25** had m.p. 152–156° (ethanol).

Anal. Calcd. for $C_{12}H_{12}O_4S_2$: C, 50.7; H, 4.2; S, 22.5. Found: C, 50.7; H, 4.4; S, 22.5.

Quinone Methides. Base-Catalyzed Condensation Reactions of Hydroxybenzyl Alcohols and Ethers

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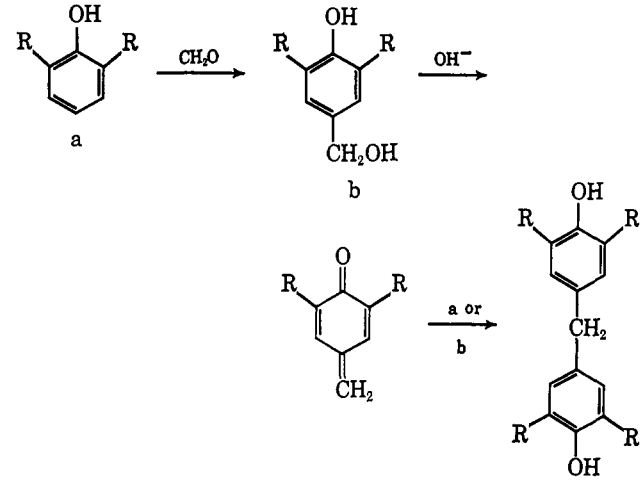
Received May 26, 1965

Of the products observed from the reaction of phenols with formaldehyde in basic medium, perhaps the most common are the diarylmethanes.[1-4] It is known that a hydroxybenzyl alcohol is initially formed and generally accepted that the symmetrical diarylmethane results from an intermediate quinone methide, *viz.*



Although this industrially important reaction is quite general, only a few attempts to utilize the intermediate quinone methide in rational syntheses have been reported. These include the use of phenol Mannich bases[5,6] and their methiodides and oxides[7] and sulfur analogs of these bases.[8]

We describe here the use of easily accessible hydroxybenzyl alcohols and their ethers as quinone methide precursors in syntheses which have proven to be very useful.

The reaction of 1-methoxymethyl-2-naphthol (I) (prepared from the methiodide of 1-dimethylaminomethyl-2-naphthol and sodium methoxide) with 2,6-

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