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BENZOXAZOLE DERIVATIVES. I. 2-MERCAPTOBENZOXAZOLES

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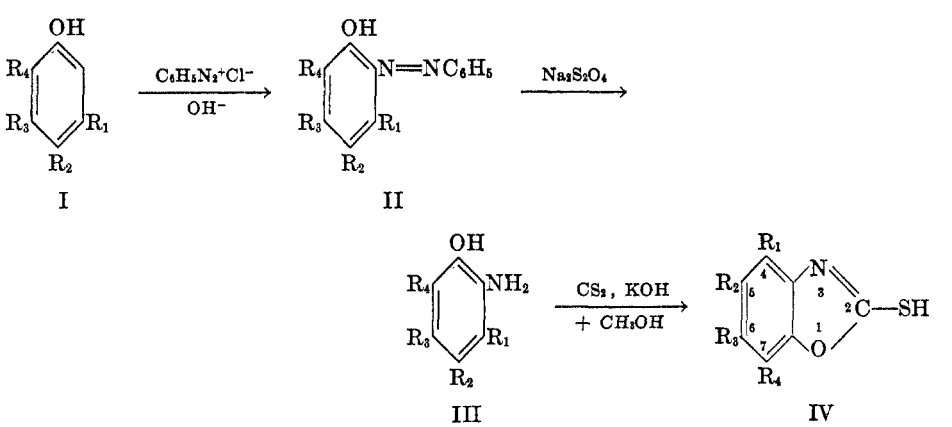
A perusal of the literature indicated that there has been relatively little interest shown in substituted 2-mercaptobenzoxazoles. Although the parent member of the series was synthesized in 1876 (1) and some substituted derivatives in 1889 (2) only three papers and two patents have been published since then describing any new members (3–7).

A systematic investigation of these compounds as potential chemotherapeutic agents was initiated in this laboratory as a result of the surprising fungicidal activity displayed by 2-hydrazinobenzoxazole (8) and also by the discovery that the presence of a sulfhydryl group in benzhydrazide derivatives (9) enhanced fungicidal activity (10).

Flow Sheet 1 illustrates the most expeditious method found for the preparation of substituted 2-mercaptobenzoxazoles (IV).

FLOW SHEET 1



A large selection of polysubstituted phenols (I) was fortunately available for this work. These compounds contained at least one substituent in the *para* position (R_2) and left at least one *ortho* position open to attack. Coupling with benzenediazonium chloride invariably took place at one of the open *ortho* positions and the 2-benzeneazo compounds (II) were isolated in good yields. The azo compounds could be reduced with little difficulty if a slight excess of sodium hydrosulfite was employed, extensive destructive oxidation supervening if no excess was present. The literature cites three reagents for the conversion of *o*-aminophenols (III) to 2-mercaptobenzoxazoles (IV); carbon bisulfide (1),

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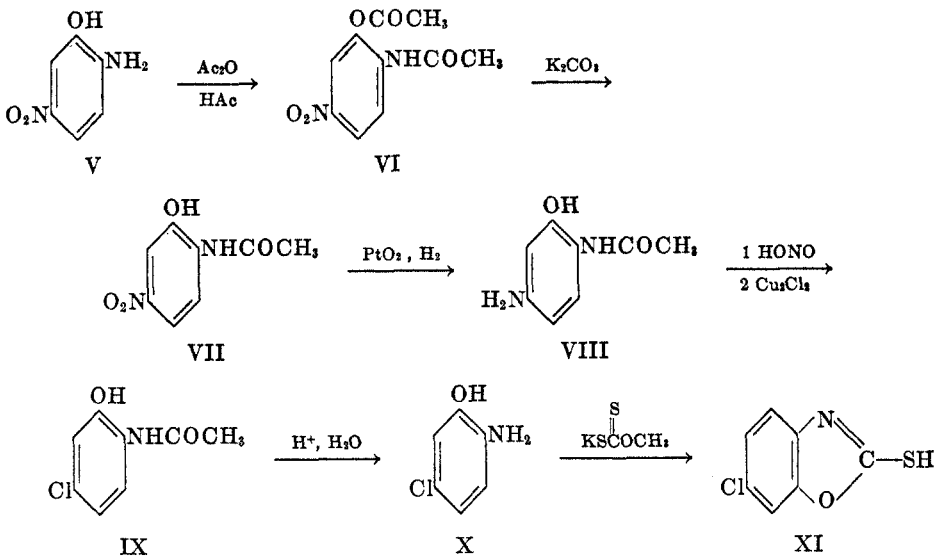
thiophosgene (3), and potassium alkyl xanthate (5). We found the last method to be successful although the reaction time required is 12–14 hours.

In some instances the requisite *o*-aminophenols were commercially available, thus obviating the coupling reaction. On the other hand a number of *o*-aminophenols, especially those with hydrogen in position 4 (R_2 = H) could be prepared only by making use of another route. 2-Amino-5-chlorophenol has been reported in the literature (11). It was prepared, however, through the difficultly obtainable 5-chloro-2-nitrophenol. The synthesis, outlined in Flow Sheet 2 made use

FLOW SHEET 2



of the commercially available 2-amino-5-nitrophenol (V). Acetylation afforded the O,N-diacetyl-2-amino-5-nitrophenol (VI) which was facilely hydrolyzed to 2-acetamino-5-nitrophenol (VII) and subsequently reduced to the 5-amino compound (VIII). The amino group was replaced by chlorine through the Sandmeyer procedure to produce 2-acetamino-5-chlorophenol (IX) and finally this was hydrolyzed to the free aminophenol (X). Condensation with potassium methyl xanthate gave the desired 6-chloro-2-mercaptobenzoxazole (XI).

Although 2-amino-6-chlorophenol has been mentioned in connection with tuberculosis research (12) details for its preparation could not be found. Ingold and Smith (13) prepared 6-chloro-2-nitrophenol by the nitration of *o*-chlorophenol and easily separated the volatile 6-isomer from the 4-isomer by steam-distillation. This procedure was found to be satisfactory and catalytic reduction afforded 2-amino-6-chlorophenol. This in turn was converted to 7-chloro-2-mercaptobenzoxazole in the usual manner.

In the preparation of 6-hydroxy-2-mercaptobenzoxazole the intermediary 4-aminoresorcinol was not isolated as a consequence of its easily oxidizable character. Instead the reaction mixture obtained by the acid hydrolysis of

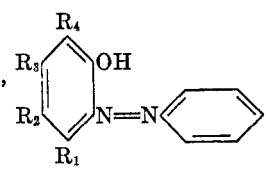
4-benzamidoresorcinol (14) was neutralized with potassium methyl xanthate and caused to react with an excess of this reagent.

In one instance it was surprising to find that the azo coupling reaction failed to yield a 2-benzeneazo derivative of sufficient purity for further work. This was the case when *p*-chlorothymol (4-chloro-2-isopropyl-5-methylphenol) was coupled with benzenediazonium chloride. An azo dye was isolated in the form of a heavy, dark-colored oil. Reduction of this substance with alkaline hydrosulfite failed to yield any crystalline material. The desired aminophenol was eventually prepared by mild nitration of *p*-chlorothymol. The 4-chloro-6-isopropyl-3-methyl-2-nitrophenol was not isolated but was reduced directly to the amino compound. Treatment with potassium methyl xanthate yielded the highly substituted 5-chloro-7-isopropyl-2-mercapto-4-methylbenzoxazole.

Both 2-mercapto-5-nitrobenzoxazole (4) and 2-mercapto-6-nitrobenzoxazole (5) have been described. Preparations in this laboratory however were found to melt significantly higher. At first it was thought that a new isomer had been isolated but reduction of the 6-nitro compound synthesized in this laboratory resulted in a substance whose melting point agreed with that reported for 6-amino-2-mercaptobenzoxazole (5). It is felt therefore that Deck and Dains (4) are correct in proposing that the nitro group undergoes a certain degree of

TABLE A

2-BENZENEAZOPHENOLS,



R_1	R_2	R_3	R_4	YIELD, %	M.P.,[a] °C.	EMPIRICAL FORMULA	ANALYSES C Calc'd	ANALYSES C Found	ANALYSES H Calc'd	ANALYSES H Found
H	OCH_3[b]	H	H	87	72–73[c]	$C_{13}H_{12}N_2O_2$[f]				
H	$OCH_2\phi$	H	H	90	92–92.5	$C_{19}H_{16}N_2O_2$[e]	75.00	75.05	5.26	5.28
H	CH_3	H	CH_3	50	88.5–90	$C_{14}H_{14}N_2O$[f]	74.31	74.35	6.24	6.00
H	*t*-Bu[d]	H	H	90	69–70	$C_{16}H_{18}N_2O$[g]	76.16	75.98	6.39	6.56
H	*t*-Bu	H	Cl	83	129–130	$C_{16}H_{17}ClN_2O$[g]	66.54	66.61	5.94	5.96
H	Cl	H	Cl	90	124–125	$C_{12}H_8Cl_2N_2O$[g]	53.96	54.28	3.01	3.05
Cl	H	Cl	Cl	81	144–145	$C_{12}H_7Cl_3N_2O$[h]	47.79	48.20	2.34	2.60

[a] M.p. for pure samples; all m.p.'s are uncorrected. [b] Compound originally prepared by Close, Tiffany, and Spielman, *J. Am. Chem. Soc.*, **71**, 1265 (1949); m.p. 72.5–75.5°. [c] All compounds crystallized from varying concentrations of aqueous alcohol. [d] Preparation described in Experimental section. [e] This compound prepared by Mr. Lawrence Karger. [f] Starting phenol obtained from Eastman Kodak Chemical Company. [g] Starting phenol obtained from Antara Chemical Company. [h] Starting material obtained from Hooker Chemical Company.

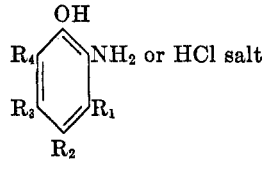
reduction when 2-amino-4- or 5-nitrophenol is caused to react with potassium methyl xanthate. This would account for discrepancies in melting points and for the significantly lower yields encountered in the preparation of these nitrobenzoxazoles.

Hydroquinone monomethyl ether had been coupled with benzenediazonium chloride by Close, *et al.* (15). This work was repeated for the preparation of 2-mercapto-5-methoxybenzoxazole and was extended to the monobenzyl ether of hydroquinone. As in the case of 2-amino-4-methoxyphenol, the 4-benzyloxy isomer could best be stored without decomposition in the form of its hydrochloride.

Table A lists the *o*-benzeneazophenols (II) prepared through the coupling of benzenediazonium chloride and the corresponding phenol (I). Table B is a tabulation of *o*-aminophenols (III) prepared either by reduction of *o*-benzene-

TABLE B

2-AMINOPHENOLS,

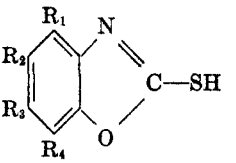


R_1	R_2	R_3	R_4	YIELD, %	M.P.,[a] °C.	EMPIRICAL FORMULA	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
H	OCH_3[b,c]	H	H	80	209–211[i]					
H	$OCH_2\phi$[b]	H	H	81	189–190[j]	$C_{13}H_{14}ClNO_2$	62.03	62.21	5.61	5.66
H	CH_3	H	CH_3	95	131–132[k]	$C_8H_{11}NO$	70.04	70.30	8.08	7.95
H	*t*-Bu	H	H	94	158–159[l]	$C_{10}H_{15}NO$	72.68	72.59	9.15	8.95
H	*t*-Bu	H	Cl[f]	70	105–106[l]	$C_{10}H_{14}ClNO$	60.15	60.20	7.07	7.11
H	H	H	Cl[f]	72	79–80[l]	C_6H_6ClNO	50.21	50.04	4.18	4.38
H	H	Cl[d,f]	H	76	153–155[m]					
CH_3	Cl	H	*i*-Pr[f,g]	51	79–81[n]	$C_{10}H_{14}ClNO$	60.15	60.51	7.07	6.99
H	Cl	H	Cl[b,e]	62	280–285[h,o]					
Cl	Cl	H	Cl	86	125–127[p]	$C_6H_4Cl_2NO$	33.91	34.07	1.90	1.98

[a] M.p. for pure samples; all m.p.'s uncorrected. [b] Isolated in form of hydrochloride salt. [c] Close, Tiffany, and Speilman, *J. Am. Chem. Soc.*, **71**, 1265 (1949). [d] Hodgson and Kirshaw, *J. Chem. Soc.*, 2073 (1928). [e] Hunter and Barnes, *J. Chem. Soc.*, 2056 (1928), give m.p. for free base as 109°. [f] Preparation described in experimental section. [g] Starting phenol obtained from Eastman Kodak Chemical Company. [h] Isolated as free base but recrystallized as hydrochloride; m.p. is that of HCl salt. [i] From alcohol. [j] From isopropyl alcohol-isopropyl ether as light purple leaflets. [k] From benzene petroleum ether (b.p. 30–60°) as white leaflets. [l] From cyclohexane as white leaflets. [m] From cyclohexane as white needles. [n] From petroleum ether (b.p. 30–60°) as white needles. [o] Free base dissolved in ether and precipitated as the hydrochloride by addition of ethereal hydrogen chloride. [p] From aqueous alcohol.

TABLE C

2-MERCAPTOBENZOXAZOLES,



No.	R_1	R_2	R_3	R_4	YIELD, %	M.P.,[a] °C.	EMPIRICAL FORMULA	ANALYSES C Calc'd	ANALYSES C Found	ANALYSES H Calc'd	ANALYSES H Found
1	H	H	H	H[b]	80	189–191[j]					
2	OH	H	H	H[g]	30	232–234[k]	$C_7H_5NO_2S$	50.28	50.34	3.01	3.09
3	H	H	OH	H	12	293–294[j]	$C_7H_5NO_2S$[i]	50.28	50.53	3.01	3.06
4	H	Cl	H	H[c,h]		260–261[j]					
5	H	H	Cl	H	48	224–225[l]	C_7H_4ClNOS	45.29	45.44	2.17	2.19
6	H	H	H	Cl	90	264–265[l]	C_7H_4ClNOS[i]	45.29	45.29	2.17	2.29
7	H	OCH_3	H	H	80	217–220[m]	$C_8H_7NO_2S$	53.02	53.06	3.89	3.95
8	H	$OCH_2\phi$	H	H	97	174–175[n]	$C_{14}H_{11}NO_2S$	65.35	65.64	4.31	4.37
9	H	NO_2	H	H[d,l]	29.5	244–245[o]	$C_6H_4N_2O_3S$	42.85	42.99	2.05	2.15
10	H	H	NO_2	H[e,h]	66	234–235[p]	$C_6H_4N_2O_3S$	42.85	43.11	2.05	2.29
11	H	NH_2	H	H	70	267–268[q]	$C_6H_6N_2OS$[i]	50.58	50.61	3.64	3.77
12	H	H	NH_2	H[f]	77	225–226[q]	$C_6H_6N_2OS$	50.58	51.18	3.64	3.93
13	H	NHAc	H	H	44	300–301[r]	$C_9H_8N_2O_2S$	51.91	51.85	3.87	4.03
14	H	H	NHAc	H	63	295–296[r]	$C_9H_8N_2O_2S$	51.91	51.90	3.87	4.01
15	H	*t*-Bu	H	H	63	125–126[q]	$C_{11}H_{13}NOS$	63.73	63.94	6.32	6.07
16	H	Cl	H	Cl	81	212–213[t]	$C_6H_3Cl_2NOS$	38.20	38.55	1.37	1.67
17	H	CH_3	H	CH_3	89	202–203[q]	C_9H_9NOS	60.30	60.11	5.06	5.38
18	H	*t*-Bu	H	Cl	74	194–195[u]	$C_{11}H_{12}ClNOS$	54.65	54.88	5.01	5.02
19	Cl	Cl	H	Cl	86	284–286[v]	$C_7H_2Cl_3NOS$	33.03	33.29	0.79	0.82
20	CH_3	Cl	H	*i*-Pr	87	197–200[w]	$C_{11}H_{12}ClNS$	54.65	55.04	5.01	5.52

[a] All m.p.'s are uncorrected. [b] Dunner, *Ber.*, **9**, 465 (1876) reported m.p. 196°. [c] Deck and Dains (4) report m.p. 261–262°. [d] Deck and Dains (4) report m.p. 235–238°. [e] Desai, *et al.*, (5) report m.p. 216–218°. [f] Desai, *et al.*, (5) report m.p. 228°. [g] Starting aminophenol obtained from Eastman Kodak Company. [h] Starting aminophenol obtained from Antara Chemical Company. [i] Preparation described in experimental section. [j] From aqueous alcohol as white leaflets. [k] From hot water as white needles. [l] From aqueous propanol-2 as white needles. [m] From aqueous alcohol as cream-colored rods. [n] From aqueous acetic acid as cream-colored rods. [o] From hot water, then chlorobenzene as tiny yellow rods. [p] From aqueous alcohol as yellow crystals, probably polymorphic (other form, m.p. 260°). [q] From aqueous alcohol as white needles. [r] From aqueous dimethylformamide as light pink needles. [t] From benzene as microscopic needles. [u] From benzene as white cubes. [v] From acetic acid as white leaflets. [w] From cyclohexane as white needles.

azophenols or *o*-nitrophenols. Table C summarizes all the 2-mercaptobenzoxazoles prepared either from *o*-aminophenols synthesized in this laboratory or those available commercially.

Microbiological activity. In Table D are contained the activities of the mer-

TABLE D

MICROBIOLOGICAL ACTIVITY (mcg./ml. necessary to completely inhibit growth)

No.	ORGANISM		
	Staph. aureus	*Proteus vulgaris*	*Brucella abortus*
2	>250	>250	125–250
3	>250	>250	250
4[a]	>250	>250	125–250
5	50–125	>250	50–125
6	50–125	>250	125–250
8	50–125	>250	50–125
15	50–125	125–250	125–250
16	50–125	125–250	12.5–25
17	125–250	>250	25–50
18	25–50	125–250	12.5–25
19	25–50	125–250	12.5–25
20	25–50	>250	25–50

[a] Tested as diethanolamine salt.

captobenzoxazoles expressed in mcg./ml. for complete inhibition of growth. It is apparent that substitution at both positions 5 and 7 is necessary for optimum effectiveness. Maximum activity is attained when this substitution is chlorine or a combination of alkyl and chlorine.

EXPERIMENTAL[3]

PREPARATION OF 2-SUBSTITUTED PHENOLS

A. o-Benzeneazophenols. The following is illustrative of the general method used to convert 4-methoxy-, 4-benzyloxy-, 4-*tert*-butyl-, 4,6-dichloro-, 4,6-dimethyl-, 4-*tert*-butyl-6-chloro-, and 2,4,5-trichloro-phenol to their *o*-benzeneazo derivatives. Table A lists the pertinent data for these compounds.

3,4,6-Trichloro-2-benzeneazophenol. A suspension of the sodium salt was prepared by adding 39.5 g. (0.20 mole) of 2,4,5-trichlorophenol to a solution of 24.5 g. (0.50 mole) of sodium hydroxide in 540 ml. of water. The mixture was heated to 90° to effect solution of the phenol and was then cooled below 10°. Benzenediazonium chloride, prepared from 18.6 g. (0.20 mole) of aniline, 250 g. of ice, 58 ml. of concentrated hydrochloric acid, and 14.3 g. (0.20 mole) of sodium nitrite, was added to the well stirred solution. Addition took one hour while the temperature was maintained at 10–15°. The deep-red, granular product separated from the reaction mixture while stirring was continued for one hour after the addition of diazonium solution was completed. The product was collected, washed with water, and dried. This crude material; m.p. 138–143°, weighed 48.0 g. (80%).

B. o-Nitrophenols. The following illustrates the method used to prepare 2-nitro-6-chlorophenol and 4-chloro-6-isopropyl-3-methyl-2-nitrophenol. The latter compound was not isolated but its reduction is described in the next section on *o*-aminophenols.

6-Chloro-2-nitrophenol. A modification of the method of Ingold and Smith (13) was followed in which a solution of *o*-chlorophenol (192.0 g., 1.5 moles), in 400 ml. of acetic acid was cooled to 10–20° and 144.0 g. (1.6 moles) of concentrated nitric acid was added over a period of 1½ hours, keeping the temperature below 20°. The reaction mixture was immediately poured onto ice and the gummy solid was separated. The 2-nitro-6-chlorophenol

[3] Analyses carried out by the Clark Microanalytical Laboratory, Urbana, Illinois.

steam-distilled as a yellow amorphous solid, m.p. 66–70°, which weighed 53.0 g. (20%). Recrystallization from water produced yellow needles, m.p. 70–71°.

PREPARATION OF *o*-AMINOPHENOLS

A. Chemical reduction of o-benzeneazophenols. The following is illustrative of the method used to convert 4-methoxy-, 4-benzyloxy-, 4-*tert*-butyl-, 4,6-dimethyl-, 4,6-dichloro-, 4-*tert*-butyl-6-chloro-, and 3,4,6-trichloro-2-benzeneazophenol to *o*-aminophenols. Table B lists the pertinent details.

2-Amino-4-tert-butylphenol. A suspension of 228.0 g. (0.90 mole) of 2-benzeneazo-4-*tert*-butylphenol was prepared in 3 l. of water containing 330 g. of sodium hydroxide. The dark red mixture was heated to 80° at which point heating was discontinued and sodium hydrosulfite (approx. 390 g.) was added over a period of 1½ hours. The exothermic reaction was capable of maintaining the 80° temperature for most of the reaction but external heating was applied during the addition of the last one-third of the sodium hydrosulfite. The suspension slowly turned to a straw-colored solution. A small excess of sodium hydrosulfite was added, and the solution was clarified with Darco and filtered. Concentrated hydrochloric acid was introduced until the solution was adjusted to *p*H 5–6. The cream-colored precipitate was collected, washed with water, and sucked dry under a rubber dam. The grey product was triturated with petroleum ether (b.p. 30–60°) and gave an almost colorless powder, m.p. 156–158°, which weighed 140.0 g. (94%). In the case of easily oxidizable *o*-aminophenols (4-methoxy, 4-benzyloxy) the free base was quickly extracted with ether and was converted to the hydrochloride by the addition of ether saturated with hydrogen chloride.

B. Catalytic reduction of nitrophenols. This section includes the reduction of 2-acetamino-5-nitrophenol along with the other steps in the synthesis of 2-amino-5-chlorophenol. The reduction of 4-chloro-6-isopropyl-3-methyl-2-nitrophenol is also described, although this nitro compound was not isolated.

2-Acetamino-5-nitrophenol. This compound was prepared by acetylation of 2-amino-5-nitrophenol in a modification of the method of Hewitt and King (16). Treatment of 16.8 g. (0.10 mole) of 2-amino-5-nitrophenol with 50 ml. of acetic anhydride in 150 ml. of acetic acid resulted in the formation of the O,N-diacetyl derivative; m.p. 190–191°, buff-colored, hair-like crystals [lit. (17); m.p. 187°), 11.0g. (46%). This product was converted to 2-acetamino-5-nitrophenol by simply dissolving it in hot 6 *N* potassium carbonate solution and collecting the deacetylated material after acidification with dilute acetic acid. 2-Acetamino-5-nitrophenol was isolated essentially pure and weighed 8.0 g. (88%); m.p. 259–260° [lit. (16), m.p. 271–272°].

2-Acetamino-5-aminophenol hydrochloride. This material was obtained by catalytic reduction (30 lbs./in.^{2}, 0.2 g. of platinum oxide for three hours) of 8.8 g. (0.045 mole) of 2-acetamino-5-nitrophenol in 175 ml. of Methyl Cellosolve.[4] The solution was rapidly filtered into 1 l. of dry ether containing 5.0 g. of hydrogen chloride and the product was collected, washed with hot ethyl acetate, ether, and dried. The crude hydrochloride, 9.2 g. (approx. quantitative) melted indistinctly. After dissolving it in hot isopropyl alcohol, decolorizing with charcoal, and adding hydrogen chloride-saturated ether to the clear filtrate, a product was obtained which melted at 203–205°. Purification was achieved by repeated precipitation from methyl alcohol with hydrogen chloride-saturated ether.

Anal. Calc'd for $C_{18}H_{11}ClN_2O_2$: C, 47.41; H, 5.47.

Found: C, 47.28; H, 5.71.

2-Acetamino-5-chlorophenol. A solution of 2-acetamino-5-aminophenol hydrochloride (10.1 g., 0.05 mole) in 25 ml. of water and 40 ml. of concentrated hydrochloric acid was treated with a solution of 5.1 g. (0.06 mole) of sodium nitrite in 10 ml. of water. The temperature was not allowed to rise above 0° during the addition. The cold diazonium solution was then added to a suspension of 5.9 g. (0.03 mole) of cuprous chloride in 50 ml. of 1:1 hydrochloric acid. The solution was stirred for one-half hour while the temperature was

[4] 2-Methoxyethanol.

raised to 40°. The greenish-grey product which separated was collected, washed with water, and dried to yield 7.2 g. (78%) of material; m.p. 168–177°. Recrystallization from aqueous isopropyl alcohol gave white needles; m.p. 188–189.5°.

Anal. Calc'd for $C_8H_8ClNO_2$: C, 51.76; H, 4.34.

Found: C, 52.08; H, 4.66.

2-Amino-5-chlorophenol. A solution consisting of 0.76 g. (0.004 mole) of 2-acetamino-5-chlorophenol in 5 ml. of 1:1 hydrochloric acid was heated under reflux for one-half hour. Neutralization of the reaction mixture resulted in the precipitation of white needles, 0.45 g. (75%); m.p. 153–155° [lit. (11), m.p. 154°].

2-Amino-4-chloro-6-isopropyl-3-methylphenol. To prepare 4-chloro-6-isopropyl-3-methyl-2-nitrophenol, the method previously described for 6-chloro-2-nitrophenol was employed. The yellow oil obtained from the nitration of 18.4 g. (0.10 mole) of *p*-chlorothymol (4-chloro-2-isopropyl-5-methylphenol) was steam-distilled. The distillate was extracted with 100 ml. of ether and this solution was placed in a Parr hydrogenation apparatus for reduction (platinum oxide catalyst, 30 lbs./in.^{2} pressure for two hours). After removal of the catalyst the colorless solution was diluted by the addition of 400 ml. of ether and dried. Hydrogen chloride gas was introduced until no further precipitation occurred. The hydrochloride salt was collected, washed with ether, and dried. The product weighed 12.0 g. (50% based on *p*-chlorothymol); m.p. 216–218°. Attempted crystallization from methyl ethyl ketone apparently resulted in some loss of hydrogen chloride for the melting point lowered significantly. Therefore the hydrochloride was dissolved in water and the free base was precipitated by the addition of sodium bicarbonate. The product was collected, dried, and recrystallized from petroleum ether (b.p. 30–60°) to give white needles; m.p. 79–81°.

PREPARATION OF 2-MERCAPTOBENZOXAZOLES

The following illustrates the method used to convert all *o*-aminophenols to 2-mercaptobenzoxazoles. In cases where the *o*-aminophenols existed as their hydrochlorides, sufficient sodium bicarbonate was added to transform them to the free base.

7-Chloro-2-mercaptobenzoxazole. A solution of potassium methyl xanthate was prepared by dissolving 3.6 g. of potassium hydroxide in 55 ml. of methanol and 10 ml. of water. Carbon disulfide (4.2 g., 0.055 mole), was added with stirring so that a clear yellow solution was formed. To this, 7.15 g. (0.05 mole) of 6-chloro-2-aminophenol was added and the mixture was heated under reflux for 15 hours. Hydrogen sulfide was evolved rapidly at first but at the time of completion of the reaction its odor was barely evident. The solution of the potassium salt was then cooled, decolorized with Darco, and filtered. The clear filtrate was heated to its boiling point and 10 ml. of acetic acid was added. The product separated almost immediately as a buff-colored solid which weighed 8.4 g. (90%); m.p. 258–262°.

6-Hydroxy-2-mercaptobenzoxazole. 2,4-Dihydroxybenzanilide (14) (32 g.) was boiled for one-half hour with 250 ml. of 1:1 hydrochloric acid under an atmosphere of nitrogen. The reaction was halted as extensive decomposition was evident. The cool reaction mixture was extracted with 100 ml. of ether. The aqueous layer was filtered, then taken to dryness *in vacuo*. Water was added to the solid residue and the insoluble material was removed. These insoluble solids which amounted to 20.0 g. proved to be starting material. The clear filtrate was neutralized by the addition of a solution containing 14.4 g. of potassium hydroxide, 16.8 g. of carbon disulfide, 40 ml. of water, and 150 ml. of methanol. This mixture was heated under reflux for three hours. At the end of this period the black solution was poured onto ice and water containing 30 ml. of acetic acid. A black solid was collected which was dissolved in hot acetic acid, treated with charcoal, and filtered. The filtrate, light pink in color, was evaporated to a volume of 5 ml. and 5 ml. of isopropyl ether was added. One gram of a pink powder separated which melted at 293–294°. This represents a yield of 12% based on unrecovered starting material.

CONVERSIONS WITHIN THE 2-MERCAPTOBENZOXAZOLE SERIES

6-Amino-2-mercaptobenzoxazole. The following method was used for the preparation of both 5- and 6-amino-2-mercaptobenzoxazoles. A beaker containing 250 ml. of water was

heated to 90–95° on a hot plate. Iron powder, 40.0 g., was introduced and then 2 ml. of concentrated hydrochloric acid was added. While stirring virogously 16.1 g. (0.086 mole) of 5-nitro-2-mercaptobenzoxazole was introduced over a period of one-half hour while the temperature was maintained between 80–92°. The reaction mixture turned black and was heated for an additional hour, then cooled. The iron was precipitated by the addition of 50 ml. of 5 *N* sodium hydroxide. The mixture was warmed to 50° and filtered through a filter aid. After washing the filter cake with three 50-ml. portions of warm water, the filtrate was cooled and neutralized. 5-Amino-2-mercaptobenzoxazole precipitated in pink flocks. It was collected, washed with water, and dried. The crude material weighed 13.5 g. but melted poorly. Recrystallization from ethanol gave 10.0 g. (75%) of white needles; m.p. 267.5–268°.

6-Acetamino-2-mercaptobenzoxazole. Essentially the same procedure was employed for the acetylation of both 5- and 6-amino-2-mercaptobenzoxazole. A solution containing 4.2 g. (0.025 mole) of 6-amino-2-mercaptobenzoxazole in 300 ml. of glacial acetic acid was heated to the boiling point. Acetic anhydride (10 ml.) was added and the solution was allowed to cool slowly. Crystals separated which were collected, washed with acetic acid, and dried. The product weighed 3.3 g. (63%); m.p. 292–293°. Recrystallization from aqueous dimethylformamide gave light tan needles; m.p. 295–296°.

SUMMARY

A series of new 2-mercaptobenzoxazoles has been prepared with substituents in all positions of the benzene ring. The intermediate *o*-benzeneazo- and *o*-aminophenols which heretofore were unknown have been characterized.

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