[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KENTUCKY AT LEXINGTON, AND THE GEORGETOWN UNIVERSITY MEDICAL SCHOOL, WASHINGTON, D. C.]

Introduction of Mannich Groups into Some Aromatic Phenolic Compounds[1a,1b]

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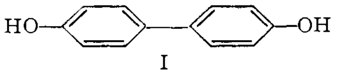
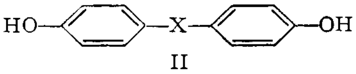
The Mannich reaction has been utilized for the addition of amino groups, such as $-CH_2NR_2$, to the nucleus of various types of phenolic compounds, of which 4,4′-bi-*o*-cresol is representative. Usually two Mannich groups were introduced in positions ortho to each of the OH groups.

The Mannich reaction has been used to prepare a number of amino derivatives of phenolic compounds whose physiological properties are being investigated. For this study certain mono- and dihydroxy compounds with two benzene rings, whether adjacent as in biphenyl or separated by some group X in the type formulas below, were selected as intermediates.

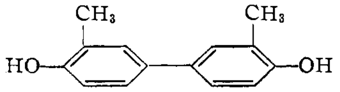


I

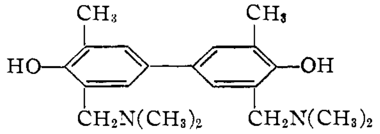


II

For instance, X in (II) above was represented by such groups as –S–, $-SO_2-$, –O–, –NH– and $-NCOCH_3-$. In order to simplify the products, intermediate phenols were selected which would favor the entrance of not more than two Mannich groups. Structure I above would permit the formation of a tetra-Mannich derivative, whereas a phenol such as 4,4′-bi-*o*-cresol (III), produced a crystalline di-Mannich derivative IV in 85–90% yield melting at 144°.



III



IV

Using methods similar to those of Burckhalter and co-workers,[3] the Mannich reaction was carried out usually in alcohol with a mixture of the appropriate phenol, formaldehyde and a secondary amine such as dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine. The phenols selected included the following: 4,4′-bi-*o*-cresol, 4,4′-thio-bis-(2,5-dimethylphenol), 4,4′-thio-bis-(2-isopropyl-5-methylphenol), 2,2′-thio-bis-(4,5-dimethylphenol), 2,2′-thio-bis-(4-chloro-5-methylphenol), 2,2′-thio-bis-(4-chloro-3-methylphenol), 2,2′-thio-bis-(4-chloro-3,5-dimethylphenol), 4,4′-oxy-bis-(2-chlorophenol), 4,4′-sulfonyl-bis-(2-acetamidophenol), *p*-anilinophenol and N-acetyl-*p*-anilinophenol.

It was necessary to synthesize many of the above thiobiphenols by using a modification of the method reported by Dunning, Dunning and Drake.[4] Those biphenols not previously described are listed in Table I. Two substances were recovered from the reaction products of 4-chloro-3-methylphenol with sulfur dichloride, and are presumed to be isomeric phenols.

The major reaction product of 3,4-dimethylphenol and sulfur dichloride was a substance, $C_{16}H_{18}SO_2$, obtained in 36% yield, m.p. 163°, to which the structure 2,2′-thio-bis-(4,5-dimethylphenol) is assigned. The only other product isolated appeared to be a disulfide.

Experimental

All melting points were taken with a Fisher–Johns apparatus, and are uncorrected. The analytical results were furnished by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

4,4′-Thio-bis-(2,5-dimethylphenol) was synthesized by a method similar to that of Dunning and co-workers.[4] The procedure was also used in the preparation of the other thiobiphenols mentioned in Tables I and II. Sixty-one grams (0.5 mole) of 2,5-dimethylphenol was dissolved in a mixture of 500 ml. of carbon tetrachloride and 75 ml. of carbon disulfide and cooled to about −15°. Sulfur dichloride, 0.25 mole (prepared by the slow addition of 8.9 g. of chlorine to 16.9 g. of sulfur monochloride in 80 ml. of carbon disulfide containing a pinch of powdered charcoal) was added slowly with constant stirring over a period of 1.5 hours, the temperature being maintained at −15°. Much hydrogen chloride was evolved through the condenser. A white powdery solid soon formed and remained suspended in the solution. Stirring was continued for an additional hour during which the temperature was allowed to rise to that of the room. A product weighing 39 g., m.p. 180–184°, was collected and recrystallized from benzene to give 34 g., 45–50%, of slightly yellow crystals, m.p. 187.5–189.0°. Analytical data are given in Table I.

With this and other similar preparations with sulfur dichloride, a large amount of an indefinite mixture of by-products was formed. On evaporating the solvent under diminished pressure, there remained 29.5 g. of a yellow oil from which it was very difficult to extract or separate any additional pure substances.

Disulfide Formation.—In the preparation of 2,2′-thio-bis-(4,5-dimethylphenol) from 3,4-dimethylphenol and sulfur dichloride (Table I, No. 2), a small amount of a yellow crystalline substance, m.p. 138–140°, was recovered as a by-product in less than 4% yield from the benzene mother liquors. Analysis indicated the approximate composition of a disulfide, $C_{16}H_{18}S_2O_2$: Calcd.: C, 62.80; H, 5.93; S, 20.96. Found: C, 63.62; H, 6.27; S, 19.72.

Preparation of Mannich Compounds.—A typical example is the preparation of the di-Mannich derivative of 4,4′-thio-bis-(2-isopropyl-5-methylphenol) (Table II, 5) from formaldehyde and dimethylamine: 33 g. (0.1 mole)

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[1] (a) Presented before the Division of Organic Chemistry, 124th Meeting of the American Chemical Society, Chicago, Ill., September 6–11, 1953. (b) Supported in part by a research grant from the Geschickter Fund for Medical Research, Inc. Acknowledgment is made for permission on the part of the Geschickter Fund to publish these results.

[2] Advisor to the Geschickter Fund for Medical Research.

[3] J. M. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlings, THIS JOURNAL, **68**, 1894 (1946); **70**, 1363 (1948).

[4] F. Dunning, B. Dunning and W. E. Drake, *ibid.*, **53**, 3466 (1931).

TABLE I

SYMMETRICAL THIO-BIPHENOLS

Name of Compound	M.p. °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4,4′-Thio-bis-(2,5-dimethylphenol)[a]	189[b]	50	$C_{16}H_{18}SO_2$	70.06	70.27	6.61	6.85	11.67	11.51
2,2′-Thio-bis-(4,5-dimethylphenol)[c]	163[b]	36	$C_{16}H_{18}SO_2$	70.06	70.26	6.61	6.62	11.67	11.52
2,2′-Thio-bis-(4-chloro-3,5-dimethylphenol)[d]	218[b]	38	$C_{16}H_{16}SCl_2O_2$	20.66 (Cl)	20.45 (Cl)			9.33	9.02
High melting point thiophenol[e] from 4-chloro-3-methylphenol	178[b]	27	$C_{14}H_{12}SCl_2O_2$	22.50 (Cl)	22.24 (Cl)			10.17	10.07
Low melting point thiophenol[f] from 4-chloro-3-methylphenol	157[g]	10	$C_{14}H_{12}SCl_2O_2$	22.50 (Cl)	22.37 (Cl)			10.17	10.41

[a] From 2,5-dimethylphenol. [b] From benzene solvent. [c] From 3,4-dimethylphenol. [d] From 4-chloro-3,5-dimethylphenol. [e,f] Apparently isomeric thiobiphenols from 4-chloro-3-methylphenol and sulfur dichloride. [g] Recovered from benzene mother liquor and recrystallized from *n*-heptane.

TABLE II

DI-MANNICH DERIVATIVES OF SOME SYMMETRICAL THIO-BIPHENOLS[a]

Substituents on each *o*-cresol ring	M.p., ° C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen % Calcd.	Nitrogen % Found
From 4,4′-thio-bi-*o*-cresols								
3,6-Dimethyl-α-dimethylamino[b]	129[c]	$C_{22}H_{32}SN_2O_2$	68.10	68.23	8.31	8.39	7.22	7.21
3,6-Dimethyl-α-diethylamino (HCl)	250[d] dec.	$C_{26}H_{40}SN_2O_2$[e]	60.38	60.53	8.19	8.48	5.41	5.03
3,6-Dimethyl-α-1-piperidyl (HCl)	255[d] dec.	$C_{28}H_{40}SN_2O_2$[e]	62.10	62.06	7.82	7.96	5.17	5.15
3,6-Dimethyl-α-4-morpholinyl	178[f]	$C_{26}H_{36}SN_2O_4$	66.16	66.40	7.69	7.82	5.94	5.79
6-Isopropyl-3-methyl-α-dimethylamino[g]	131[c]	$C_{26}H_{40}SN_2O_2$	70.23	70.27	9.07	8.89	6.30	6.13
6-Isopropyl-3-methyl-α-diethylamino	111.5[c]	$C_{30}H_{48}SN_2O_2$	72.06	72.20	9.68	9.70	5.60	5.93
6-Isopropyl-3-methyl-α-1-pyrrolidyl	128.5[h]	$C_{30}H_{44}SN_2O_2$	72.54	72.61	8.93	8.99	5.64	5.41
6-Isopropyl-3-methyl-α-1-piperidyl	156.5[h]	$C_{32}H_{48}SN_2O_2$	73.34	73.58	9.23	9.43	5.34	5.31
6-Isopropyl-3-methyl-α-4-morpholinyl	167[h]	$C_{30}H_{44}SN_2O_4$	68.24	68.44	8.40	8.22	5.31	5.51
From 6,6′-thio-bi-*o*-cresols								
3,4-Dimethyl-α-dimethylamino[i]	148.5[c]	$C_{22}H_{32}SN_2O_2$	68.10	68.14	8.31	8.16	7.22	7.46
3,4-Dimethyl-α-1-pyrrolidyl	129[c]	$C_{26}H_{36}SN_2O_2$	70.87	70.78	8.24	8.55	6.36	6.06
3,4-Dimethyl-α-1-piperidyl	174[h]	$C_{28}H_{40}SN_2O_2$	71.85	71.97	8.62	8.74	5.99	5.85
3,4-Dimethyl-α-4-morpholinyl	191[h]	$C_{26}H_{36}SN_2O_4$	66.16	66.17	7.69	7.66	5.94	6.16
4-Chloro-3(or 5)-methyl-α-dimethylamino[j]	173[h]	$C_{20}H_{26}SCl_2N_2O_2$	55.93	56.15	6.11	6.38	6.52	6.46
4-Chloro-5(or 3)-methyl-α-dimethylamino[k]	154[h]	$C_{20}H_{26}SCl_2N_2O_2$	55.93	55.98	6.11	6.34	6.52	6.51
4-Chloro-3-methyl-α-diethylamino[l]	153[c]	$C_{19}H_{23}SCl_2NO_2$[l]	57.05	56.94	5.80	5.82	3.52	3.72
4-Chloro-3-methyl-α-1-pyrrolidyl	164.5[m]	$C_{24}H_{30}SCl_2N_2O_2$	59.85	60.17	6.28	6.47	5.82	5.69
4-Chloro-3-methyl-α-1-piperidyl	205[m]	$C_{26}H_{34}SCl_2N_2O_2$	61.28	61.63	6.73	6.94	5.50	5.39
4-Chloro-3-methyl-α-4-morpholinyl	193[h]	$C_{24}H_{30}SCl_2N_2O_4$	56.12	56.18	5.89	6.19	5.45	5.31
4-Chloro-3,5-dimethyl-α-dimethylamino[n]	226[m] dec.	$C_{22}H_{30}SCl_2N_2O_2$	57.75	57.89	6.61	6.89	6.12	5.97
4-Chloro-3,5-dimethyl-α-diethylamino[l]	145[h]	$C_{21}H_{27}SCl_2NO_2$[l]	58.92	59.12	6.36	6.52	3.27	3.41
4-Chloro-3,5-dimethyl-α-4-morpholinyl	191[h]	$C_{26}H_{34}SCl_2N_2O_4$	57.67	57.97	6.33	6.58	5.17	4.90

[a] All compounds except second and third obtained as free Mannich bases in crystalline form. [b] Intermediate phenol synthesized from 2,5-dimethylphenol (see Experimental part). [c] From methanol. [d] Rx as crystalline dihydrochlorides from alcohol–ether. [e] Contains also 2HCl. [f] From acetone–petroleum ether first; followed by ethanol. [g] Intermediate phenol synthesized from thymol, m.p. 154°; melting point reported by Tassinari,[5] 152–153°; and by Dunning and associates,[4] 152.5–153.5°. [h] From ethanol. [i] Intermediate phenol prepared from 3,4-dimethylphenol. [j] From higher melting intermediate phenol from 4-chloro-3-methylphenol. [k] From lower melting intermediate phenol; from 4-chloro-3-methylphenol. [l] Obtained as the mono-Mannich derivative. [m] From benzene–methanol. [n] Intermediate phenol from 4-chloro-3,5-dimethylphenol.

of the phenol was dissolved in 100 ml. of ethanol, cooled, and 99 g. (0.55 mole) of a 25% solution of dimethylamine added slowly. To the cold mixture (0 to 5°) 30 g. (0.37 mole) of aqueous formaldehyde (37%) was gradually added over a 30-minute period with intermittent shaking. The temperature of the mixture was kept low during addition of formaldehyde. After standing 30 minutes to 1 hour at room temperature, the flask was placed on a water-bath and the solution refluxed gently for about 4 hours. The excess solvent was removed by distillation under reduced pressure, and the oily residue was then dissolved in a minimum amount of fresh warm methanol. The alcoholic solution was chilled and the mass of fine crystals formed was collected, 39 g., 87%, m.p. 125–128°. Recrystallization from methanol usually produced a white crystalline product, m.p. 130–131° (see Table II for analyses).

N-Acetyl Derivative of *p*-Anilinophenol.—Equimolar portions of *p*-anilinophenol, m.p. 67–68°, and acetic anhydride (0.05 mole) were refluxed in 24 ml. of glacial acetic acid for about three hours, cooled and an equal volume of water added. The lavender colored crystals which were deposited on standing in an ice-bath were collected and dried, 8 g. (70%). Two recrystallizations from aqueous

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(5) G. Tassinari, *Chem. Centr.*, **20**, 1354 (1888); *J. Chem. Soc.*, **56**, 245 (1889).

TABLE III

MISCELLANEOUS MANNICH DERIVATIVES OF SYMMETRICAL BIPHENOLS[a]

Substituents on each o-cresol ring	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
		From 4,4'-bi-*o*-cresol						
6-Methyl-α-dimethylamino[b]	144[c]	$C_{20}H_{28}N_2O_2$	73.23	73.40	8.60	8.86	8.54	8.65
6-Methyl-α-diethylamino[d]	75[e]	$C_{24}H_{36}N_2O_2$	75.06	75.02	9.45	9.60	7.29	7.47
6-Methyl-α-1-pyrrolidyl	135[c]	$C_{24}H_{32}N_2O_2$	75.75	75.73	8.48	8.78	7.36	7.35
6-Methyl-α-1-piperidyl	181[c]	$C_{26}H_{36}N_2O_2$	76.53	76.66	8.89	8.92	6.86	6.98
6-Methyl-α-4-morpholinyl	203[c]	$C_{24}H_{32}N_2O_4$	69.96	70.09	7.83	7.89	6.80	6.99
		From 4,4'-oxy-bis-(2-chlorophenol)						
6-Chloro-α-dimethylamino[f]	132[e]	$C_{18}H_{22}Cl_2N_2O_3$	56.11	56.35	5.76	5.87	7.27	6.99
6-Chloro-α-pyrrolidyl	159.5[e]	$C_{22}H_{26}Cl_2N_2O_3$	60.46	60.47	6.00	6.15	6.41	6.55
6-Chloro-α-piperidyl	166.5[c]	$C_{24}H_{30}Cl_2N_2O_3$	61.99	62.08	6.50	6.65	6.02	6.16
6-Chloro-α-4-morpholinyl	161.5[c]	$C_{22}H_{26}Cl_2N_2O_5$	56.34	56.52	5.59	5.83	5.95	5.66
		From 4,4'-sulfonyl-bis-(2-acetamidophenol)						
6-Acetamido-α-diethylamino[g]	178[h] dec.	$C_{26}H_{38}SN_4O_6$	58.40	58.58	7.16	7.25	10.48	10.36

[a] All derivatives obtained as free bases. [b] Full name of compound: 6,6'-dimethyl-bis-(α,α'-dimethylamino)-4,4'-bi-*o*-cresol. [c] From ethanol. [d] The dihydrochloride of this compound was reported by Burckhalter and co-workers,[3] m.p. 215°. [e] From methanol. [f] Complete name: 4,4'-oxy-bis-(6-chloro-α-dimethylamino-*o*-cresol). [g] Full name: 4,4'-sulfonyl-bis-(6-acetamido-α-diethylamino-*o*-cresol). [h] Yellow crystals from isopropyl alcohol–ether.

TABLE IV

DIMETHYLAMINOMETHYL DERIVATIVES OF *p*-ANILINOPHENOL[a]

Name of compound	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4-Anilino-2-dimethylaminomethylphenol	98.5[b]	$C_{15}H_{18}N_2O$	74.35	74.48	7.49	7.28	11.56	11.31
4-Anilino-2,6-bis-(dimethylaminomethyl)-phenol	117[c]	$C_{18}H_{25}N_3O$	72.29	72.19	8.43	8.72	14.03	13.71
4-(N-Acetyl-anilino)-2,6-bis-(dimethylaminomethyl)-phenol[d]	113[e]	$C_{20}H_{27}N_3O_2$	70.43	70.35	7.97	7.98	12.32	12.60

[a] Intermediate phenol was obtained from B. F. Goodrich Chemical Co. [b] From methanol. [c] From benzene–petroleum ether first, then two recryst. from benzene. [d] *p*-Anilinophenol was acetylated with Ac_2O before introduction of two Mannich groups. [e] Flesh colored crystals from benzene–petroleum ether.

methanol produced a pink or flesh-colored product, m.p. 164–165°. *Anal.* Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.17. Found: C, 73.93; H, 5.63; N, 6.25.

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Acetoxymethylation of Aromatic Compounds[1]

BY LAWRENCE SUMMERS

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Methoxymethyl acetate in acetic acid reacted with mesitylene, isodurene, pentamethylbenzene, *m*-xylene, anisole or diphenyl ether, in the presence of a trace of strong acid. With mesitylene, the products were 2,4,6-trimethylbenzyl acetate (up to 37%), bis-(2,4,6-trimethylphenyl)-methane (up to 15%), polymer (up to 72%) and recovered mesitylene. Lower temperatures or shorter reaction times led to optimum yields of the monomeric ester. Higher temperatures led to polymer as the almost exclusive product. Compared to chloromethylation, this acetoxymethylation reaction differs chiefly in the greater tendency toward polymer formation. This limits the utility of acetoxymethylation as a preparative method for the monomeric esters. The polymer is readily obtained in good yield. Isodurene gave 18%, and pentamethylbenzene 20%, of the monomeric esters. The other aromatic compounds mentioned gave largely polymer, as did mesitylene with methylene diacetate or with paraformaldehyde in acetic acid.

Solutions of chloromethyl methyl ether in acetic acid conceivably contain methoxymethyl acetate. The latter compound has been isolated after attempts to chloromethylate terpenes with such solutions.[2] Also, the preparation of α-butoxyethyl acetate in 85% yield by heating α-chloroethyl butyl ether with acetic acid has been described.[3] Acetic

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[1] Presented at the 124th Meeting of the American Chemical Society, Chicago, 1953; see Abstracts of Papers, p. 71–O.

[2] J. Allard, *Bull. soc. chim.*, 731 (1947).

[3] M. F. Shostakovskiĭ and A. V. Bogdanova, *Zhur. Obshcheĭ Khim.*, **17**, 565 (1947).