

Reactions of Dichloromaleimides with Alcohols, Phenols, and Thiols

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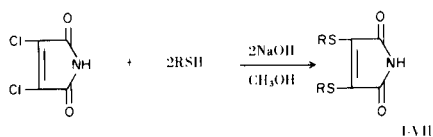
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Thiols react with dichloromaleimides in the presence of base to give 2,3-bis[alkyl(aryl)mercapto]maleimides. Alcohols and phenols in equivalent amounts give 2-alkyl(aryl)oxy-3-chloromaleimides. With two equivalents, phenols give 2,3-bis(aryloxy)maleimides, but alcohols give 2-chloro-3,3-dialkoxy succinimides in protic solvents and dimeric compounds in aprotic solvents.

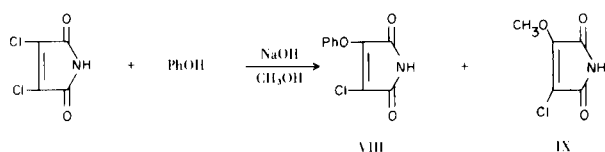
Although reactions of dihalomaleimides have been studied previously (1,2,3), reactions with alcoholates and phenolates have not been investigated, and until recently reactions with thiols (4,5) had not been reported with the exception of hydrogen sulfide (6). We have prepared a number of derivatives by nucleophilic substitution at the vinyl carbon atoms and have encountered some unexpected side reactions.

Mercaptans in alcoholic sodium hydroxide reacted readily with dichloromaleimide to give the bis substituted compounds I-VII (Table I). These compounds have

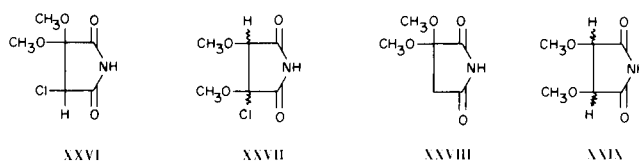


typical imide carbonyl absorptions in the infrared at 1730 (strong, broad) and 1780 (medium to strong, sharp) cm^{-1} with little or no carbon-carbon double bond absorption, which would be expected for a symmetrically substituted double bond. A careful attempt was made to prepare a monosubstituted compound (see Experimental) but a 77% yield (based on benzenethiol) of the bis derivative VII was obtained. A recent German patent (4) claims the preparation of monosubstituted alkylmercapto imides using 100% excess mercaptan with sodium acetate in acetic acid.

When the reaction with one equivalent of phenol was attempted in an effort to prepare VIII, a mixture was obtained from which VIII and IX were isolated in low yield. In contrast to the bis mercaptoimides these



unsymmetrical compounds have a strong carbon-carbon double bond absorption at about 1660 cm^{-1} . The formation of IX prompted us to try the reaction in the absence of phenol. This procedure failed to give a pure product; however, when two equivalents of sodium hydroxide were employed in the absence of phenol the ketal succinimide XXVI was formed in good yield. The



isomeric structure XXVII was excluded by reductive catalytic hydrogenation to XXVIII. This conclusion was supported by a two-proton nmr singlet at higher field than the methoxyl signal; the methine protons in XXIX would be expected to be a singlet at lower field than the methoxyl signal (whether *cis* or *trans*). Additionally, the ^{13}C satellites of the two-proton signal were shown to be singlets ($H\text{-}100$, $J_{13\text{C},\text{H}} = 134 \text{ Hz}$), whereas doublets with a coupling constant of 3.7-9.0 Hz (7) would be expected for structure XXIX.

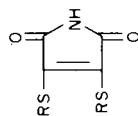
Preparation of the diethoxy analog of XXVI, using ethanol as solvent was successful but the yield was quite low. When sodium ethoxide, prepared from sodium and ethanol, was employed the yield increased but was still poor.

The ketal XXVI is remarkably stable to hydrolysis; overnight reflux in aqueous sulfuric acid gave a mixture shown by tlc to consist mostly of starting material, some IX and some highly polar material. This stability can be attributed to the keto and chloro groups which discourage α -carbonium ion formation.

When the alcoholic sodium hydroxide conditions were tried on *N*-phenyldichloromaleimide the reaction was complicated by opening of the imide ring to give mixtures.

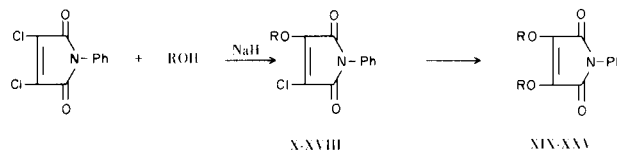
TABLE I
2,3-Bis[alkyl(aryl)mercapto]maleimides

Compd.	R	M.p. or b.p. (mm), °C	% Yield	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
I	<i>n</i> -C ₄ H ₉	163-172 (0.15)	71	C ₁₂ H ₁₉ NO ₂ S ₂	52.61	52.71	7.08	7.00	5.13	5.12	23.77	23.45
II	<i>n</i> -C ₆ H ₁₃	(a)	87	C ₁₆ H ₂₇ NO ₂ S ₂	58.22	58.32	8.28	8.26	4.36	4.25	19.35	19.46
III	<i>n</i> -C ₈ H ₁₇	(a)	60	C ₂₀ H ₃₅ NO ₂ S ₂	62.29	62.29	9.36	9.15	3.58	3.63	16.51	16.63
IV	<i>sec</i> -C ₈ H ₁₇	(a)	90	C ₂₀ H ₃₅ NO ₂ S ₂	62.29	62.29	9.36	9.15	3.58	3.63	16.21	16.63
V	<i>n</i> -C ₁₀ H ₂₁	(a)	65	C ₂₄ H ₄₃ NO ₂ S ₂	65.10	65.26	10.07	9.81	3.21	3.17	14.55	14.52
VI	PhCH ₂	94-96 (b)	70	C ₁₈ H ₁₅ NO ₂ S ₂	63.07	63.32	4.33	4.43	4.04	4.10	18.82	18.78
VII	Ph	123-126 (b)	64	C ₁₆ H ₁₁ NO ₂ S ₂	61.45	61.32	3.59	3.54	4.54	4.47	20.77	20.46



(a) The compound was distilled in a Kugelrohr apparatus without a vapor thermometer. (b) The compound was crystallized from 95% ethanol.

If the salt of the phenol or alcohol was prepared in dioxane with sodium hydride and added slowly to the imide, good yields of the monosubstituted compounds X-XXVIII (Table II) were obtained. If another equivalent of phenolate was

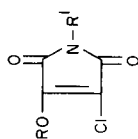


added the *bis* compounds XIX-XXV (Table III) were formed. The monosubstituted compounds again show typical ir carbonyl absorption at 1740 (strong, broad) and 1800 (weak) cm^{-1} with a strong carbon-carbon double bond absorption at about 1660 cm^{-1} .

The results suggest that the choice among isomeric transition states is determined by the relative stability of anions resulting from nucleophilic addition. Thus, attack of methoxide on the intermediate IX appears to give a carbanion analogous to XXXIV stabilized preferably by an α -chlorine rather than by an α -methoxy group (8), whereas with the thiols the carbanion is stabilized preferably by an α -sulfur rather than an α -chlorine. The formation of *bis*(aryloxy)maleimides rather than the ketal type structure XXVI may be due to a combination of a steric factor and the greater inductive effect of aryloxy over alkyloxy. The possibility, however, of XXVI being a kinetically controlled product and XIX-XXV thermodynamically controlled products does not appear to be ruled out.

In some instances (see Experimental) the sodium salts were insoluble, hence the salt slurries were added rapidly to the substrate. In some cases this technique failed to give clean products. For example, the rapid addition of one equivalent of sodium methoxide (from methanol and sodium hydride) to *N*-phenyldichloromaleimide gave a mixture from which X had to be separated by column chromatography (the same result was obtained when the slurry was added slowly). When two equivalents of methoxide were employed, either by slow or rapid addition, a pure compound was isolated in 13-15% yield. The ir spectrum and combustion analysis agreed reasonably well with the *bis* substituted maleimide structure except that the carbon-carbon double bond frequency was strong at 1661 cm^{-1} which was more consistent with a monosubstituted imide. However, the nmr spectrum (see Experimental) indicated a more complex structure with at least three different types of methoxyl groups and two different types of phenyl groups. A mass spectrum showed the compound to be dimeric. Structure XXX is postulated for this material for the following reasons. The major mass peaks are shown with a suggested fragmentation scheme. Frag-

TABLE II
2-Alkyl(aryl)oxy-3-chloromaleimides

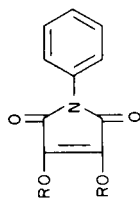


Compd.	R	R ¹	M.p., °C	% Yield	Formula	Carbon, %		Hydrogen, %		Chlorine, %		Nitrogen, %	
						Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
VIII	Ph	H	115-117	8	C ₁₀ H ₆ ClNO ₃	53.83	53.71	2.74	2.71	16.18	15.85	6.23	6.26
IX	CH ₃	H	165-167	16	C ₅ H ₄ ClNO ₃	37.31	37.17	2.44	2.50	21.91	21.95	8.78	8.67
X	CH ₃	Ph	118-120	34	C ₁₁ H ₈ ClNO ₃	55.51	55.59	3.32	3.39	14.91	14.92	5.91	5.90
XI	Ph	Ph	130-132	46	C ₁₆ H ₁₀ ClNO ₃	63.90	64.12	3.36	3.36	12.18	11.83	4.62	4.67
XII	4-ClPh	Ph	137-140	55	C ₁₆ H ₉ Cl ₂ NO ₃	57.53	57.51	2.70	2.72	21.14	21.22	4.22	4.19
XIII	3-ClPh	Ph	111-114	66	C ₁₆ H ₉ Cl ₂ NO ₃	57.50	57.51	2.69	2.72	21.09	21.22	4.19	4.19
XIV	2-C ₁₀ H ₇	Ph	162-164	48	C ₂₀ H ₁₂ ClNO ₃	68.75	68.67	3.39	3.46	9.66	10.14	4.06	4.01
XV	2,4-Cl ₂ Ph	Ph	109-111	66	C ₁₆ H ₈ Cl ₃ NO ₃	52.22	52.13	1.95	2.19	28.39	28.86	3.81	3.80
XVI	4-CH ₃ SPh	Ph	127-129	74	C ₁₇ H ₁₂ ClNO ₃ S	58.62	59.04	3.31	3.50	10.23	10.25	4.05	4.05
XVII	3-CH ₃ , 4-CH ₃ SPh	Ph	134-136	75	C ₁₈ H ₁₄ ClNO ₃ S	59.99	60.08	3.92	3.92	9.76	9.85	3.84	3.89
XVIII	PhCH ₂	Ph	113-115	41	C ₁₇ H ₁₂ ClNO ₃	64.76	65.08	3.87	3.86	11.29	11.30	4.47	4.47

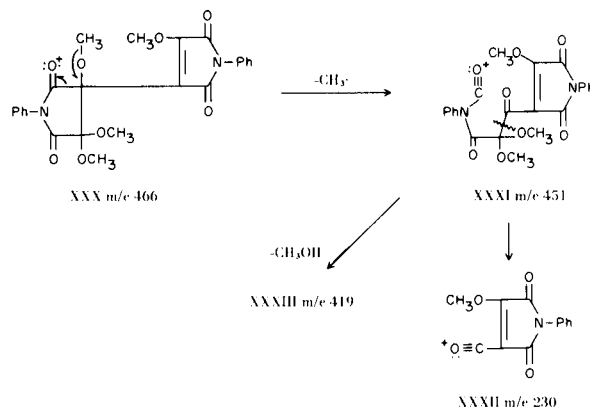
Compounds VIII and IX were recrystallized from benzene-hexane, compound X from methanol, compounds XI-XVII from 95% ethanol, and XVIII from ether.

TABLE III
2,3-Bis(aryloxy)-N-phenylmaleimides

Compd.	R	M.p., °C	% Yield	Crystn Solvent	Formula	Carbon, %		Hydrogen, %		Chlorine, %		Nitrogen, %	
						Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
XIX	Ph	164-166	40	EtOH	C ₂₂ H ₁₅ NO ₄	74.07	73.94	4.24	4.23	4.08	4.08	3.92	3.92
XX	2-CH ₃ , 4-ClPh	124-126	34	EtOH	C ₂₄ H ₁₇ Cl ₂ NO ₄	63.68	63.45	3.78	3.78	15.34	15.34	3.08	3.08
XXI	4-ClPh	214-216	63	Dioxane	C ₂₂ H ₁₃ Cl ₂ NO ₄	62.46	61.99	3.08	3.07	16.85	16.64	3.36	3.29
XXII	3-ClPh	132-134	41	CHCl ₃ -Et ₂ O	C ₂₂ H ₁₃ Cl ₂ NO ₄	62.15	61.99	3.01	3.07	16.67	16.64	3.34	3.29
XXIII	4-CH ₃ SPh	163-166	65	CCl ₄	C ₂₄ H ₁₉ NO ₄ S ₂	63.80	64.12	4.27	4.26	3.02	3.02	2.89	3.12
XXIV	3-CH ₃ , 4-CH ₃ SPh	177-179	62	CCl ₄	C ₂₆ H ₂₃ NO ₄ S ₂	65.08	65.38	4.77	4.85	2.89	2.89	2.93	2.93
XXV	4-NO ₂ Ph	203-205	62	CHCl ₃	C ₂₂ H ₁₃ N ₃ O ₈	58.79	59.07	3.02	2.93	9.35	9.35	9.39	9.39

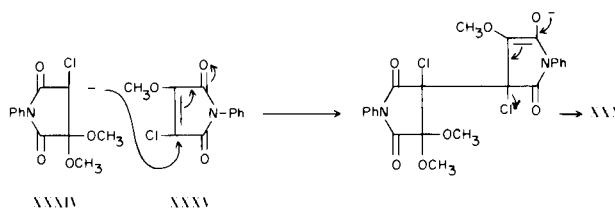


mentations XXXI → XXXII and XXXI → XXXIII both have metastable peaks, and the empirical formulas were verified by exact mass measurements. Although other

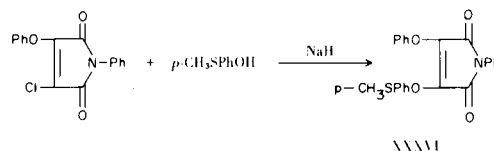


dimers may be drawn, one containing a C-C bridge as in XXX is necessary in order to accommodate the fragment XXXII, which contains the same number of carbon atoms as the monomer, but three less hydrogens. The loss of methanol from XXXI is surprising, but the same problem is presented by any structure with only phenyl and methoxyl groups. A 50 Hz downfield shift of one methoxyl from the other three in the nmr spectrum is also consistent with XXX, which would be expected to have a lower field vinyl methoxyl signal.

Mechanistically, compound XXX could arise by attack of methoxide on monomer to give the stabilized carbanion XXXIV which in the absence of a proton source, attacks another monomer XXXV in a nucleophilic substitution reaction at the vinyl carbon.

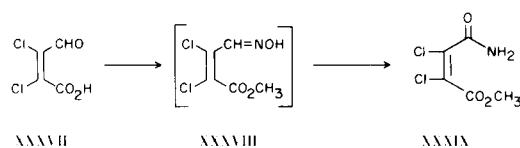


Attempts to prepare mixed substituted products such as XXXVI gave complex mixtures. It appears that an equilibrium is set up with phenoxide from the substrate



resulting in the production of bis substituted compounds. For example, tlc analysis of the above reaction mixture indicated the presence of both XIX and XXIII.

In the course of this study dichloromaleimide was prepared (see Experimental) from mucochloric acid (XXXVII). This method involves the treatment of XXXVII



with hydroxylamine hydrochloride in aqueous methanol which gives a compound that was reported to be the methyl ester of mucochloric acid oxime (XXXVIII) (9). Our results indicate that this material is actually the amide ester XXXIX formed by a Beckmann rearrangement of the oxime with hydrogen migration. The ir spectrum (3520 and 3409 cm^{-1} , medium, ν NH; 1738 cm^{-1} , strong; ν C=O ester; 1691 cm^{-1} , strong, ν C=O amide; 1593 cm^{-1} , strong, δ NH; 1574 cm^{-1} , strong and sharp, ν C=C; 1% deuteriochloroform) and nmr spectrum [δ 3.83; s (3H, OCH₃); 7.33, broad (2H, NH₂); deuterioacetone of this compound are consistent only with structure XXXIX. Although hydrogen migration is rare in Beckmann rearrangements (10), it has been reported to occur with oximes of certain aromatic aldehydes (11).

EXPERIMENTAL

All melting points are corrected; boiling points are uncorrected. Microanalyses were carried out by Mr. V. Raushel and his staff. Ir spectra were recorded by Mr. W. H. Washburn and associates on a Perkin-Elmer Model 421 or 521 grating spectrophotometer in chloroform unless another solvent is indicated. Unless otherwise specified, nmr data were obtained using a Varian A-60 instrument by Dr. R. S. Egan and associates with TMS as internal standard. Mass spectra were recorded by Dr. M. Levenberg and Mrs. Sandra Mueller on an A.E.I. MS-902 instrument. Catalytic reductions were performed by Mr. D. Dunnigan, and tlc by Dr. R. Hasbrouck and Mrs. Evelyn Baker.

Dichloromaleimide.

(A) From Mucochloric Acid.

To a solution of 16.9 g. (0.1 mole) of mucochloric acid (Eastman Organic Chemicals) in 25 ml. of methanol was added 7.02 g. (0.101 mole) of hydroxylamine hydrochloride dissolved in 10 ml. of water. This solution was allowed to stand for three days at room temperature. After standing several hours at 4°, white crystals separated. The mixture was filtered with suction and the crystals were washed with water and dried at room temperature *in vacuo* overnight. The crystals weighed 5.85 g. (30%) and melted at 123-127°. In another run of lower yield a purer sample was obtained, m.p. 133-135°.

Anal. Calcd. for C₅H₅Cl₂NO₃: C, 30.33; H, 2.55; Cl, 35.81; N, 7.07. Found: C, 30.47; H, 2.55; Cl, 35.58; N, 7.02.

Although a similar procedure (9) has been reported to give the methyl ester of mucochloroxime (XXXVIII), our results indicate (see discussion) that the compound is the methyl ester of dichloromaleamic acid (XXXIX). Attempts to improve the reaction by the addition of acid, and by using excess hydroxylamine hydrochloride failed.

Dichloromaleimide, m.p. 175-177° [lit. (9) m.p. 173-174°], separates chromatographically pure from a boiled aqueous solution of the amic acid in 53% yield. Deleting the water from the amic acid preparation and heating gives the imide directly, but in the

same low yield.

(B) From Dichloromaleic Anhydride.

1. Formamide.

A mixture of 200 g. (1.2 moles) of dichloromaleic anhydride, 52.3 ml. (59.3 g., 1.32 moles) of formamide and 200 ml. of glacial acetic acid was heated at 70° for 12 hours and allowed to cool to room temperature. The mixture was poured into 500 ml. of water, chilled at 4° and filtered with suction. Crystallization of the crude solid from 95% ethanol gave 61.2 g. (43%) of light amber crystals, m.p. 175-179°. A somewhat lower yield was obtained when the reaction was run neat.

2. Urea.

The fusion of urea with dichloromaleic anhydride (12) at 110-115° gave the imide in 37% yield but purification was extremely difficult. The most convenient laboratory method of preparation involves a fusion in the presence of sodium chloride

(13). This procedure gives excellent yields of good material but requires caution due to an exothermic rapid evolution of carbon dioxide.

The reaction of urea with dichloromaleic anhydride in acetic acid followed by dehydration of the *N*-carbonylmaleamic acid, and cleavage of the *N*-carbonylmaleimide in dimethyl formamide to dichloromaleimide, patterned after a preparation of maleimide (14), gave impure intermediates and a 28% overall yield of dichloromaleimide.

Other preparations (15,16,17,18) of dichloromaleimide are not as convenient as the aforementioned sodium chloride fusion.

2,3-Bis[alkyl(aryl)mercapto]maleimides (Table I).

To a stirred solution of 0.15 equivalent of sodium hydroxide in 100 ml. of methanol was added rapidly 0.15 mole of the thiol dissolved in 30 ml. of methanol. To this solution was added rapidly 0.075 mole of dichloromaleimide dissolved in 100 ml. of methanol. This mixture was stirred overnight at room temperature or heated under reflux for two hours, cooled, diluted with water and filtered with suction if a solid separated. If the product was an oil, the mixture was extracted with ether, the extract washed with water, dried (magnesium sulfate), and the solvent evaporated.

In an attempt to prepare 2-chloro-3-(phenylmercapto)maleimide a solution of 0.075 mole of benzenethiol in 75 ml. of methanol containing 0.075 equivalents of sodium hydroxide was added dropwise over a 2 hour period to a stirred and ice-cooled solution of 0.075 mole of dichloromaleimide in 100 ml. of methanol. The mixture was stirred in the ice bath and allowed to come to room temperature overnight. Workup as described above gave a 77% yield (based on benzenethiol) of the *bis*-mercapto compound VII.

Reactions of Dichloromaleimides with Alcoholic Sodium Hydroxide.

(A) 2-Chloro-3-phenoxy-maleimide (VIII) and 2-Chloro-3-methoxy-maleimide (IX).

To a stirred and ice-cooled solution of 12.44 g. (0.075 mole) of dichloromaleimide in 100 ml. of methanol was added dropwise, over a period of 1.5 hours, a solution of 7.05 g. (0.075 mole) of phenol and 3.00 g. (0.075 equivalent) of sodium hydroxide in 100 ml. of methanol. The mixture was allowed to come to room temperature overnight with stirring. The solution was diluted with 500 ml. of water, acidified with 10% hydrochloric acid, and chilled to 4°. This gave 1.82 g. of solid (A), m.p. 114-116°.

Recrystallization from benzene-hexane afforded 1.35 g. of VIII as amber crystals, m.p. 115-117°.

Concentration of the filtrate from the solid A and chilling to 4° gave 4.43 g. of crude solid (B). Crystallization from benzene-hexane afforded 1.89 g. solid, m.p. 163-165° which on recrystallization from benzene gave IX as pale yellow crystals, m.p. 165-167°.

(B) 2-Chloro-3,3-dimethoxysuccinimide (XXVI).

The above procedure (A) on deletion of the phenol with two equivalents of sodium hydroxide gave a 69% yield of 2-chloro-3,3-dimethoxysuccinimide as white crystals, m.p. 113-115° (benzene); ir: 3390, 3240 (broad), 1812 (medium), 1745 cm⁻¹; nmr: δ 3.67, s (3H, OCH₃); 3.70, s (3H, OCH₃); 5.63, s (1H, CH); 11.58, s (1H, NH) (deuteriopyridine).

Anal. Calcd. for C₆H₈ClNO₄: C, 37.23; H, 4.17; Cl, 18.31; N, 7.24. Found: C, 37.49; H, 4.18; Cl, 18.52; N, 7.36.

(C) 2-Chloro-3,3-diethoxysuccinimide.

Repetition of the above reaction in ethanol gave only an 8% yield of the diethoxy analog of XXVI as white crystals, m.p. 93-96° (ethanol).

Anal. Calcd. for C₈H₁₂ClNO₄: C, 43.35; H, 5.46; Cl, 16.00; N, 6.32. Found: C, 43.11; H, 5.42; Cl, 15.65; N, 6.33.

When the reaction was run with two g. atoms of sodium in ethanol a 14% yield of the diethoxy compound was obtained.

2,2-Dimethoxysuccinimide (XXVIII).

A 323 mg. sample of XXVI was hydrogenated in methanol-triethylamine with a 5% Pd-C catalyst at 3 atm. The mixture was filtered, the filtrate was concentrated *in vacuo*, the residue was dissolved in water and extracted continuously with ether overnight. The ether extract was dried (magnesium sulfate), the solvent evaporated, and the residue was crystallized from benzene-hexane to give 113 mg. of white crystals, m.p. 77-79°; ir: 3395, 3235, 1797 (medium), 1730 cm⁻¹; nmr: δ 2.85, s (2H, CH₂); 3.42, s (6H, OCH₃) (deuteriochloroform).

Anal. Calcd. for C₆H₉NO₄: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.50; H, 5.85; N, 8.83.

2-Alkyl(aryl)oxy-3-chloro-N-phenylmaleimides (Table II).

To a stirred suspension of 57% sodium hydride oil dispersion (0.091 mole sodium hydride) in 50 ml. of dioxane was added dropwise, over a period of 1 hour, 0.084 mole of the phenol dissolved in 150 ml. of dioxane. The mixture was stirred for 15 minutes and then added dropwise with stirring, over a period of 1 hour, to 0.083 mole of N-phenyldichloromaleimide (19), in 100 ml. of dioxane. The mixture was stirred at room temperature overnight, concentrated *in vacuo*, and diluted with water. If solid, the product was removed by filtration, washed with water and recrystallized. If oily, the aqueous phase was decanted and the product was dissolved in chloroform, washed with water, dried (magnesium sulfate), the solvent evaporated and the residue triturated under ether or pentane to give solid that was recrystallized from a suitable solvent (see Table II).

In the preparation of X and XVIII the sodium salts of the alcohols were insoluble in dioxane, therefore the salt slurries were added rapidly to the dichloromaleimide. Compound X had to be separated from N-phenyldichloromaleimide on a silica gel column with benzene elution.

2,3-Bis(aryloxy)-N-phenylmaleimides (Table III).

These compounds were prepared in the same manner as described for the 2-alkyl(aryl)oxy-3-chloro-N-phenylmaleimides using 0.182 mole of sodium hydride and 0.168 mole of the phenol. Compound XXV was prepared in DMSO instead of dioxane. In the case of XX and XXI the sodium salts of the

phenols were insoluble in dioxane, therefore the salt slurries were added rapidly to the dichloromaleimide.

The Reaction of Methanol-Sodium Hydride with N-Phenyldichloromaleimide.

To a stirred suspension of 7.65 g. of 57% sodium hydride oil dispersion (4.36 g. of sodium hydride, 0.182 mole) in 50 ml. of dioxane was added dropwise, over a period of 1.3 hours, 6.74 ml. (5.34 g., 0.167 mole) of methanol in 100 ml. of dioxane. The mixture was stirred for 15 minutes (solution not attained) and added rapidly to a stirred suspension of 20 g. (0.026 mole) of N-phenyldichloromaleimide in 100 ml. of dioxane. The mixture was stirred at room temperature overnight, concentrated *in vacuo*, and diluted with water. The mixture was extracted with ether, the ether extract was washed with water, dried (magnesium sulfate) and the solvent evaporated. Trituration under ether-hexane afforded 3.06 g. of solid. Crystallization from 95% ethanol afforded 2.47 g. of XXX as faint yellow crystals, m.p. 193-195°; ir: 1781 (weak), 1720, 1661, 1599 (medium cm⁻¹ (deuteriochloroform); nmr: δ 3.50, s (3H, OCH₃); 3.60, s (6H, OCH₃); 4.43, s (3H, OCH₃); 4.08, s (5H, ArH); 4.13, s (5H, ArH) (deuteriochloroform); Mol. wt. (MS) Calcd. 466.1376. Found: 466.1383.

Anal. Calcd. for C₂₄H₂₂N₂O₈: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.47; H, 4.84; N, 5.94.

Acknowledgments.

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