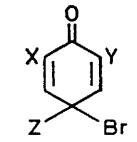
Solvent Effect on the *ortho* : *para* Ratio in the Bromination of Phenols. Bromination with Bromocyclohexadienones and *N*-Bromosuccinimide

By **Vincenzo Calò,* Luigi Lopez,** and **Giovanni Pesce,** Istituto di Chimica Organica, Università, via Amendola 173, 70126 Bari, Italy
Francesco Ciminale and **Paolo Edgardo Todesco,** Istituto di Chimica Organica, Università viale Risorgimento 4, 40136 Bologna, Italy

Bromination of phenol with *N*-bromosuccinimide and 2,4,4,6-tetrabromocyclohexa-2,5-dienone has been studied in various solvents. In contrast to bromination with molecular bromine, when these reagents are used the *ortho* : *para* ratio is greatly influenced by the solvent and by the concentration of hydrobromic acid concentration present in the reaction medium. The selectivity of these reagents is not due to their ability to furnish very low bromine concentrations, but to their properties as very efficient hydrobromic acid scavengers. The high *ortho* : *para* ratios observed during bromination in chlorinated solvents are better explained by an ionic mechanism rather than a radical one involving bromination of the phenoxyl radical.

THIS investigation was begun in order to find suitable reagents for bromination of phenols which influenced the *ortho* : *para* ratio of products in a simple, direct way; additionally it was hoped to explain the anomaly of almost complete *para*-bromination of phenols. In contrast to most electrophilic aromatic substitutions, in the bromination of phenols almost no solvent effect is observed on the orientation of product and the *para*-brominated isomer is predominant in CS_2,[1] and formed almost exclusively in CCl_4,[2] CH_3CO_2H,[3] and ethylene chloride.[4] The problem of obtaining *ortho*-brominated phenols was partially solved by using as brominating agents bromine or its sources and metal phenoxides [5] or simply bromine in the presence of bases in weakly polar solvents.[6] Preferential *ortho*-substitution was generally explained by postulating the formation of a phenyl hypobromite which rearranged to the *ortho*-substituted phenol.[5,7] But the yields of monobrominated products were not high enough for this to be regarded as a satisfactory synthetic method.

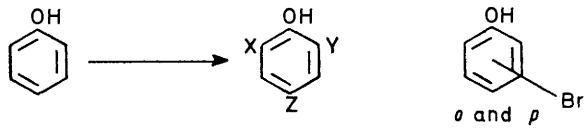
In a preliminary communication,[8] we showed that bromination of phenols with the bromocyclohexadienones (I)—(III) leads to preferential *ortho*- or *para*-substitution depending on the medium of reaction. In order to elucidate the influence of these reagents and the solvent on the products, we have investigated the reaction of the bromocyclohexadienone (I) with phenol and anisole. It was of interest to see whether the behaviour of reagent (I) was unique or can be correlated with that of other brominating reagents such as *N*-bromosuccinimide (NBS).



(I) X = Y = Z = Br
(II) X = Y = Z = Cl
(III) X = Y = Br, Z = Me

RESULTS

The bromination of phenol with (I) proceeds as in Scheme 1 and gives only monobrominated products in high



SCHEME 1

yield even when carried out with stoicheiometric amounts of reagents. But, in contrast to bromination with molecular bromine, the reaction of (I) or NBS with phenol is strongly influenced by the solvent. The *ortho* : *para* ratio reaches its highest value in dry CCl_4 and $CHCl_3$ and the lowest in acetic acid and acetonitrile. The reaction is catalysed by light but not by added azobisisobutyronitrile. Nevertheless the product ratio does not change if

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[2] L. M. Yeddanapalli and N. S. Gnanapragasam, *J. Chem. Soc.*, 1956, 4934.
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the reaction is carried either in the light or in the dark. Interestingly, the addition of small quantities of gaseous hydrobromic acid to chloroform reduces the *ortho*-content. The results together with those obtained by brominating phenol with molecular bromine are reported in the Table.

Bromination of phenol in various solvent with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (a), NBS (b), and bromine (c)

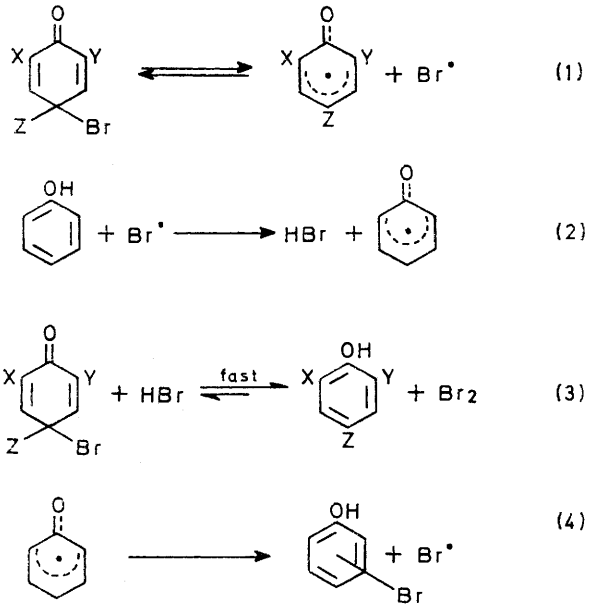
Solvent		Orientation (%) *o*	*p*
Carbon tetrachloride	(a)	87	13
	(b)	86	14
	(c)	11	89
Chloroform	(a)	84	16
	(b)	81	19
	(c)	8	92
Chloroform [a]	(a)	40	60
Acetic acid	(a)	11	89
	(c) [b]	4	96
Acetonitrile	(a)	4	96
	(b)	3	97
	(c)	3	97

[a] With added gaseous HBr ($1{\cdot}3 \times 10^{-3}$M). [b] Ref. 3.

Bromination under the same conditions which gave a high yield of *o*-bromophenol failed with anisole since the reaction was much slower and only the *para*-brominated product was obtained. Bromination of phenol with another reagent which gives a low bromine concentration such as dibromopyrrolidone hydrobromide (PHT) yields almost exclusively *p*-bromophenol in all the solvent used.

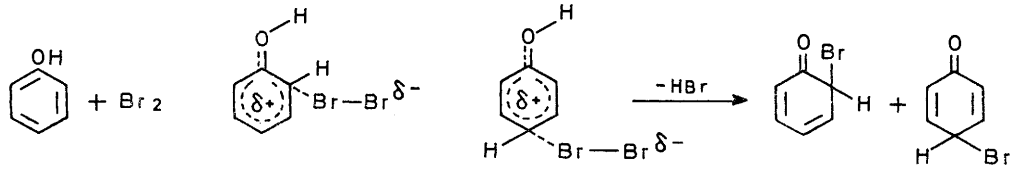
DISCUSSION

From the results it appeared that both reagent (I) and NBS brominate phenol by a different mechanism from that of molecular bromine. Previous work [9] on bromination with reagent (I) of some benzene derivatives suggested either a free radical or an ionic mechanism, and in the bromination of alkylarenes Kennedy and Ingold [10] showed that a similar mechanism for benzylic bromination can be written for reagents (I)—(III) and NBS. It follows that the reaction of (I) with phenol could proceed as in equations (1)—(4). This free radical process explains some of the results such as the photocatalysis, and the predominant *ortho*-substitution in media of low polarity.[11] But it does not explain the effect of solvent on orientation. In acetonitrile and acetic acid reagent (I) and NBS have the same selectivity in all solvents and other factors play a decisive role on the orientation of products. There is an alternative ionic mechanism which can explain the observed results.



Traces of hydrobromic acid due to photo-catalysed decomposition of (I) or NBS could react with the reagents to give a very low concentration of bromine which may brominate phenol according to reaction (3). The cyclohexadienone (I) slowly decomposes if kept at room temperature or in the presence of light, its i.r. spectrum developing a band at 3500 cm^{-1} (OH). This decomposition is very fast in the presence of hydrobromic acid leading to the almost quantitative production of molecular bromine. The same is true for NBS [12] and therefore both reagents are sources of a very low bromine concentration and act simultaneously as efficient hydrobromic acid scavengers. If the electrophile is bromine generated by reaction (3) the orientation of products can be influenced by (i) bromine concentration, (ii) hydrobromic acid, and (iii) solvent.

The fact that a low bromine concentration does not



SCHEME 2

as molecular bromine. Therefore, either the mechanism of bromination changes with solvent or the species responsible for bromination is the same (*e.g.* bromine) influence the orientation was demonstrated by bromination with PHT (see earlier) which is a source of very low bromine concentrations [13] and is a poor hydrobromic acid scavenger. In order to correlate the influence of hydrobromic acid and the solvent on the orientation a brief summary on the mechanism of the halogenation of

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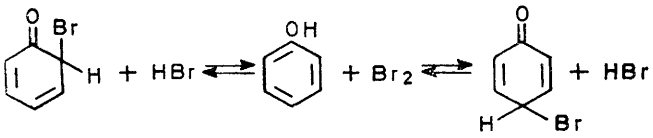
phenols is necessary. The commonly accepted mechanism for the bromination of phenols with molecular bromine is shown in Scheme 2.[3] That cyclohexadienones are intermediates in bromination was firmly established by the isolation of these compounds from the bromination of some substituted phenols.[14] The *o*-quinonoid forms are characterized by their tendency to rearrange to the more stable *p*-quinonoid forms. U.v. light,[15] polar solvents [16] including acetic acid,[17] and hydracids [18] can effect the transformation. Bromine migrates more easily than chlorine, and many phenols which give *o*-dienones on chlorination in weakly polar solvents,[17,18] give only the *para*-isomer on careful bromination.[16] This rearrangement may be due to the presence of the hydracids. Cyclohexadienones are vinylogues of α-bromo-ketones and for their aromatization a 'push and pull' mechanism similar to that accepted for the reduction of α-bromo-ketones [19] can be written. The preponderance of the *ortho*-brominated product in the bromination of phenol with reagent (I) or NBS in CCl_4 and $CHCl_3$, implies that phenol is brominated under kinetic control to give an *o*-dienone intermediate which in an acid catalysed prototropic step reacts with hydrobromic acid, according to the principle of microscopic reversibility, to give, *via* reduction to phenol, the more stable *p*-dienone which subsequently rearranges to the *p*-bromophenol (Scheme 3).



SCHEME 3

If hydrobromic acid is neutralized in a faster reaction, *i.e.* before the rearrangement of the *o*-quinonoid form, *o*-bromophenol would be isolated. Reagent (I) and NBS at least in chlorinated solvents fulfill this condition.

This assumption is supported by the reaction of (I) with phenol in $CHCl_3$ with added hydrobromic acid where the excess of acid transforms the *o*-dienone to the *para*-isomer. We suggest the following explanation for preferential *ortho*-bromination. If acids are absent phenol reacts with bromine *via* a cyclic six-membered transition state as suggested [20] for chlorination of phenol with chlorine in carbon tetrachloride. Further evidence supporting this is the exclusive *para*-bromination of anisole which is probably due to the absence of a free hydroxy-group. More difficult to explain is the effect of solvent on the orientation of product. However certain tentative conclusions can be drawn. (*a*) By increasing the solvating power of the solvent, a Wheland type *para*-intermediate is more solvated leading to a higher proportion of *p*-substitution. (*b*) Formation of hydrogen bonds between the phenolic proton and the solvent [21] sterically hinders the *ortho*-approach of the electrophile. These aspects are fully discussed in the following paper.

In conclusion molecular bromine appears to be the electrophile in the halogenation of phenol with reagent (I) or NBS and the results are better explained by an ionic attack of bromine on phenol rather than by a radical mechanism involving attack on the phenoxyl radical.

EXPERIMENTAL

Materials.—Phenol and the solvents were purified by standard procedures. 2,4,4,6-Tetrabromocyclohexa-2,5-dienone was synthesized as previously reported.[22] NBS and PHT were reagent grade products and used without further purification.

Bromination of Phenol.—(a) *With bromocyclohexadienone* (I). The dienone (I) (2·18 g, 1 mol. equiv.) was added in portions with stirring at room temperature to phenol (0·5 g, 1 mol. equiv.) in solvent (35 ml). Decolouration of the yellow solution of (I) occurs almost immediately (depending on the solvent) after each addition. The isomer composition was determined directly on the reaction mixture by g.l.c., using a 6 ft column packed with silicone SE 30 on Chromosorb A W. DMCS 60—80. A calibration curve of peak height against composition was constructed by using mixtures of authentic *o*- and *p*-bromophenol. Only peaks due to monobrominated phenols are present. The total yield of bromophenols, isolated by preparative t.l.c. on silica gel (eluant chloroform) was >95%. The composition of the reaction mixture does not change if the reaction is carried out in the dark or on irradiation by a 40 W tungsten filament lamp.

(b) *With NBS.* The reaction of phenol with NBS in the various solvents was performed under the same conditions as for reagent (I). In this case also the yield of monobrominated products was >95%.

Bromination of Phenol with PHT.—Dibromopyrrolidone hydrobromide (3 g, 1 mol. equiv.) was added in portions with stirring at room temperature to phenol (0·57 g, 1 mol. equiv.) in CCl_4 (35 ml). G.l.c. analysis showed peaks due to *o*- and *p*-bromophenol in the ratio 1 : 9.

Bromination of Anisole.—The bromination of anisole under the conditions used for phenol yields after *ca.* 14 days only *p*-bromophenol in all the solvents used.

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