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INSERTION OF ISOPRENE UNITS INTO PHENOL SYSTEM

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Phenolic derivatives bearing isoprenoid substituents are frequently found in a wide range of natural materials[1].

We have already discussed the possibility of introducing isoprenic units directly into indole[2] and phenol substrates[3] under very mild conditions.

We now report new interesting results obtained from the isoprenisation of phenols under biogenetic like conditions: the synthesis were carried out at room temperature in buffered protic solvents[4].

Isopentenylbromide was used as the reagent, as the derivatives have a good leaving group, similar to the pyrophosphate of the hypothetic biogenetic alkylating agent[7]. The influence of the substituent present in the phenolic system was studied in acetic buffer (see Tab. 1)[6].

Table 1

Reaction of phenols with γ,γ-dimethylallylbromide in acetic buffer[a]

	Relative weight % composition			
Substrate	Unreacted product	O-alkylation	C-alkylation	C-dialkylation
Phenol	100	-	-	-
4-Hydroxy-benzoic acid	100	-	-	-
2-Methylphenol	81	1	18[b]	-
4-Mehtylphenol	85	3	12[c]	-
Resorcinol	35	-	31[d]	34[e]
Hydroquinone	60	8	31[f]	1
2-Naphthol	66	-	31[g]	3

a - At room temperature; reaction time 24 hr; molar ratio phenol:reagent = 1:1; for buffer composition see Tab.2.

b - 3% 2-Methyl-6-γ,γ-dimethylallylphenol, 15% 2-methyl-4-γ,γ-dimethylallylphenol

c - 2-γ,γ-Dimethylallyl-4-methylphenol.

d - 3-Hydroxy-4-γ,γ-dimethylallylphenol.

e - Five unidentified products.

f - 2-γ,γ-dimethylallyl-4-hydroxyphenol.

g - 1-γ,γ-dimethyl-2-naphtol.

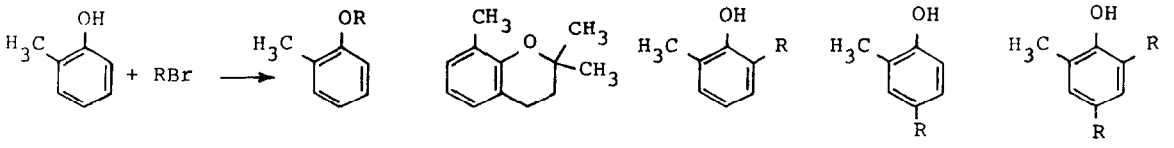
To operate in an homogeneous medium we used an excess of acetic acid (CH_3COOH 80%, H_2O 20%); similar results were also obtained using medium with higher percentages of water, but under these conditions the isopentenylbromide was insoluble.

Under these conditions phenols with electron-withdrawing substituents and phenol itself do not react at all, but in the case of the o-methylphenol, attack at the ortho and para positions is obtained. The examination of the influence of the medium on the pathway of the reaction has allowed the selection of the reaction conditions in relation to the reactivity of the substrate.

Indeed, with more acidic media (formic or monochloroacetic buffer) it was possible to obtain significant yields, even with phenols having lower reactivities, but in the case of the reactive phenols, which are particularly interesting in biogenetic processes, it is possible to operate with milder conditions (biological like) in order to decrease the formation of polyalkylated products (see Tab. 2 and 3).[6]

Table 2

Reaction of o-cresol and γ,γ-dimethylallylbromide in different buffers[a]



(I) (II) (III) (IV) (V)

R = $-CH_2-CH=C(CH_3)_2$

	Relative weight % composition						
Buffer	Unreacted product	I	II	III	IV	V	Other Products
Citric[b]	91	-*	-	1	8	-	-
Acetic	81	1	-	3	15	-	-
Monochloroacetic	39	-	1	8	35	14	3
Formic[b]	31	-	1	10	40	11	7

a - At room temperature; reaction time 24 hr; molar ratio phenol : reagent = 1 : 1.
b - Heterogeneous medium.
* - Traces.

Buffer composition for 0·02 moles of phenol :
Citric : citric acid 10 g; NaOH 2N 60 ml; EtOH 95% 60 ml;
Acetic : glacial acid 40 ml; H_2O 10 ml; $CH_3COONa \cdot 3H_2O$ ç g;
Monochloroacetic : monochloroacetic acid 36·6 g; H_2O 8 ml; $CH_2ClCOONa$ 4·65 g;
Formic : formic acid 99% 30 ml; H_2O 8 ml; HCOONa 2·7 g.

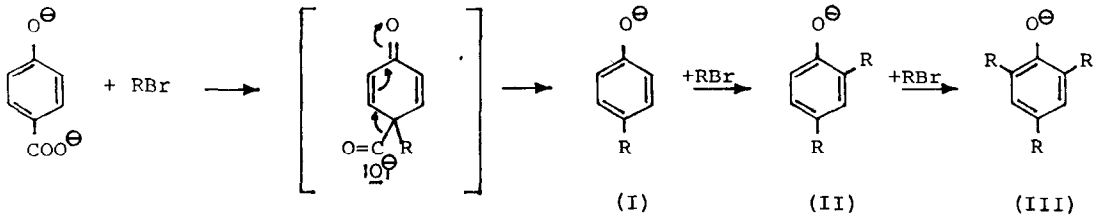
Table 3

Reaction of resorcinol and phenol with γ,γ-dimethylallylbromide in different buffers[a].

		Relative weight % composition		
Phenol	Buffer[b]	Unreacted product	Main product	Other products
Resorcinol	citric	76	20[c]	4
Resorcinol	acetic	35	31[c]	34
Phenol	acetic	100	-	-
Phenol	formic	62	24[d]	14

a - At room temperature; reaction time 24 hr; molar ratio phenol:reagent = 1:1.
b - For composition see Tab. 2.
c - 3-Hydroxy-4-γ,γ-dimethylallylphenol.
d - 4,γ,γ-Dimethylallylphenol.

Moreover,we have succeeded in introducing isoprenic units into the bisodium salt of hydroxybenzoic acid, in a process studied as a possible reaction model for ubiquinone [7] biosynthesis; with these conditions we were able to isolate, as main products, the compounds (I, II, III)[6] reported in the following scheme:



R = $-CH_2-CH=C(CH_3)_2$

In all the cases examined we observed only the insertion of isoprenic units, by linkage at the tail, into the aromatic substrate; we have not succeeded in demonstrating any significant quantities of chroman type derivatives[4a]. The formation of ether is also dramatically decreased in these protic acid media, due to the specific solvation and the shielding-effect exercised by the proton on the oxygen.

The reaction could be particularly important from a synthetic point of view: an example is provided by the ready synthesis of 1-isopentenyl-2-naphtol (see Tab. 1).

References

[1] The Biosynthesis of Steroids, Terpens and Acetogenins, pag. 108. J. H. Richards and J. B. Hendrickson. W. A. Benjamin Inc. 1964.

[2] G. Casnati, M. Francioni, A. Guareschi and A. Pochini, Tetrahedron Letters 2485, 1969.

[3] A. Guareschi and A. Pochini, Ateneo Parmense, Sez. 2, 20, 1969; C. A. 74, 99205h, 1971.

[4] Recent attempt to introduce an isoprenic unit directly into activated phenols gave chromane derivatives[a] or were carried out under relatively drastic conditions (80°, HCOOH, H_2O)[b].

[a] R. J. Molineux and L. Jurd, Tetrahedron 26, 4743 (1970).

[b] L. Jurd, K. Stevens and G. Manners, Tetrahedron Letters 2275, 1971.

[5] A. J. Birch, Fortschr. Chem. Org. Naturstoffe 14, 186 (1957).

[6] All the products were isolated by chromatography on silica-gel, and were found to sgree with analytical and spectrographic data.

[7] J. L. J. Nillson, I. M. Nillson, J. Scholler and K. Folkers, Int. Z. Vitaminforsch. 40, 374 (1970).