HETEROCYCLES, Vol 20, No 5, 1983

THE PREPARATION OF SOME (1)-BENZOFURANO-(2,3-c)-(6H,12H-1)-BENZOXEPIN-6-ONES

Vernon G.S. Box[*,1] and Yvette A. Jackson
Department of Chemistry, University of The West Indies, Kingston 7,
Jamaica, W.I.

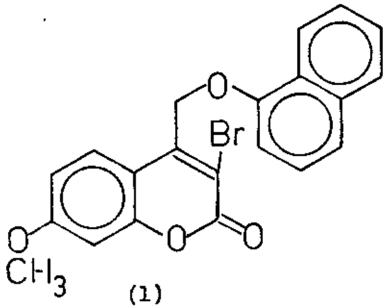
Abstract — The title compounds were prepared by the acid catalysed rearrangements of some 2-carbethoxy-3-aryloxymethylbenzofurans to the 2-carbethoxy-3-(2'-hydroxyarylmethyl)-benzofurans, followed by their lactonisation. These 2-carbethoxy-3-aryloxymethylbenzofurans do not undergo the Claisen rearrangement.

Our interest in the synthetic approaches to novel benzopyran-benzopyrans has led us to investigate the preparation of the compound (1) and its Claisen rearrangement to the benzopyran-benzopyran (2)[2]. A method of transforming the compound (2) into the isomeric benzopyran-benzopyran (3) has been recognised[2], and so the compound (2) became an interesting synthetic intermediate. Alternative approaches to the synthesis of this compound (2) were therefore sought.

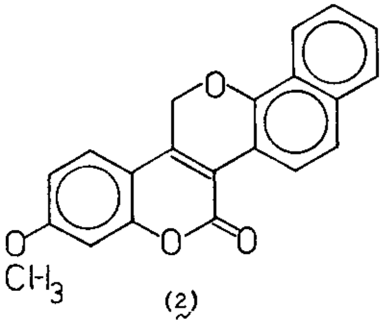
The mechanistic appreciation of the rearrangement of the compound (1) to the compound (2) suggested that the preparation of similar benzopyran-benzopyrans might be achieved by a Claisen rearrangement of the 2-carbethoxy-3-phenoxymethylbenzofuran (4), as shown in scheme 1.

Ethyl 5,6-dimethoxy-3-methylbenzo-(b)-furan-2-carboxylate, (5), reference 3, was readily converted into the 3-bromomethylbenzofuran (6), in very good yield, by N-bromosuccinimide in carbon tetrachloride, on irradiation with a high intensity (visible) lamp.

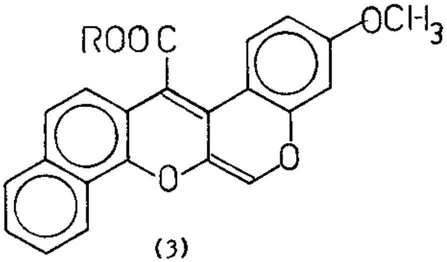
The reaction of the compound (6) with sodium 3-methoxyphenoxide in refluxing benzene gave the ether (7) as the major product (23%) and the isomeric C-alkylated products (8), (9) and (10) in 7%, 10% and 8% yields, respectively. While the isomeric compounds (8) and (9) were not easily distinguishable by their basic spectroscopic properties, they were identified by chemical transformation as will



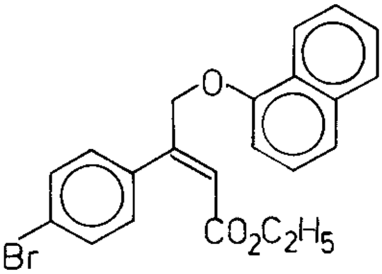
(1)



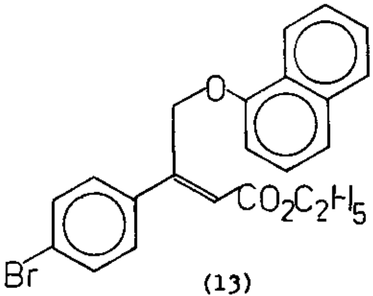
(2)



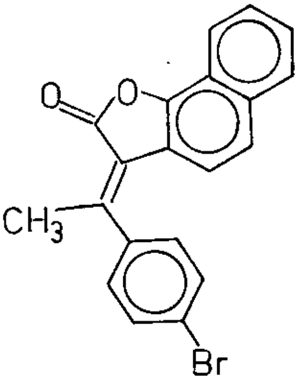
(3)



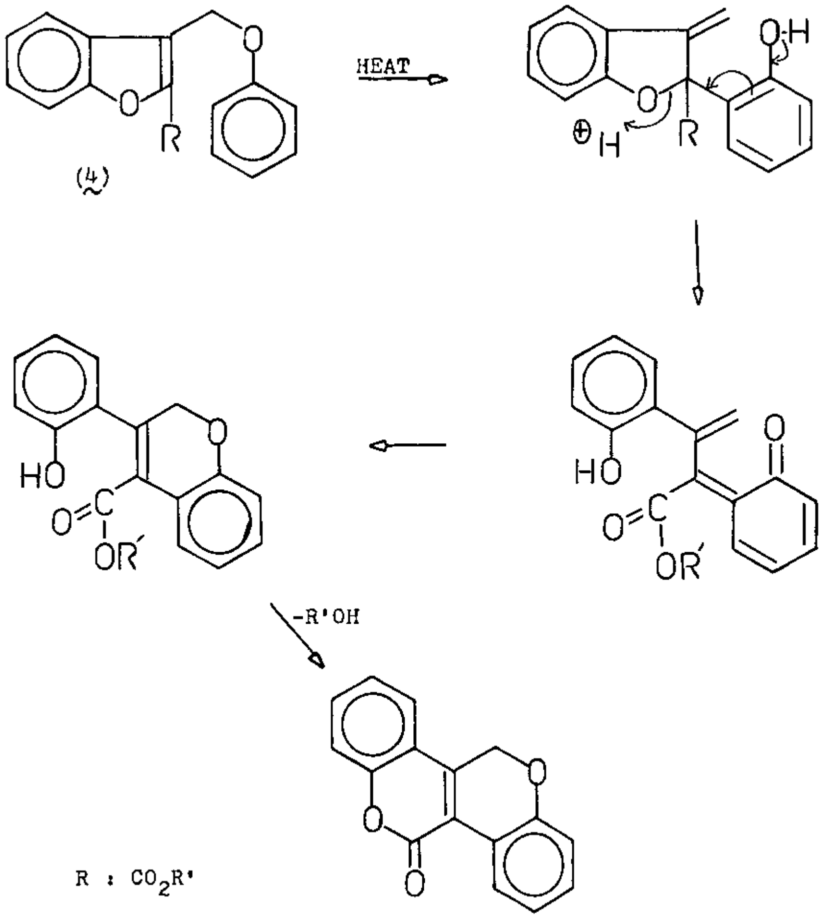
(11)



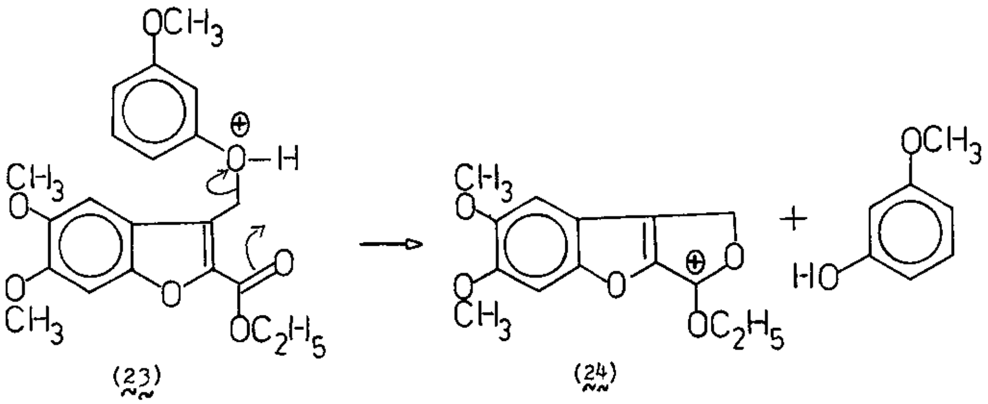
(13)



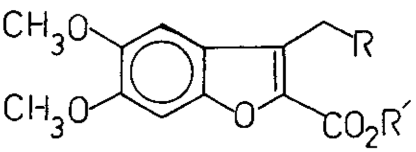
(12)



SCHEME 1.



SCHEME 2.



(5) R : H, R' : Et.

(6) R : Br, R' : Et.

(7) R : 3-methoxyphenoxy, R' : Et.

(8) R : 2-hydroxy-4-methoxyphenyl, R' : Et.

(9) R : 4-hydroxy-2-methoxyphenyl, R' : Et.

(10) R : 2-hydroxy-6-methoxyphenyl, R' : Et.

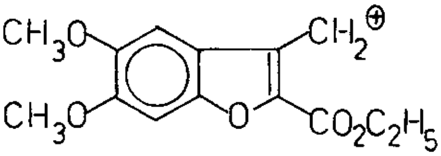
(14) R : 2-hydroxy-4-methoxyphenyl, R' : H.

(17) R : 1-naphthyloxy, R' : Et.

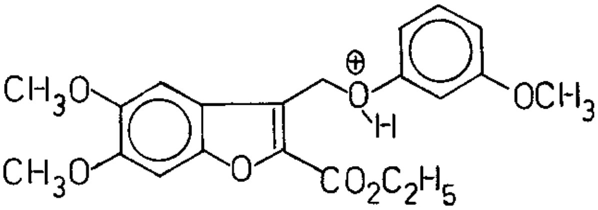
(18) R : 1-hydroxy-2-naphthyl, R' : Et.

(19) R : 1-hydroxy-2-naphthyl, R' : H.

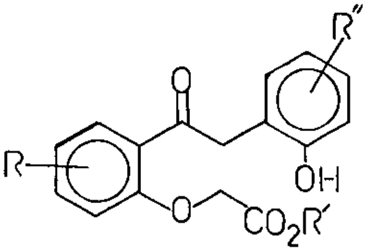
(21) R : 4-hydroxy-1-naphthyl, R' : Et.



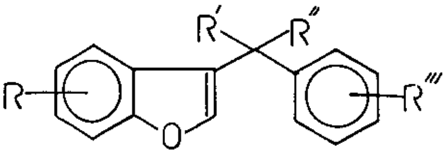
(22)



(23)

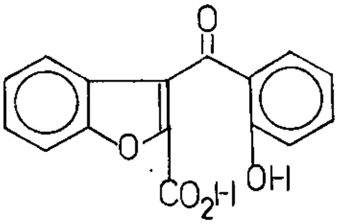


(25)

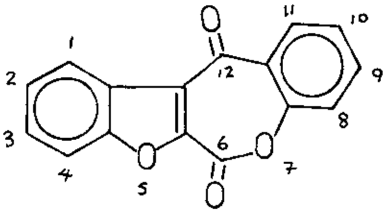


(26) R' : R" : O

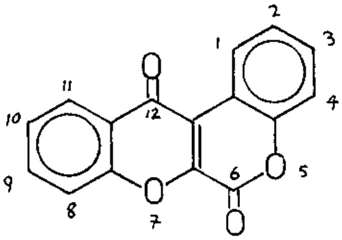
(27) R' : R" : H



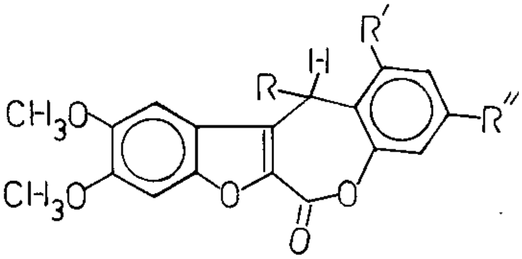
(28)



(29)



(30)



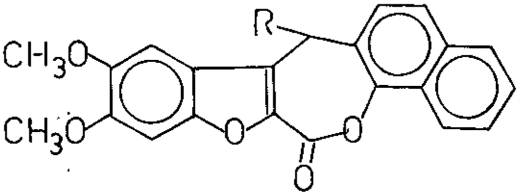
(15) R : R' : H, R" : OCH_3

(16) R : R" : H, R' : OCH_3

(31) R : Br, R' : H, R" : OCH_3

(33) R : OEt, R' : H, R" : OCH_3

(35) R : ⊕ (carbonium ion)



(20) R : H

(32) R : Br

(34) R : OEt

be seen shortly, and by the fact that both gave the same tetramethyl ether on methylation with methyl iodide/potassium carbonate in acetone.

The reaction of the compound (**6**) with 3-methoxyphenol in acetone containing potassium carbonate, provided the ether (**7**) in 89% yield.

Unfortunately, the ether (**7**) resisted all attempts to induce it to participate in a Claisen rearrangement at elevated temperatures, and was recovered from these reactions. While it was possible that the Claisen rearrangement was not favoured by the reduced double bond character of the 2,3 bond of the benzofuran, the geometry of the system might be a key factor. It has been demonstrated[4] that the compound (**11**) participated in the Claisen rearrangement process in refluxing diethylaniline, to yield eventually the lactone (**12**), while the isomeric compound (**13**) was relatively inert under those conditions and was recovered from the reaction mixtures.

Because the Claisen rearrangement is known to be dramatically catalysed by trifluoroacetic acid[5], the rearrangement of the ether (**7**) in refluxing trifluoroacetic acid was attempted, but while a rearrangement was achieved, the products of the reaction were the compounds (**8**) and (**10**) in 45% and 22% yields respectively.

Basic hydrolysis of the compound (**8**) produced the acid (**14**) quantitatively, and this was cyclised to the lactone (**15**) by thionyl chloride in pyridine, in 80% yield. This sequence of reactions distinguished, unequivocally, the isomer (**8**) from the compound (**9**) which could not produce a lactone. By a similar sequence of reactions, the compound (**10**) was converted into the tetracyclic lactone (**16**) in 85% yield.

In order to explore the scope of the reaction, the naphthyl ether (**17**), prepared by reaction of the benzofuran (**6**) with 1-naphthol in acetone and potassium carbonate, was similarly rearranged to the compound (**18**), in 28% yield. Basic hydrolysis of the compound (**18**) gave the carboxylic acid (**19**) quantitatively, and this was cyclised to the lactone (**20**) in 90% yield.

The rearrangement of the ether (**17**) did not produce a detectable amount of the isomeric compound (**21**), the product of para- rearrangement, thus suggesting that this rearrangement will provide a viable route to the 3-(2'-hydroxyarylmethyl)-benzofurans.

The rearrangements of aryl alkyl ethers by Lewis acids have been investigated by Dewar et al.[6], and a carbonium ion mediated mechanism has been proposed for these reactions.

The carbonium ion intermediate (22), which might be formed by fragmentation of the protonated ether (23) , should not be as stable as the carbonium ion (24), formed as shown in scheme 2. The carbonium ion structure (22) represents one of *three* possible canonical forms, in two of which the site of the positive charge is α- or vinylogously α- to the electron-withdrawing ethoxycarbonyl group. On the other hand, the carbonium ion structure (24) represents one of *nine* possible canonical forms, none of which possesses the undesirable feature of having the site of the positive charge adjacent to an electron-withdrawing group.

We therefore suggest that the ion (24) was the co-fragment in the cleavage-recombination process, and that this reaction should be generally applicable to all compounds of structure similar to compounds (7) and (17), provided that the molecules do not contain additional features which would either destabilise the intermediate carbonium ion, or reduce the nucleophilicity of the phenolic co-fragment. It also seems very likely that the substitution reactions of the bromo compound (6) proceed via the ion (24).

This method of preparing compounds like (15), (16) and (20) is distinctly more efficacious to preparations which would require the deoxybenzoins, like compound (25), because of the problems inherent in the preparation of these deoxybenzoins. Whalley et al.[7] have investigated the preparation and chemistry of these compounds and they have drawn attention to the difficulty of preparing 3-aroylbenzofurans (26), even by oxidation of compounds like (27), as well as to the easy conversion of compounds like (28) and (29) into the rotenonoid molecule (30).

Both lactones (15) and (20) were quantitatively converted into the bromo compounds (31) and (32) respectively, by irradiating their solutions in carbon tetrachloride containing N-bromosuccinimide, with a high intensity visible lamp.

These bromo compounds were very susceptible to nucleophilic substitution and by refluxing their solutions in ethanol were converted, quantitatively, into the ethers (33) and (34) respectively.

These substitution reactions might well be Sn1 reactions, as the carbonium ion intermediate, for example (35), should possess some aromatic character, and hence appreciable stability, so leading to its easy formation.

REFERENCES

1. Present address: Schering Corporation, 60 Orange Street, Bloomfield, New Jersey 07003, U.S.A.

2. V.G.S. Box and C.G. Humes, *Heterocycles*, 1980, **14**, 1775.
3. W.B. Whalley, *J. Chem. Soc.*, 1953, 3479.
4. V.G.S. Box and K.A.L. Allen, *Rev. Latinoamer. Quim.*, 1979, **10**, 160.
5. H. Schmid, U. Widmer and H.-J. Hansen, *Helv. Chim. Acta*, 1973, **56**, 105; H. Schmid, U. Widmer and H.-J. Hansen, *Helv. Chim. Acta*, 1973, **56**, 2644.
6. M.J.S. Dewar and N.A. Puttmann, *J. Chem. Soc.*, 1960, 959; M.J.S. Dewar and P.A. Spanninger, *J. Chem. Soc., Perkin Trans. II*, 1972, 1204.
7. W.B. Whalley and G. Lloyd, *J. Chem. Soc.*, 1956, 3213; W.B. Whalley and S.A. Bokhari, *J. Chem. Soc.*, 1963, 5322.

Received, 7th December, 1982