Tetrahedron Vol. 41, No. 20, pp. 4685 to 4690, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

A NEW TYPE OF ABNORMAL REIMER-TIEMANN REACTION

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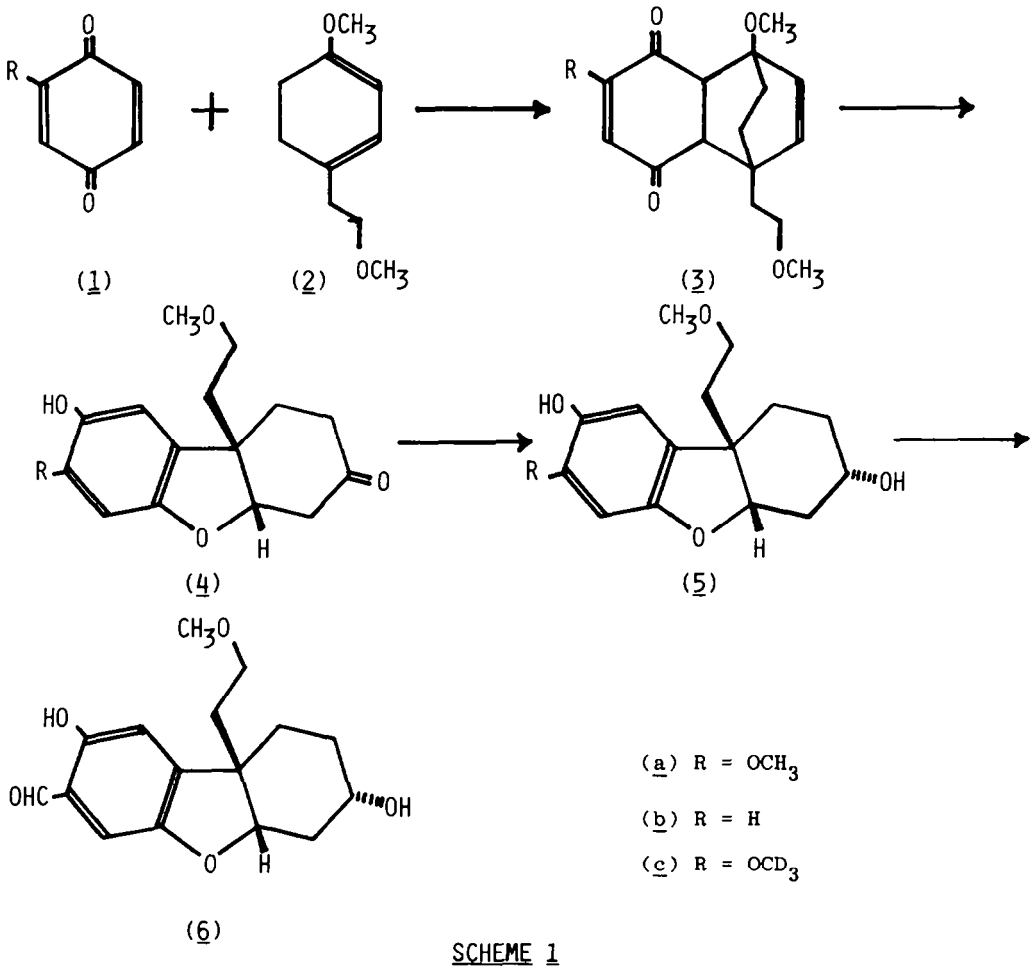
(*Received in UK* 28 *June* 1985)

Abstract- The treatment of 1,2,3,4,4a,9b-hexahydro-3,8-dihydroxy-7-methoxy-9b-(2'-methoxyethyl)dibenzofuran with chloroform and aqueous potassium hydroxide under conventional Reimer-Tiemann reaction conditions resulted in the replacement of the 7-methoxyl group by a carbaldehyde one. A choice between alternative pathways for this novel displacement has been facilitated by examination of the behaviour of the corresponding 7-trideuteromethoxy compound. Dichlorocarbene attack at position 7 rather than at the unsubstituted position 9 is shown to be due to steric encumbrance at the latter site.

Since its discovery some hundred or so years ago the Reimer-Tieman reaction has become the standard method for the introduction of an ortho or para carbaldehyde group into a phenol under alkaline conditions[1]. Despite the relative antiquity of the reaction very few complicating features have been uncovered. The only notable difficulty is the tendency of o- or p-alkylphenols to undergo dichlorocarbene attack at the substituted ring carbon atom leading to cyclohexadienone formation, a process generally referred to as the "abnormal" Reimer-Tiemann reaction. In the course of a synthetic investigation we desired to introduce a functionalised carbon atom at position 9 of the dibenzofuran (5a) and attempted to utilise the Reimer-Tiemann reaction for this purpose. This paper reports the unexpected consequences of the reaction together with observations which establish its pathway and raison d'etre.

The synthesis of the dibenzofuran (5a) and related substrates is outlined in Scheme 1. The diene (2) was prepared by reduction of p-(methoxyethyl)anisole with calcium in liquid ammonia and ethanol to the cyclohexa-1,4-diene, followed by conjugation by heating in the presence of propionic acid to give an equilibrium mixture of the 1,3-diene (2) and its 1,4-isomer in the approximate ratio of 2:1, as estimated by nmr. Diels-Alder addition of 2-methoxybenzoquinone to this diene mixture provided the adduct (3a) with spectroscopic properties in full accord with the assigned structure. As anticipated the adduct was very sensitive to traces of acid and was readily rearranged by acid treatment[2] to the ketone (4a). Subsequent reduction of (4a) with sodium borohydride in ethanol yielded the dibenzofuran (5a).

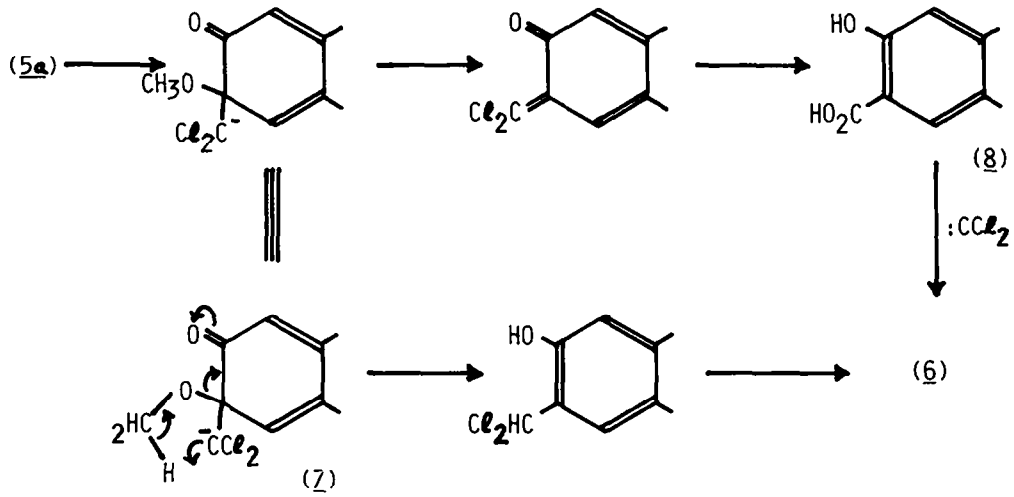
+A preliminary report on part of this work has already appeared: C. W. Bird and A. L. Brown, Chem. Ind. (London), 1983, 827.



SCHEME 1

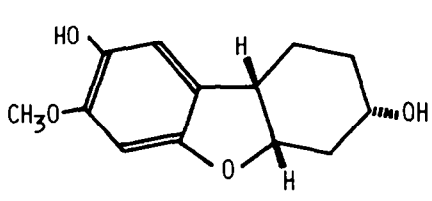
The reaction of the dibenzofuran (5a) with chloroform in aqueous potassium hydroxide solution provided a product readily identified as an ortho phenolic aldehyde by virtue of a strong hydrogen-bonded carbonyl absorption at 1660 cm^{-1} in its infrared spectrum, and singlets at 9.78 and 11.03 ppm in the ^1H nmr spectrum for the aldehyde and phenolic hydroxyl protons respectively. However, two rather than one aromatic proton remained as indicated by singlets at 6.35 and 6.64 ppm although only one of the original methoxyl singlets was present. This information led to the inescapable conclusion that the product had the structure (6), in which the original phenolic methoxyl group had been replaced by the carbaldehyde one. That this was indeed the correct structure was confirmed by preparing the same compound by a similar Reimer-Tiemann reaction on the phenol (5b).

An intriguing feature of the unprecedented formation of (6) from (5a) was the formal reduction implicit in its generation. Two pathways appeared possible for this transformation and are summarised in Scheme 2. The first entails formation of the hydroxycarboxylic acid (8) by replacement of the methoxyl group, followed by a further attack by dichlorocarbene and displacement of the carboxyl group. Although no appreciable amount of (8) appeared to accumulate during the reaction, such a displacement occurs to a very minor extent during the Reimer-Tiemann



SCHEME 2

reaction on salicylic acid[3]. A more economical possibility entailed an intramolecular proton transfer in the intermediate (7) leading to the departure of the methoxyl group as formaldehyde. Despite failure to detect the formation of any formaldehyde during the conversion of (5a) to (6) the attractiveness of the latter route led us to seek more definitive evidence. For this purpose the trideuteromethoxydibenzofuran (5c) was synthesised following the sequence depicted in Scheme 1. The requisite 2-trideuteromethoxybenzoquinone was obtained by oxidation of m-trideuteromethoxyphenol with potassium nitrosodisulphonate (Fremy's salt). Subjection of (5c) to the Reimer-Tiemann reaction provided the aldehyde (6) with no deuterium enrichment of the carbaldehyde proton detectable by nmr. Consequently we conclude that the overall displacement of the methoxyl by the carbaldehyde group proceeds via the intermediate (8).



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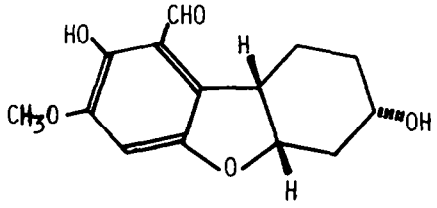

(10)

In neither of the Reimer-Tiemann reactions conducted on (5a) or (5b) was any of the isomeric 9-carbaldehyde detected. Examination of molecular models shows that the 9-position is subject to considerable steric hindrance which would obstruct the approach of the dichlorocarbene to this potential reaction site. This situation does not appertain in the dibenzofuran (9), which was prepared from 1-methoxycyclohexa-1,3-diene and 2-methoxybenzoquinone following the route shown in Scheme 1. Subjection of (9) to the Riemer-Tiemann reaction provided solely the 9-carboxaldehyde (10), and no evidence was obtained for the formation

of an aldehyde resulting from displacement of the methoxyl group. These observations thus support our conclusion that steric hindrance is responsible for the observed course of the Reimer-Tiemann reaction on the dibenzofuran (5a).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded for nujol mulls or liquid films on a Pye-Unicam SP200 or Perkin-Elmer 157 spectrophotometer. Nmr spectra were recorded at90 Mhz on a Perkin-Elmer spectrometer and at 200 MHz on a Nicolet NT200 spectrometer for $CDCl_3$ solutions with internal TMS. Mass spectra were obtained by the ULIRS Mass Spectrometry Service at QEC (MS25) and accurate masses by the service at the School of Pharmacy.

Methylation of p-Methoxyphenethyl alcohol

A solution of p-methoxyphenethyl alcohol (20.9g) in THF (60ml) was added dropwise to a stirred suspension of sodium hydride (11.2g) in refluxing THF (200ml). When hydrogen evolution had ceased, a solution of iodomethane (13ml) in THF (40ml) was added dropwise and the resulting mixture heated under reflux for a further 3 hours. The reaction mixture was then cooled in an ice-bath and the excess sodium hydride destroyed by the careful addition of water. The aqueous phase was separated and extracted with diethyl ether. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4) and the solvents removed in vacuo to afford p-(2'-methoxyethyl)anisole (21.2g,93%) as a colourless liquid, bp. 92-94° at 1.8 mmHg(Found:C,72.41;H,8.47.Calc. for $C_{10}H_{14}O_2$:C,72.26;H,8.49%);Nmr 2.78(t,2H, H-1',J=7.0Hz),3.30(s,3H,OCH_3),3.51(t,2H,H-2',J=7.0Hz),3.70(s,3H,ArOCH_3),6.79(d,2H, H-2 and H-6,J=8.7Hz),7.09(d,2H,H-3 and H-5).

1-Methoxy-4-(2'-methoxyethyl)cyclohexa-1,3-diene(2)

Calcium (13.9g) was dissolved in distilled liquid ammonia (600ml) stirred under nitrogen at -60°. A solution of p-(2'-methoxyethyl)anisole (19.0g) in dry hexane (50ml) was added dropwise, followed by ethanol (40ml) in hexane (150ml) over a period of 1½ hours. The cooling bath was removed and additional hexane (300ml) added slowly. The reaction mixture was allowed to stir at room temperature under a nitrogen atmosphere overnight to permit complete evaporation of the ammonia. The precipitated calcium ethoxide was filtered off and the filtrate evaporated in vacuo to give 1-methoxy-4-(2'-methoxyethyl)cyclohexa-1,4-diene as a colourless liquid (15.5g,81%)(Found: M^+ 168. Calc. for $C_{10}H_{16}O_2$:M^+ 168);Nmr 2.28(t,2H,H-1', J=7.0Hz),2.68-2.78(m,4H,H-3 and H-6),3.34(s,3H,OCH_3),3.48(t,2H,H-2',J=7.0Hz), 3.54(s,3H,OCH_3),4.60-4.65(m,1H,H-2),5.43-5.48(m,1H,H-5).

The 1,4-diene (10.5g) was heated with propionic acid (0.1ml) at 170° for 6 hours when nmr monitoring indicated that an equilibrium with the 1,3-isomer had been reached. The principal distinguishing features of the nmr spectrum of the 1,3-diene (2) were at 2.25(br.s,H-5 and H-6),4.90(d,H-2,J=6.4Hz) and 5.61(d,H-3,J=6.4 Hz). The nmr spectrum indicated that the mixture comprised the 1,3-diene 62%, 1,4-diene 30% and p-(2'-methoxyethyl)anisole 8% formed by re-aromatisation. The mixture was used directly for the Diels-Alder reactions.

2-Trideuteromethoxybenzo-1,4-quinone(1c)

Resorcinol (6.6g) was added to a solution of sodium methoxide (from 0.7g sodium) in methanol (30ml) and the solution heated under reflux. Trideuteromethyl p-toluenesulphonate[4](5.7g) was added and refluxing continued for a further 2 hours. The mixture was allowed to stand at room temperature until precipitation of sodium p-toluenesulphonate was complete and then filtered. The filtrate was evaporated in vacuo and the residue chromatographed on silica gel in toluene-ethyl acetate (9:1) to give 3-trideuteromethoxyphenol (42%),(Found: M^+ 127. Calc.

for $C_7H_5D_3O_2$:M^+ 127);IR 3350br(OH),2250,2220,2120 and 2060(C-D stretches)cm^{-1}; Nmr 6.3-6.5(m,3H,H-3,4 and 5),6.72(s,1H,OH),6.9-7.3(m,1H,H-5).

The phenol (3.2g) was dissolved in methanol (125ml) and added to a solution of potassium nitrosodisulphonate (15.1g) in water (755ml) containing sodium acetate (2.0g). The mixture was allowed to stand in the dark for 1 hour and the methanol then evaporated in vacuo. The crude product was isolated by ether extraction and crystallised from 40/60°petroleum ether to give the pure quinone (23%).(Found: M^+ 141. Calc. for $C_7H_3D_3O_2$: M^+ 141); Nmr 5.94(s,1H,H-3),6.69(s,2H,H-5 and H-6).

Preparation of Diels-Alder Adducts

1-Methoxy-4-(2'-methoxyethyl)cyclohexa-1,3-diene (10.5g,62%) and 2-methoxybenzo-1,4-quinone[5](5.3g) in dry benzene (100ml) were heated under reflux for 4 hours. The benzene was evaporated in vacuo and the residue chromatographed on silica gel in toluene-ethyl acetate (7:3) to yield 1,4,4a,8a-tetrahydro-1,7-dimethoxy-4-(2'-methoxyethyl)-1,4-ethanonaphthalene-5,8-dione (3a) (9.3g,79%) as a brown powder, mp. 92-94°(Found:C,65.97;H,8.20. Calc. for $C_{17}H_{22}O_5$: C,66.01; H,8.08%);IR 1695, 1655, 1612 cm^{-1}; Nmr 1.56-1.70(m,3H),1.88-2.00(m,3H),2.91(d,1H,H-4a,J=8.4Hz), 3.34(s,3H,2'-OCH_3),3.42(s,3H,1-OCH_3),3.55-3.68(m,3H,H-8a and H-2'),3.72(s,3H,7-OCH_3),5.84(s,1H,H-6),5.96(d,1H,H-2,J=8.6Hz),6.13(d,1H,H-3,J=8.6Hz),

The same basic procedure was used to prepare the following adducts:-

(i) The adduct (3c) from 2-trideuteromethoxybenzoquinone and the diene (2)(16%) (Found:M^+ 309. Calc. for $C_{17}H_{19}D_3O_5$:M^+ 309);Nmr identical to that for (3a) above except for the absence of the methoxyl singlet at 3.72ppm.

(ii) 1,4,4a,8a-Tetrahydro-1-methoxy-4-(2'-methoxyethyl)-1,4-ethanonaphthalene-5,8-dione (3b) (76%) from benzoquinone and the diene (2) was obtained as a gum which rearranged on attempts to induce crystallisation. Nmr 1.38-1.80(m,4H, CH_2CH_2),1.92(t,2H,H-1',J=7Hz),2.95(d,1H,H-4a,J=9Hz),3.30(d,1H,H-8a,J=9Hz), 3.33(s,3H,2'-OCH_3),3.42(s,3H,1-OCH_3),3.57(t,2H,H-2',J=7Hz),5.93(d,1H,H-2,J=9Hz),6.20(d,1H,H-3,J=9Hz),6.60(s,2H,H-6 and H-7).

(iii) 1,4,4a,8a-Tetrahydro-1,7-dimethoxy-1,4-ethanonaphthalene-5,8-dione (72%) from 2-methoxybenzoquinone and methoxycyclohexa-1,3-diene,mp.130-132°(Found: C,68.01;H,6.56.Calc. for $C_{14}H_{16}O_4$:C,67.72;H,6.56%);IR 1690,1640,1600 cm^{-1};Nmr 1.4-2.1(m,4H,CH_2CH_2),2.17(s,1H,H-4),3.05(d,1H,H-4a,J=9Hz),3.35(d,1H,H-8a,J=9Hz),3.45(s,3H,1-OCH_3),3.75(s,3H,7-OCH_3),5.90(s,1H,H-6),6.15-6.25(m,2H,H-2 and H-3).

Rearrangement of Diels-Alder Adducts

Hydrochloric acid (2M,20ml) was added to a solution of the adduct (3a) (9.3g) in ethanol (100ml) and the reaction mixture allowed to stand at room temperature overnight. Filtration gave 1,2,3,4,4a,9b-hexahydro-8-hydroxy-7-methoxy-9b-(2'-methoxyethyl)-3-oxodibenzofuran (4a) (6.0g,68%),mp.137-139° from ethyl acetate (Found:C,65.85;H,6.90. Calc. for $C_{16}H_{20}O_5$:C,65.74;H,6.90%);IR 3360,1725 cm^{-1}; Nmr 1.81(m,6H,H-1,1' and 2),2.72(dd,1H,H-4,J=16.5 and 3.3Hz),2.83(dd,1H,H-4,J=16.5 and 3.3Hz),3.28(s,3H,2'-OCH_3),3.47(t,2H,H-2',J=6.5Hz),3.84(s,3H,7-OCH_3),5.04(t,1H, H-4a,J=3.3Hz),5.38(s,1H,OH),6.35(s,1H,H-6),6.64(s,1H,H-9).

The same procedure was used to prepare the following dibenzofurans:-

(i) The dibenzofuran (4c) (62%) from (3c)(Found: M^+ 295. Calc. for $C_{16}H_{17}D_3O_5$: M^+ 295);Nmr identical to that of (4a) except for the absence of the methoxyl singlet at 3.84ppm.

(ii) 1,2,3,4,4a,9b-Hexahydro-8-hydroxy-9b-(2'-methoxyethyl)-3-oxodibenzofuran[6](4b) (77%) did not crystallise out and was isolated by evaporation of the reaction mixture and chromatography of the residue on silica gel in toluene-ethyl acetate (7:3),mp.114-117° from toluene-ethyl acetate(Found:C,69.14;H,7.21.

Calc. for $C_{15}H_{18}O_4$:C,68.68;H,6.92%);IR 3380,1725cm^{-1};Nmr 1.75-2.38(m,6H,H-1,1'and 2),2.66(dd,1H,H-4,J=17 and 3.5Hz),2.88(dd,1H,H-4,J=17 and 3.5Hz),3.29(s,3H,2'-OCH_3) 3.49(t,2H,H-2',J=7Hz),5.04(t,1H,H-4a,J=3.5Hz),6.29(s,1H,OH),6.61(s,3H,H-6,7 and 9). (iii) 1,2,3,4,4a,9b-Hexahydro-8-hydroxy-7-methoxy-3-oxodibenzofuran (62%) had mp. 140-142°(Found:C,66.69;H,6.10. Calc. for $C_{13}H_{14}O_4$:C,66.65;H,6.02%);IR 3350,1710cm^{-1} Nmr 1.85-2.3(m,4H),2.7-2.9(m,2H),3.55-3.9(m,1H,H-9b),3.84(s,3H,OCH_3),5.1-5.35(m, 1H,H-4a),6.38(s,1H,H-9),6.76(s,1H,H-6).

Reduction of Dibenzofuranones

Sodium borohydride(135mg) was added portionwise to a solution of the dibenzofuranone (4a) (1.0g) in ethanol (15ml) and the reaction mixture allowed to stand at room temperature overnight. Water was added to destroy any remaining borohydride and the ethanol then evaporated *in vacuo*. The residue was then extracted with chloroform to isolate the alcohol (5a) as a gum (Found:M^+ 294. Calc. for $C_{16}H_{22}O_5$: M^+ 294);IR 3400cm^{-1};Nmr 1.25-2.25(m,6H,H-1,2 and 4),1.83(t,2H,H-1',J=7Hz),2.15(s, 1H,OH),3.24(s,3H,2'-OCH_3),3.33(t,2H,H-2',J=7Hz),3.60-3.91(m,1H,H-3),3.81(s,3H,7-OCH_3),4.51(t,1H,H-4a,J=6Hz),6.45(s,1H,H-6),6.65(s,1H,H-9).

Similarly reduction of (4c) gave (5c) whose spectral properties only differed from (5a) in lacking the methoxyl singlet at 3.81ppm. Also (4b) yielded (5b) as a gum (Found:M^+ 264. Calc. for $C_{15}H_{20}O_4$:M^+ 264);IR 3350cm^{-1};Nmr 1.15-2.20(m,8H,H-1, 1',2 and 4),3.23(s,3H,2'-OCH_3),3.42(t,2H,H-2',J=7Hz),3.51(s,1H,OH),3.60-3.85(m,1H, H-3),4.48(t,1H,H-4a,J=6Hz),6.59(s,3H,H-6,7 and 9),7.65(s,1H,OH) and reduction of the corresponding dibenzofuranone gave (9)(Found:M^+ 236. Calc. for $C_{13}H_{16}O_4$:M^+ 236);Nmr 1.20-2.10(m,6H,H-1,2 and 4),2.16(s,1H,OH),3.1-3.4(m,1H,H-9b),3.65-4.0(m +s,4H,H-3 and OCH_3),4.6-4.9(m,1H,H-4a),6.45(s,1H,H-9),6.72(s,1H,H-6),7.3(s,1H,OH).

Reimer-Tiemann Reactions

The phenol (5a) (0.4g) and chloroform (2ml) were added to potassium hydroxide solution (15%,15ml) and the mixture heated at 80° for 2 hours under nitrogen. The cooled mixture was acidified (aq HCl) and the product isolated by chloroform extraction. Subsequent chromatography on silica gel in toluene-ethyl acetate (1:1) afforded 7-formyl-1,2,3,4,4a,9b-hexahydro-3,8-dihydroxy-9b-(2'-methoxyethyl)dibenzofuran (6) (115mg,29%) as a gum (Found:M^+292.1306. Calc. for $C_{16}H_{20}O_5$:292.1311) IR 3420,1660cm^{-1};Nmr 1.20-2.34(m,6H,H-1,2 and 4),1.92(t,2H,H-1',J=7Hz),2.26(s,1H, OH),3.25(s,3H,2'-OCH_3),3.36(t,2H,H-2',J=7Hz),3.70-4.05(m,1H,H-3),4.62(t,1H,H-4a, J=6Hz),6.76(s,1H,H-9),6.93(s,1H,H-6),9.78(s,1H,CHO),11.03(s,1H,OH). The same aldehyde was obtained from (5b) (23%) and (5c) (29%).

Under the same conditions (9) yielded 9-formyl-1,2,3,4,4a,9b-hexahydro-3,8-dihydroxy-7-methoxy-dibenzofuran (10) (34%) as an oil(Found:M^+264.1005. Calc. for $C_{14}H_{16}O_5$:M^+ 264.0998);IR 3440,1650cm^{-1};Nmr 1.6-2.7(m,7H,H-1,2,4 and OH),3.3-3.7 (m,1H,H-9b),3.84(s,3H,OCH_3),4.0-4.3(m,1H,H-3),4.6-4.7(m,1H,H-4a),6.76(s,1H,H-6), 10.10(s,1H,CHO),10.20(s,1H,OH).

Acknowledgements- We wish to thank Professor Carl H. Snyder for invaluable comments and the S.E.R.C. for financial support (A.L.B.).

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