A GENERAL APPROACH TO THE SYNTHESIS OF SUBSTITUTED 5a,11a-DEHYDRO-[1]BENZOPYRAN [4,3-C][1]BENZOPYRAN-5-ONES

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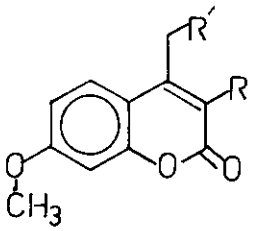
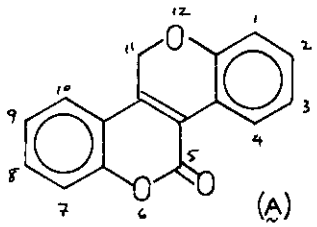
Abstract: A general approach to the syntheses of 5a,11a-Dehydro-[1]benzopyran[4,3-C][1]benzopyran-5-ones by the Claisen rearrangement of 3-bromo-4-Aryloxymethyl-coumarins is outlined. The possible uses of these 5a-11a-Dehydro-[1]benzopyran [4,3-C][1]benzopyran-5-ones in the syntheses of isoflavanoids and rotenoids are discussed.

4-Methylcoumarins are readily available in high yields by the Pechmann reactions of phenols with ethyl acetoacetate, under the influence of various catalysts[1]. We have sought to use these simple coumarins as intermediates in the syntheses of isoflavanoids and the closely related rotenoid molecules, and now wish to present one of our approaches to the isoflavanoid/rotenoid skeleton via the 5a,11a-dehydro-[1]benzopyran[4,3-C][1]benzopyran-5-one skeleton (A).

4-methyl-7-methoxycoumarin(1) was converted quantitatively into the 3-bromo-coumarin (2) by treatment with Br_2 in $CHCl_3$, in the presence of anhydrous K_2CO_3 to remove the HBr formed. (2) was then converted into the 3-bromo-4-bromomethyl-7-methoxycoumarin(3) by N-bromosuccinimide in CCl_4 on exposure to high intensity visible light, in 98% yield. (3), m.p. 182-184° showed ν_{max} 1724, 1621 and 1601 cm^{-1}; $\delta_{CDCl_3 + DMSO}$ 3.90 (3H, s), 4.76 (2H, s, $-CH_2-Br$), 6.87 and 6.93 (each 1H, H-8 and H-6 respectively) and 7.72 (1H, d, J = 8.5 Hz, H-5). The dibromide (3) was treated with the sodium salt of the model phenol, 1-naphthol, in benzene, conditions conducive to the C-alkylation of phenols[2], in the hope of preparing the compound (4) which could then be cyclised to the rotenoid (5). We did not isolate from our reaction any material corresponding to (4) or (5), but obtained the ether (6) in 23% yield, along with some, as yet, unidentified materials. The phase transfer reaction[3] of the benzene solution of the dibromide (3) with aqueous sodium 1-napthoxide, catalysed by tetra-n-butylammonium iodide, yielded the same reaction products but with an improvement in the yield of (6) to 53%.

(6), m.p. 171-173°, ν_{max} 1731, 1625 and 1604 cm^{-1}; δ_{CDCl_3} 3.83 (3H, s), 5.53(2H, s, $-CH_2-O-Ar$), 6.67 to 8.20 (10H, m, aromatic protons) was rearranged into the compound (7) in 48% yield by refluxing its solution in diethylaniline for 30 minutes. (7) m.p. 212-215°, ν_{max} 1724 and 1620 cm^{-1}, δ_{CDCl_3} 3.80 (3H, s), 5.30 (2H, s), 5.78 (2H, m, H-1 and H-3), 7.17 to 7.87 (5H, m), 8.12





(A)

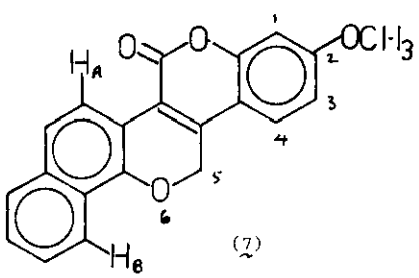
(1) R = R' = H

(2) R = Br, R' = H

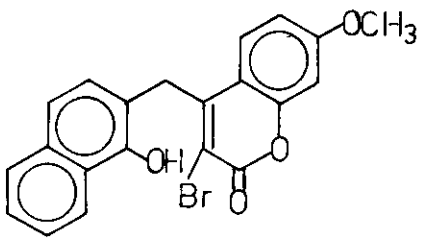
(3) R = R' = Br

(6) R = Br, R' = 1-naphthoxyl

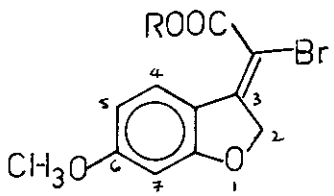
(8) R = Br, R' = Eto-



(7)

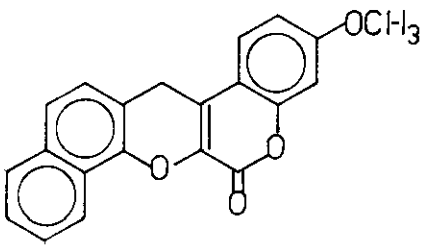


(4)

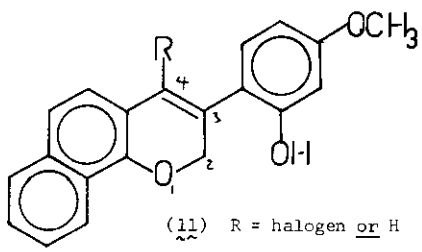


(9) R = H

(10) R = CH_3

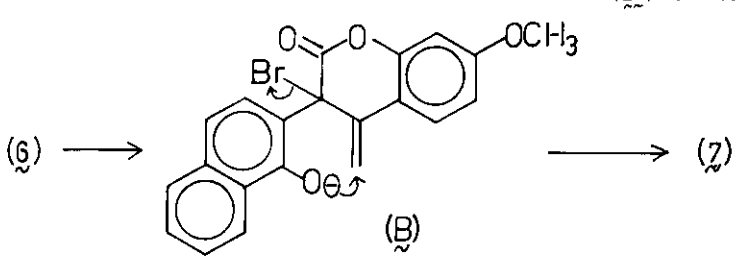


(5)



(11) R = halogen or H

(12) R = COOR'



(6) → (B) → (7)

SCHEME I

(1H, m, H_B) and 8.52 (1H, d, J = 8.5 Hz, H_A) was no doubt formed as shown in scheme I, via the Claisen rearrangement product (6).

During attempts to optimise the yield of the ether (6) by varying the solvent, base and other conditions, the instability of the dibromo-compound (3) in alkaline solutions was noted. Treatment of (3) in 95% aqueous ethanol with 2 moles of sodium hydroxide rapidly resulted in the formation of (8) in 5% yield and the benzofuranoid compound[4] (9) in 94% yield.

(8), m.p. 112-115°, showed ν_{max} 1730 and 1620 cm^{-1}, and signals in the N.M.R. spectrum at δ_{CDCl_3} 1.23 (3H, t, J = 7.0 Hz), 3.60 (2H, q, J = 7.0 Hz), 3,87 (3H, s), 4.85 (2H, s), 6.75 and 6.83 (2H, H-8 and H-6 respectively), 7.78 (1H, d, J = 8.0 Hz, H-5).

(9) m.p. 165-166°, showed ν_{max} 3300-2200 (carboxylic - OH) and 1670 cm^{-1}; δ_{CDCl_3} 3.75 (3H, s), 5.10 (2H, s, H-2), 6.48 (2H, m, H-5 and H-7), and 8.32 (1H, d, J = 9.0 Hz, H-4), it was not phenolic but was indisputably a carboxylic acid which could be methylated with diazomethane to the unstable ester (10) which showed ν_{max} 1732, 1624 and 1604 cm^{-1}; δ_{CDCl_3} 3.78 and 3.82 (each 3H,s), 5.08 (2H, s, H-2), 6.37 and 6.48 (each 1H, H-7 and H-5 respectively) and 8.42 (1H, d, J = 8.5 Hz, H-4).

The stereochemistry of the olefinic bond of (9) was as shown, since this olefinic bond was not involved in the reaction of (3) with hydroxide, which seemed to be a simple saponification of the lactone followed by an intramolecular Sn2 displacement of bromide by phenoxide. The N.M.R. deshielding of H-4 also attested to the stereochemistry of the olefinic bond, as its chemical shift had gone from δ7.72 as in (3), and δ7.78 as in (8), to δ8.32 in (9) and δ8.42 in (10).

We regard (7) as a very useful synthetic intermediate as its hydrolysis and decarboxylation would provide an isoflavanoid of structure (11). Further, C-2 of the ester (12) is now the potential site of a carbanion and hence able to be the site of attachment of the appropriate one carbon unit needed to complete the synthesis of a rotenoid skeleton. It should be noted that the molecule (5) is skeletally identical to the rotenoid proposed from (12), and so our lack of success with the C-alkylation study should become insignificant.

Acknowledgement

We wish to acknowledge the able assistance of Mr. Kingsley A. Thomas, a U.W.I. summer student, (1979), in the preparation of the 3-bromo-4-bromomethyl-7-methoxycoumarin.

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Received, 14th July, 1980