IMPROVED PREPARATION OF PRECOCENE II. UNEXPECTED RESULTS IN THE REDUCTION OF ALKOXY SUBSTITUTED ACETOPHENONES AND 4-CHROMANONES WITH SODIUM BOROHYDRIDE

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Abstract - An improved preparation of natural pro-allatocidin precocene II (6) is reported. Starting from methoxyhydroquinone (1), Fries condensation with acid 2 led to the hydroxychromanone 3, which by further methylation, reduction and dehydration afforded chromene 6 in 77% overall yield. In addition, complementary studies related to the synthetic sequence have also been carried out, i.e., the influence of water contents on the initial Fries rearrangement and the scope of an anomalous reaction course in the reduction of aromatic ketones with $NaBH_4$/MeOH in which, depending upon the activation of the carbonyl group, the formation of the methyl ether instead of that of the corresponding alcohol might be observed.

INTRODUCTION

Toxicity exhibited by precocenes, particularly in vertebrates [1,2] has tone down the potential interest of these compounds for insect control. However, their peculiar properties, in terms of mechanism of bioactivation and reactivity, have led to consider these chromene structures as valuable models for toxicological studies [3,4]. Thus, recent results from our laboratory on the reactivity of 3,4-epoxyprecocene II (the postulated bioactivated intermediate responsible for the biological activity of precocene II (6) in invertebrate [5,6] and vertebrate organisms[1]), with different nucleophilic substrates, have questioned the role of this intermediate in the cytotoxic process. From our preliminary study, it seems that an alternative mechanism, probably involving radical species, could be envisaged. Consequently, the toxicological studies needed for confirming our hypothesis would demand precocene II to be available in important amounts.

In this context, several synthetic sequences for preparation of 2H-1-benzopyran structures related to precocenes have been published [7-11]. We considered that the route which involves the condensation of an appropriate phenol with 3-methylbut-2-enoic acid (2) to afford the corresponding 4-chromanone derivative 5, followed by reduction and dehydration, was the most convenient approach for synthesis of natural precocenes. Thus, compound 5 is a versatile intermediate for an easy preparation of different analogs potentially useful for our mechanistic and toxicological studies, such as the corresponding 3,4-dihydroderivatives or those isotopically labelled with ^2H at C-3 and with ^2H or ^{13}C at C-4 [3,12].

However, the above procedure still presents some practical drawbacks for the case of precocene II, since 3,4-dimethoxyphenol, the starting phenol, is not a readily available compound. Likewise, the preparation of this phenol from 3,4-dimethoxybenzaldehyde, through a Baeyer-Villiger oxidation with a peracid followed by hydrolysis of the intermediate formate [13], is tedious and also rather expensive. Therefore, we anticipated that the use of methoxyhydroquinone (1) as starting material might be an advantageous alternative. This compound had been previously used in a preparation of chromene 6, which involved a different synthetic approach based on an initial prenylation with 2-methyl-3-but-2-enol [8].

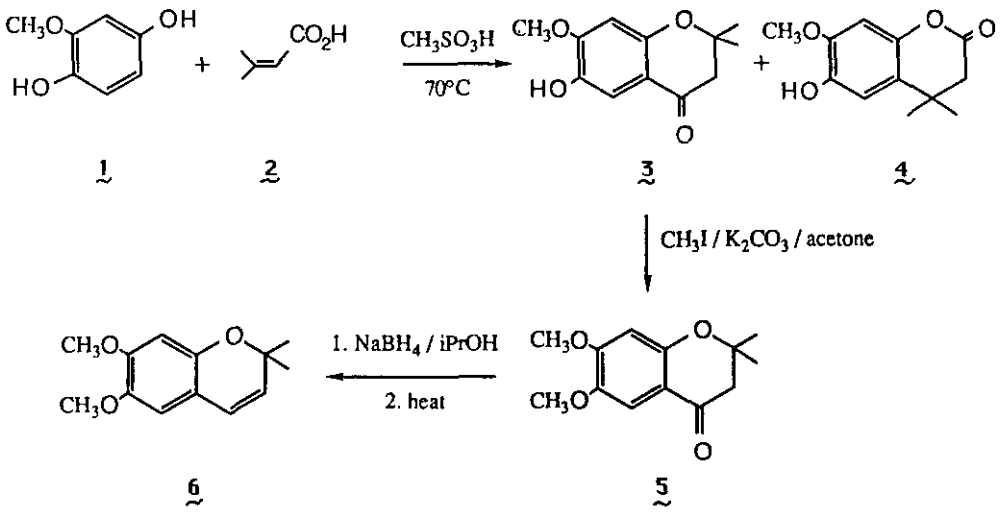
Another step of our synthetic sequence which could be optimized was the reduction of the

4-chromanone 5, usually carried out with $LiAlH_4$. In fact, this reduction had also been described by using $NaBH_4/PdCl_2$ [14], although a great excess of the former reagent and also a light excess of the latter are required for the reaction to proceed satisfactorily.

In the present paper we report on our results of an improved preparation of precocene II, which involved the use of methoxyhydroquinone as starting phenol. Additionally, a study of the reduction of 4-chromanone 5 and structurally related acetophenones with $NaBH_4$ in alcoholic solvents is also presented.

RESULTS AND DISCUSSION

The synthetic sequence used for the preparation of precocene II is depicted in Scheme 1.



Scheme I

Several years ago we reported the use of anhydrous methanesulfonic acid as solvent and catalyst for the condensation of activated phenols with acid 2 [15]. Since methanesulfonic acid is usually available in 70% aqueoussolution, we decided to study the influence of water contents on the reaction course of phenol 1 with acid 2, to explore whether the anhydrisation step could be avoided.

However, as shown in Table 1, the presence of water led to an increasing abundance of dihydrocoumarin 4 in the reaction mixture. This compound could only be separated from the chromanone 3 by chromatographic procedures. Moreover, the overall conversion yields of 3 and 4 decreased with increasing water contents.

The formation of compounds like 4 had been found in the Fries rearrangement of o- and p-methoxyphenyl 3-methylbut-2-enoates by using different solvents and catalysts, including anhydrous methanesulfonic acid, but not when the corresponding methoxy group was at the meta position [6]. In the case of phenol 1, it can be considered that both o and p positions contain oxygenated substituents. Therefore, it seems that the presence of water, rather than the formation of 4, would preclude in some extent the mechanism leading to 4-chromanone 3.

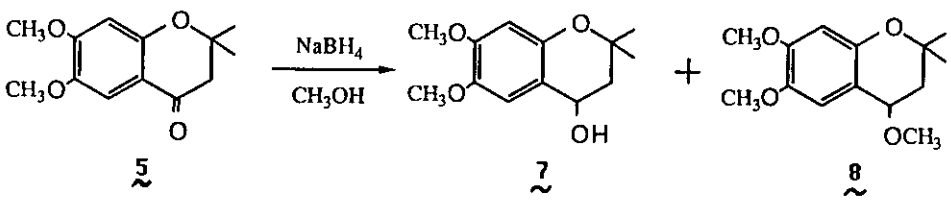
Table 1. Influence of water contents of methanesulfonic acid on the condensation of methoxyhydroquinone (1) with 3-methylbut-2-enoic acid (2).

Solvent[a]	3:4 molar ratio[b]	Overall conversion yield 3 + 4 (%)
CH_3SO_3H 89%	3:1	50
" 95%	5.5:1	60
" 98.5%	18:1	97

[a]Water contents determined by Karl Fischer method.
[b]Estimated by ^1H nmr

In any case, the procedure combining the condensation of phenol 1 with acid 2 in anhydrous methanesulfonic acid with the subsequent methylation of resulting compound 3, afforded excellent overall yields of 4-chromanone 5, being thus much more advantageous than the previously described route.

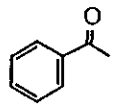
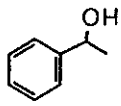
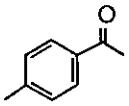
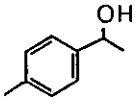
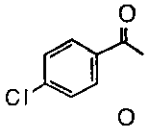
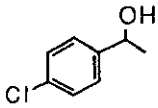
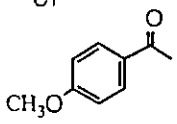
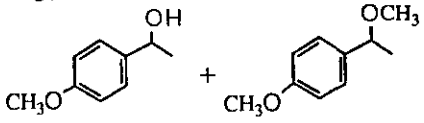
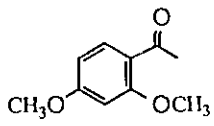
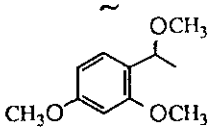
As mentioned above, the reduction of intermediate 5 was another subject of our study. Thus, reaction of 5 with $NaBH_4$ in methanol led to a mixture of the expected chromanol 7 and a compound which was identified as the trimethoxy derivative 8 (Scheme II). This compound was unstable in solution and slowly decomposed on standing to give, as it occurs with chromanol 7, precocene II (6). To our knowledge, there are no precedents of this side-reaction with the $NaBH_4$/MeOH system. Accordingly, we decided to explore its scope, by assaying this reduction on different acetophenones as model substrates, and results of this study are shown in Table 2. Thus, for acetophenone and the corresponding 4-methyl and 4-chloro derivatives, only the reduction product was obtained in good conversion yields. Conversely, the reaction with activated acetophenones led to the concomitant formation of the corresponding methyl ether, which was the sole reaction product for 2,4-dimethoxyacetophenone. From these results, it can be concluded that the formation of the methoxy derivative is closely dependent on the substitution of the aromatic ring, and specifically on the overall electronic effect of this substitution over the benzylic carbon atom subjected to reduction. As shown, significative yields of the methyl ether were only obtained in the presence of strong +M substituents.



5 7 8

Scheme II

Table 2. Influence of the substituents on the reaction of different acetophenones with $NaBH_4$ in methanol.[a]

Substrate	Products	Isolated yield (%)
		88
		90
		96
	 **9** + **10**	76 [b]
		95

[a] Reactions were carried out at room temperature, by using a 1:2:94 substrate: hydride: solvent molecular ratio. For more details, see Experimental.

[b] Referred to methyl ether 10.

On the other hand, the nucleophilicity of the interacting alcohol seemed to be also important. Thus, reduction of 4-methoxyacetophenone in ethanol afforded a minor amount of the corresponding ethoxy derivative, and the use of isopropyl alcohol solely led to the formation of the reduced compound. In view of these results, reduction of chromanone 5 was assayed in isopropyl alcohol. The reaction required a 100% molar excess of $NaBH_4$ for completion, but it cleanly gave chromanol 7, which by subsequent dehydration afforded precocene II (6) in 81% overall yield from 5. In summary, preparation of precocene II was then accomplished through a simple three-step sequence from readily available compounds, in 77% overall yield.

Finally, in order to obtain more information on the putative intermediates accounting for the substitution reaction observed in the $NaBH_4$ reductions, some additional assays with alcohol 9 were carried out. Thus, while treatment of 9 either with methanol or sodium methoxide did not yield the substitution product 10, treatment with $NaBH_4$ in methanol led to the formation of this methoxy

derivative. These results suggest that methanol is in fact the nucleophile which operates, and that reaction probably takes place via an alkoxy boron intermediate. Then, the balance between the nucleofugicity of this moiety - strongly dependent upon the electronic character of the involved benzylic carbon atom -, the relative nucleophilicity of the different species present in the medium and the solvent effects in terms of conditioning the degree of homogeneity among the reagents, might determine the extent of the substitution reaction, and therefore, its potential synthetic utility. Work along this line is now in progress in our laboratory.

EXPERIMENTAL

Ir spectra were registered in carbon tetrachloride solutions on a Perkin Elmer 399B instrument. Nmr were recorded in deuterochloroform solutions on a Bruker Wp-80 SY apparatus operating at 30.13 MHz for ^{1}H. GC-Ms analyses with electron impact were performed with a Hewlett-Packard Model 5995-C instrument, using a OV-101 glass capillary column (25 m). Microanalyses were performed with a Carlo Erba Model 1106 instrument. Unless otherwise stated, organic extracts obtained from treatment of reaction crudes were dried over magnesium sulfate and solvent was removed by evaporation under vacuum. Acetophenone, 4-methylacetophenone, 4-chloroacetophenone and 4-methoxyacetophenone were from Fluka AG. 2,4-Dimethoxyacetophenone was obtained in 95% yield from 2,4-dihydroxyacetophenone by using the procedure described below for preparation of compound 5. nmr (δ, ppm) : 2.56 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 6.4-6.5 (2H), 7.82 (d, 1H, J 9Hz).

Reaction of methoxyhydroquinone (1) with 3-methylbut-2-enoic acid (2). A mixture of phenol 1 (1.12 g, 8 mmol) and acid 2 (0.80 g, 8 mmol) in methanesulfonic acid (10 ml, 1.5% H_2O according to Karl Fischer analysis) was vigorously stirred at 70°C. When reaction was completed (TLC and GC monitoring), the crude reaction mixture was allowed to cool, poured into ice-water (200 g) and extracted with ether (3 x 50 ml). The organic fractions were washed with 1N NaOH solution (3 x 50 ml) and the joined basic fractions were acidified and extracted with ether (3 x 50 ml). The acid organic fractions were washed with water, brine and dried. The residue obtained after elimination of solvent crystallized on standing to afford compound 3 (1.73 g, 97% yield), which was identified by comparison with an authentic sample [15].

When the reaction was carried out under the same conditions, but using a methanesulfonic acid with a higher H_2O content (i.e. 5 or 11%), treatment of the crude reaction mixture gave a residue which contained a mixture of compounds 3 and 4 in different isomeric ratios (see Table 1). Separation of these compounds was achieved by flash chromatography (hexane:ethyl acetate from 4:1 to 2:1, respectively).

3,4-Dihydro-6-hydroxy-7-methoxy-4,4-dimethyl-2H-1-benzopyran-2-one (4) : mp 117-9°C ($CHCl_3$); ir (ν, cm^{-1}): 3540, 1770; nmr (δ, ppm): 1.31 (s, 6H), 2.02 (br, 1H), 2.60 (s, 2H), 3.88 (s, 3H), 6.60 (s, 1H), 6.85 (s, 1H); ms (m/z): 222 (M^+, 77%), 207 (100%). Calc. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.90; H, 6.44.

2,3-Dihydro-6,7-dimethoxy-2,2-dimethyl-4H-1-benzopyran-4-one (5). A solution of chromanone 3 (3.51 g, 16 mmol) in DMF (100 ml) was treated with K_2CO_3 (6.63 g, 48 mmol) and methyl iodide (2 ml, 32 mmol). The mixture was stirred at 40°C until reaction was completed (20 h, GC monitoring). Then, the reaction mixture was poured into 2 N HCl (250 ml) and extracted with benzene (3 x 100 ml). The joined organic extracts were washed with 0.5 N NaOH, H_2O, brine and dried. The residue obtained after elimination of solvent was identified as compound 5 by comparison with an authentic sample [15] (3.66 g, 98% yield).

Reduction of chromanone 5 with $NaBH_4$ in methanol: $NaBH_4$ (0.19 g, 5 mmol) was added to a solution of

chromanone 5 (1.18 g, 5 mmol) in methanol (15 ml) and the mixture was stirred at room temperature for 3 h. Then, an additional equimolecular amount of the hydride was added and stirring was prolonged until reaction was completed (6 h, TLC and GC monitoring). After careful acidification with 2N HCl, methanol was removed under vacuum and the residue was extracted with ether (2 x 25 ml). The joined organic extracts were washed with $NaHCO_3$ solution, brine and dried. The residue obtained after removal of solvent was distilled bulb-to-bulb under vacuum (125-130°C/0.2-0.3 Torr) to give 0.87 g of a colorless oil, which contained a mixture of the expected 4-chromanol 7 [14] and the corresponding methyl ether derivative 8. The mixture was separated by preparative TLC (hexane:ether 95:5) to afford pure compound 8 (0.14 g), which was relatively stable in solution and slowly decomposed on standing to give precocene II.

2,3-Dihydro-6,6-dimethoxy-2,2-dimethyl-4H-1-benzopyran-4-ol (7): yield: 0.67 g; ir (ν, cm^{-1}): 3620-3140, 2980, 2830, 1620; nmr (δ, ppm): 1.32 (s, 3H), 1.40 (s, 3H), 1.68 (s,1H), 2.00 (dd, 2H, J_1 13.4, J_2 7.2 Hz), 3.80 (s, 3H), 3.83 (s, 3H), 4.77 (t, 1H, J 7.2 Hz), 6.35 (s, 1H), 6.81 (s, 1H).

2,3-Dihydro-4,6,7-trimethoxy-2,2-dimethyl-2H-1-benzopyran (8): mp 60-1°C; ir (ν, cm^{-1}): 2965, 2820, 1620; nmr (δ, ppm): 1.32 (s, 3H), 1.41 (s, 3H), 1.99 (dd, 2H, J_1 6.5 Hz, J_2 2 Hz), 3.44 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 4.38 (t, 1H 6.5 Hz), 6.35 (s, 1H), 6.85 (s, 1H); ms (m/z): 252 (M^+, 49%), 205 (100%). Calc. for $C_{14}H_{20}O_4$: C, 66.67; H, 7.94. Found: C, 66.80; H, 8.27.

Reduction of chromanone 5 with $NaBH_4$ in isopropyl alcohol: precocene II (6). $NaBH_4$ (0.38 g, 10 mmol) was added to a solution of chromanone 5 (1.18 g, 5 mmol) in isopropyl alcohol (20 ml) and the mixture was heated overnight under reflux. Treatment of the crude reaction mixture as above led to a residue which only contained chromanol 7 (1.18 g). Through bulb-to-bulb distillation under vacuum (120-5°C/0.2-0.3 Torr), alcohol 7 underwent spontaneous dehydration to afford precocene II (6) [8] (0.89 g, 81% overall yield).

Reaction of substituted acetophenones with $NaBH_4$ in methanol. General procedure: A mixture of the corresponding acetophenone, $NaBH_4$ and methanol (1:2:94 molecular ratio) was allowed to react at room temperature until TLC and GC controls showed that the reaction had been completed (3-5 h). Treatment of the crude reaction mixture as described above afforded a residue which was purified and identified as follows (for yields see Table 2):

- Acetophenone gave 1-phenylethanol[16] nmr (δ, ppm): 1.51 (d, 3H, J 6.5 Hz), 4.91 (q, 1H, J 6.5 Hz), 7.36 (s, 5H).
- 1-(4-Methylphenyl)ethanol[17] nmr (δ, ppm): 1.45 (d, 3H, J 6 Hz), 2.30 (s, 3H), 4.12 (q, 1H, J 6 Hz).
- 1-(-Chlorophenyl)ethanol[18] nmr (δ, ppm): 1.48 (d, 3H, J 6.5 Hz), 3.40 (br, 1H), 4.85 (q, 1H, J 6.5 Hz), 7.30 (s, 4H).
- 1-(4-Methoxyphenyl)ethanol[19] nmr (δ, ppm): 1.43 (d, 3H, J 6 Hz), 1.77 (br, 1H), 3.80 (s, 3H), 4.85 (q, 1H, J 6 Hz), 6.87 (d, 2H, J 9 Hz), 7.30 (d, 2H, J 9 Hz)
- 1-Methoxy-1-(4-methoxyphenyl)ethane[20] nmr (δ, ppm): 1.42 (d, 3H, J 6 Hz), 3.19 (s, 3H), 3.80 (s, 3H), 4.25 (q, 1H, J 6 Hz), 6.87 (d, 2H, J 8 Hz), 7.23 (d, 2H, J 8 Hz). ms (m/z): 166 (M^+, 13%), 151 (100%).
- 1-Methoxy-1-(2,4-dimethoxyphenyl)ethane. nmr (δ, ppm): 1.36 (d, 3H, J 6Hz, 3.23 (s, 3H), 3.80 (s, 5H), 4.68 (q, 1H, J 6 Hz), 6.4-6.5 (2H), 7.27 (d, 1H, J 8 Hz) ms (m/z): 196 (M^+, 18%), 181 (100%). Calculated for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.35; H, 7.88.

ACKNOWLEDGEMENTS

Financial support from CSIC (85/263), CAICYT (Grant 84-0087) and FISS (Grant 87/1670) is gratefully acknowledged.

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Received, 21st June, 1988