

A New Regioselective Synthesis of 2,3,4,5-Tetrahydro-6*H*-oxepino[3,2-*c*]pyran-6-ones, and [1]Benzopyran-6-ones

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Through an anti-Markovnikow hydration of some olefin derivatives of 4-hydroxy-2-pyrone, and 4-hydroxy-coumarins, followed by a regioselective intramolecular dehydration, involving the primary alcohols obtained and the enolic oxygen of the rings, promoted by Amberlyst 15 in boiling toluene, the new heterocycles 2,3,4,5-tetrahydro-6*H*-oxepino[3,2-*c*]pyran-6-one (**3**) and [1]benzopyran-6-ones **ba,c** were obtained in fair yields.

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Among the naturally occurring cyclic hemiterpenoid compounds derived through cyclization of prenylated hydroxy precursors, oxygen heterocycles possessing a 2-isopropylfuran or a 2,2-dimethylpyran skeleton are by far more rare than those with a 3-methyloxepin [1]. For that reason the cyclization of olefins to fused furans or pyrans have been much more studied than those aimed to obtain fused oxepin ring systems [2].

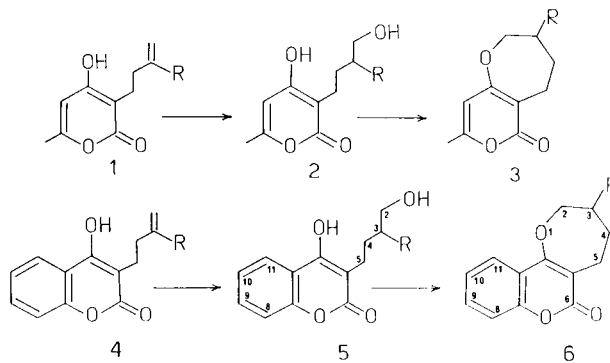
Our interest in cyclization reactions of 2-substituted-1-buten-4-yl-derivatives of cyclic β -ketoacid lactones or cyclic β -ketoamides was stimulated by the different possibilities that those open chain intermediates do have to cyclize, not only to fused pyran or oxepin ring systems, but at the same time also on the oxygen belonging to the ester or amide group, or alternatively on one of the β -enolic ketones. The challenge was therefore to determine conditions to bring about selectively all the different possible processes. Following our reports on annulation of those olefins to fused pyrans by mercury-II species [3], by iodine [4] and by *m*-chloroperbenzoic acid [5] we wish to report here a highly regioselective cyclization to tetrahydro-oxepins fused on the oxygen of the β -enolic ketone.

Results and Discussion.

Starting olefins 4-hydroxy-6-methyl-3-(2-methyl-1-buten-4-yl)-2-pyrone **1**, 3-(2-methyl-1-buten-4-yl)-, 3-(2,2-dimethyl-3-methylene-pentan-5-yl)-, and 3-(2-(4'-methylphenyl)-1-buten-4-yl)-4-hydroxycoumarins **4a**, **4b**, and **4c** were synthesized by Wittig methenylation of the corresponding ketones [6]. They were submitted to hydroboration with sodium borohydride and boron trifluoride etherate in tetrahydrofuran at room temperature. *In situ* oxidation by hydrogen peroxide in alkaline aqueous medium afforded the corresponding primary alcohols **2** and **5a,c** in good yields. Dehydration in boiling toluene in the presence of Amberlyst 15 ion exchange resin as catalyst, and elimination of water by azeotropic distillation in a Markuss apparatus gave, in acceptable to good yields, 3,8-dimethyl-

2,3,4,5-tetrahydro-6*H*-oxepino[3,2-*c*]pyran-6-one **3**, 3-methyl-, 3-*t*-butyl-, and 3-(4-methylphenyl)-2,3,4,5-tetrahydro-6*H*-oxepino[3,2-*c*][1]benzopyran-6-ones **6a-c**. The instability of the final products in the reaction medium, and a competing transposition of the 4-methylphenyl substituent, probably through the formation of a three membered phenonium cation, occurring during the dehydration of **5c** and from the 2-*p*-tolyl-substituted oxepin **6c** already formed, account for the lowering of the yields of the desired products **3** and **6c** respectively. 2-(4-Methylphenyl)methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one **7** was obtained through dehydration of **5c** in variable yields (10-27%) depending mainly on the reaction time, and also from **6c** when heated in toluene in the presence of Amberlyst 15 (7% and 15% after 30 minutes and one hour respectively).

Chemical, and physical and some of the spectroscopic data for new compounds, namely, the primary alcohols **2** and **5a-c**, and oxepins **3** and **6a-c** are reported in Table 1. Their ¹H nmr spectra are reported in Table 2 or in the experimental.



a, R = CH₃

b, R = C(CH₃)₃

c, R = 4-CH₃C₆H₄

Table 1

Compound No.	R	Yields %	MP °C (solvent)	IR, cm ⁻¹	Molecular Formula (Molecular Weight)	Analysis (%)	
						Found	Calcd.
2	CH ₃	94	148-150 (benzene)	1675	C ₁₁ H ₁₆ O ₄ (212.24)	61.9	7.3
3	CH ₃	40	liquid	1710	C ₁₁ H ₁₄ O ₃ (194.22)	61.2	7.6
5a	CH ₃	76	121-122 (hexane/AcOEt)	1660	C ₁₄ H ₁₆ O ₄ (248.27)	68.2	7.0
5b	C(CH ₃) ₃	80	169-170 (AcOEt)	1675	C ₁₇ H ₂₂ O ₄ (290.35)	68.0	7.2
5c	4-CH ₃ -C ₆ H ₄	72	135-136 (AcOEt)	1670	C ₂₀ H ₂₀ O ₄ (324.36)	70.3	7.6
6a	CH ₃	73	88-89 (hexane)	1690	C ₁₄ H ₁₄ O ₃ (230.25)	74.0	6.2
6b	C(CH ₃) ₃	67	103-104 (hexane)	1705	C ₁₇ H ₂₀ O ₃ (272.33)	74.0	6.2
6c	4-CH ₃ -C ₆ H ₄	50	134-135 (AcOEt)	1710	C ₂₀ H ₁₈ O ₃ (306.34)	73.3	6.4
						74.8	7.4
						74.9	7.4
						78.6	6.3
						78.4	5.9

Table 2

¹H NMR Data for Compounds **5** and **6** (Deuteriochloroform, H, ppm, J, Hz)

	5a	6a	5b	6b	5c	6c		5a	5b	6a	6c
2a	3.93	4.52	4.23	4.64	3.99	4.76	2a, 2b	9.8	9.5	11.9	12.1
2b	3.67	4.04	3.78	4.55	3.93	4.40	2a, 3	3.3	3.5	4.2	4.4
3	1.81	2.30	1.31	1.81	2.80	3.31	2b, 3	9.3	9.2	7.0	6.0
4a	1.85	2.13	2.12	2.11	2.13	2.34	3, 4a	—	1.9	6.4	6.3
4b	1.65	1.57	1.50	1.87	2.08	2.07	3, 4b	10.0	10.5	7.5	9.5
5a	2.97	2.97	2.90	3.05	2.93	3.20	3, R-3	6.7	—	6.9	—
5b	2.78	2.70	2.75	2.69	2.80	2.80	4a, 4b	14.0	14.0	14.2	14.0
8	7.30	7.28	7.30	7.28	7.28	7.30	4a, 5a	11.0	11.5	8.7	7.7
9	7.50	7.48	7.50	7.47	7.50	7.51	4a, 5b	5.5	6.7	2.1	2.0
10	7.27	7.25	7.27	7.24	7.27	2.22	4b, 5a	5.2	6.2	2.2	2.0
11	7.89	7.78	7.87	7.76	7.88	7.83	4b, 5b	4.3	3.5	10.5	11.5
R	0.85	1.08	0.86	1.01	2.26 [a]	2.35 [a]	5a, 5b	14.1	14.3	17.0	17.0
OH-2	4.15	—	3.16	—	3.50	—					
OH	7.00	—	7.25	—	9.80	—					

[a] Aromatic protons are omitted.

The structure of primary alcohols is straightforward, while the structure of the new tetrahydroxepino rings formed follows mainly from extensive experiments and analysis of their ¹H nmr spectra. For example, the ¹H nmr spectrum of **6a** exhibits four vicinal aromatic protons, two geminally coupled ethereal protons centered at δ 4.52 and 4.04 (J = 11.9 Hz, H-2), signals at δ 1.57, 2.13 and 2.70 and 2.97 due to the C(4)H-C(5)H, methylene protons, at δ 2.30 due to the methine proton (H-3) vicinally coupled to H-2, H-4 and to the methyl protons (CH-3) which resonate at δ 1.08. Moreover, upon addition of deuterium oxide to all the samples, no change was observed in their ¹H nmr spectra, and this in conjunction with the results obtained for the determination of the molecular formula, precludes non cyclic structure alternatives. The oxepino-

[3,2-c]pyrano and 1-benzopyran type of annulation, e.g. the ring closure on the oxygen of the enolic ketone, instead of the [2,3-b] one, involving the lactone oxygen, follows from the ¹H nmr chemical shifts of the aromatic H-11 proton (δ 7.76-7.83) in compounds **6a-c**, of H-9 (δ 5.73) in compound **3** and of H-10 (δ 7.72) in the sub-product **7** (pyrano[3,2-c][1]benzopyrano annulated compound) which compare well with the corresponding protons in some related pyrano[3,2-c]pyran or 1-benzopyran derivatives previously reported. In the [2,3-b] annulated regioisomeric compounds the corresponding protons always resonate at lower fields (δ 0.07-0.40 ppm) [5].

Also the structure of sub-product **7** was firmly established by ¹H nmr spectral analysis. In fact the spectrum reported in the experimental part contains an ABMN pattern for the C(3)H-C(4)H methylene protons, and the

ethereal methine proton (H-a), this last centered at δ 4.38 and vicinally coupled to the benzylic protons resonating at δ 3.15 and 3.00 and to the H-3 protons resonating at δ 1.77 and 2.14. Even if in the reported cases the expected regioselectivity was always followed, the dehydration of some 2-hydroxyphenyl-substituted primary and secondary alcohols we have also performed, showed how care must be taken in extending the prediction of the regioselectivity of the dehydration process here described. In fact while the primary alcohol 3-(2-hydroxyphenyl)-1-propanol and the secondary isomer, the 3-(2-hydroxyphenyl)-2-propanol gave as expected the 3,4-dihydro-2H-1-benzopyran and the 2-methyl-2,3-dihydro-1-benzofuran in 88% and 82% yields respectively, the 4-(2-hydroxyphenyl)-2-methyl-1-butanol (the phenol substituted by the same alkyl chain containing a primary alcohol as in compounds **2** and **5**) gave instead under the same reaction conditions only the transposed 3,4-dihydro-2,2-dimethyl-2H-1-benzopyran in 67% yield.

EXPERIMENTAL

Hydration of Olefins **1** and **4** to Primary Alcohols **2** and **5**. (General Procedure) [7].

To a slurry of sodium borohydride (1.13 g, 0.03 mole) in anhydrous tetrahydrofuran (50 ml) and containing the starting compounds **1** or **4a,c** (0.01 mole), a solution of borotrifluoride etherate (5 ml, 0.04 mole) in the same solvent (10 ml) was slowly added (45 minutes) while stirring and cooling the mixture (below 25). Stirring was continued for an additional 60 minutes, water (15 ml) was added and the mixture was warmed at about 40°. Sodium hydroxide solution (3 N, 11 ml) and hydrogen peroxide (30% v/v, 11 ml) were added with stirring. The mixture was poured into a saturated sodium chloride solution (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure. The crude product, purified by flash chromatography on silica gel by using hexane-ethyl acetate 70-30 mixture as eluent was crystallized from the appropriate solvent.

Yields and physical data for all compounds are reported in Table 1 and the ¹H nmr spectral data for **5a-c** in Table 2. The ¹H nmr spectrum of **2** (deuteriochloroform) showed the following signals centered at [δ (proton)]: 5.93 (2), 2.50 (5a), 2.33 (5b), 1.1-1.7 (4 and 3), 3.42 (2a), 3.42 (2b), 2.19 (Me-8), 0.92 (Me-3), 10.5 (OH-10) and 4.15 (OH-2).

Dehydration of Primary Alcohols [8].

A solution of the primary alcohol **2** or **5a-c** (0.01 mole) in toluene (40 ml) and Amberlist 15 ion exchange resin (0.2 g) was poured into a Marcusson apparatus and heated at reflux until the separation of water ceased (2-3 hours). The mixture was solvent evaporated under vacuum, and the residue flash chromatographed on silica gel by using a hexane-ethyl acetate 9 to 1 eluting mixture. Yields and physical data for compounds **3** and **6a-c** obtained are reported in Table 1 and some ¹H nmr spectral data for compounds **6a-c** are reported in Table 2. The ¹H nmr

spectra of **3**, taken in deuteriochloroform showed the following signals centered at [δ (proton)]: 4.32 (2a), 3.88 (2b), 2.20 (3), 2.10 (4a), 1.50 (4b), 2.73 (5a), 2.56 (5b), 5.73 (9), 1.02 (Me-3) and 2.19 (Me-8).

When reacting compound **5c** for 3 hours under those conditions the secondary product **7** was obtained in 27% yield, mp 155-157° (from ethyl acetate); ir (nujol): 1720 cm⁻¹.

Anal. Calcd. for C₂₀H₁₈O₃: C, 78.41; H, 5.92. Found: C, 78.38; H, 5.86.

The ¹H nmr spectra of **7** taken in deuteriochloroform shows the following signals centered at [δ (proton)]: 4.38 (2), 2.14 (3a), 1.77 (3b), 2.68 (4a), 2.49 (4b), 7.29 (7), 7.49 (8), 7.25 (9), 7.72 (10), 3.15 (CHa-2), 3.00 (4, CHb-2), 7.18 and 7.16 (Ph), and 2.35 (Me) with the following coupling constant [J (protons)]: 6.8 (2, CHa-2), 6.1 (2, CHb-2), 2.4 (2, 3a), 10.4 (2, 3b), 13.9 (3a, 3b), 3.5 (3a, 4a), 6.1 (3a, 4b), 5.7 (3b, 4a), 10.5 (3b, 4b), 17.4 (4a, 4b) and 13.8 (CHa-2, CHb-2).

3-(2-Hydroxyphenyl)-1-propanol, 3-(2-Hydroxyphenyl)-2-propanol or 4-(2-Hydroxyphenyl)-2-methyl-1-butanol.

A solution of the appropriate alcohol (0.01 mole) in toluene (50 ml) and Amberlist-15 were heated at reflux in a Marcusson apparatus for 3 hours. The resin was filtered off and the residue was solvent evaporated and flash chromatographed on silica gel. 3,4-Dihydro-2H-1-benzopyran (88% yield), 2-methyl-2,3-dihydro-1-benzofuran (82% yield) and 3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (67% yield) were obtained respectively. The structure was deduced by comparing spectral parameters with those reported for synthetic samples [3,9].

Reaction of 3-(4-Methylphenyl)-2,3,4,5-tetrahydro-6H-oxepino[3,2-c][1]-benzopyran-6-one **6c** with Amberlyst-15.

A solution of **7** (1 mmole) in toluene (10 ml) and Amberlist-15 ion exchange resin (0.05 g) were heated under reflux. The course of the reaction was followed by ¹H nmr analysis (deuteriochloroform): of the product mixture obtained by evaporating a portion of the solution at different times; the 4-methyl proton integrals of **6c** and **7** were compared.

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