ELECTROGENERATION AND STRUCTURAL DISCUSSION OF 6-BENZYL-3,5-DIPHENYLHYDROXYPYRANONES

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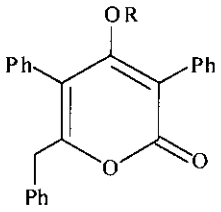
Abstract - The cathodic reduction of 2-chloro-2-phenylacetyl chloride in dichloromethane-tetraethylammonium chloride on mercury cathode led to the formation of either a mixture of α- and γ- 6-benzyl-3,5-diphenylhydroxypyranones or corresponding phenylacetate derivative of the latter depending on the conditions, in only one step. A study of these compounds solved the controversy which existed in the literature about the correct assignment of these structures.

In connection with our studies on the electrochemical reduction of acyl halides in aprotic media,[1,2] we carried out the cathodic reduction of acyl chlorides with an halogen atom in their α position as possible precursors of interesting ketenic reaction intermediates. Some ketenic intermediates were electrogenerated by us in the cathodic reduction of cinnamoyl chloride[3] and phthalyl chloride[4] yielding, in the first case, benzylketene which dimerized through a [2+2] cycloadition to the 2,4-dibenzylcyclobutanedione, and, in the second case, an ortho-quinoid bisketene which dimerized to 2-benzopyrano[4.3-ς][2]benzopyran-6,12-dione. However in the literature there are also described trimerization, tetramerization and even more polymerization reactions for the ketene group.[5]

Hydroxypyranones have been isolated from different natural products. So anibine (isolated from different species of rosewood), 4-methoxyparacotoin, 5,6-dehydrokavain and yangonin (the major constituent of kawa resin) have a structure of 4-hydroxy-α-pyranone,[6] while pseudoyangonin, maltol and pyromeconic acid are examples of natural hydroxy-γ-pyranones.[7] These facts justify the attention directed to the study of the cathodic reduction

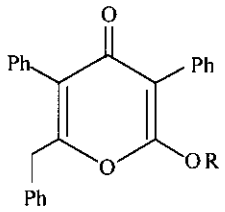
of α-chlorinated acyl chlorides from the viewpoint of the electrosynthesis of interesting heterocyclic organic compounds.

We carried out the cathodic reduction of 2-chloro 2-phenylacetyl chloride in dichloromethane-tetraethylammonium chloride under argon atmosphere at two different current densities. Although the electrolyses were set to consume 2 F mol^{-1} in both cases the major products were different. At higher current density a mixture of products was obtained. After their separation two major products A (34%) and B (28%) were found, with small amounts of dibenzyl ketone **(5)** and phenylacetic acid, which showed in ms the same molecular ion M^+ m/z 354; however in ir compound A had a strong band in the carbonyl group range at 1756 cm^{-1}, while for B it appeared at 1677 cm^{-1}. Considering their mps, ^1H and ^{13}C-nmr data the compounds A and B were identified as 6-benzyl-4-hydroxy-3,5-diphenyl-2H-pyran-2-one **(1)**[8] and 6-benzyl-2-hydroxy-3,5-diphenyl-4H-pyran-4-one **(3)**,[5] respectively.



1 : R = H

2 : R = $COCH_2Ph$



3 : R = H

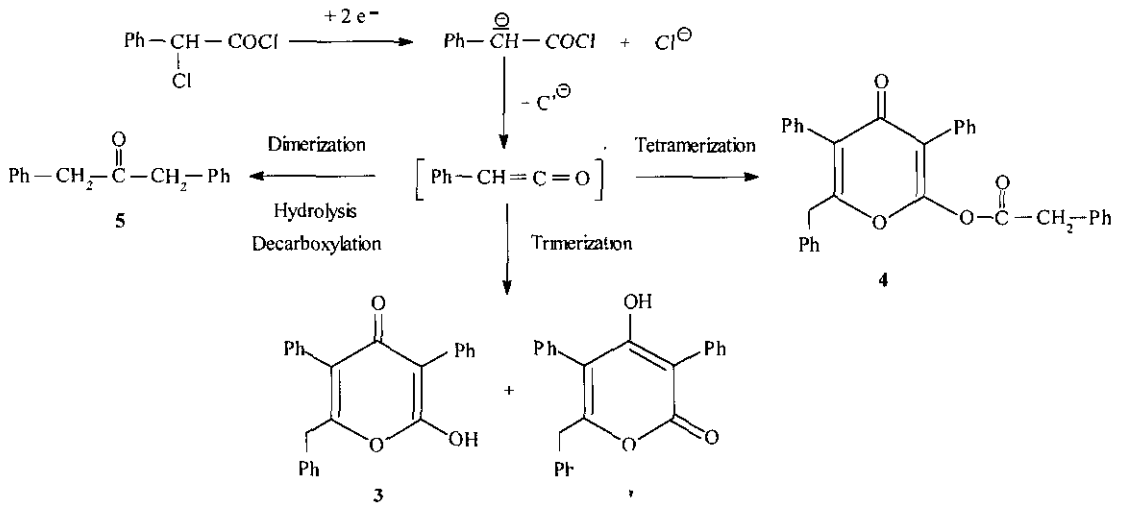
4 : R = $COCH_2Ph$

We also carried out the cathodic reduction under the same conditions except at lower current density. After column chromatography, compound C (mp 86-88 °C) was obtained as the major product (40%) , which showed in ms a M^+ m/z 472 and also peaks at m/z 354 and 236, both of them being multiples of 118 (phenylketene), thus indicating a phenylketene tetramer. At least two possible structures could be postulated for this tetramer: **2** or **4**. Compound **(2)** is described in the literature[8] by Chakrabarty et al., but neither its physical nor spectroscopical properties coincided with our values. The structure **(4)** has already been proposed by Kuznetsov[9] but again their data were not in agreement with ours, but were coincident (mp, ir and ^1H-nmr) with those found

by Chakrabarty. These facts indicated that both mentioned works described the same product. Considering that Chakrabarty's group presented an unequivocal assignment of its structure, both are to be identified as 6-benzyl-2-oxo-3,5-diphenyl-2H-pyran-4-yl phenylacetate **(2)**. Hydrolysis of C in 30% refluxing KOH led to **3**, which in principle could indicate that the structure C corresponded to **4**. However we have found that **1** undergoes isomerization to **3** in acid or basic media but not in the opposite direction. This fact led to the conclusion that **3** is the most stable isomer. Therefore the formation of **3** in the saponification reaction is not enough for an unequivocal assignment of the structure to compound C because during the saponification process an isomerization reaction could take place forming the most thermodynamically stable pyranone **(3)**. In order to determine the right structure for C we carried out chemical preparation of **2** and **4** by acylation of **1** and **3** respectively with phenylacetyl chloride. The product obtained from **3** was totally coincident in its physical and spectroscopical properties with C and therefore the electrogenerated product was identified as 6-benzyl-4-oxo-3,5-diphenyl-4H-pyran-2-yl phenylacetate **(4)**.

The mechanism for the formation of the reaction products is shown in Scheme 1. The first step is the cleavage of the chloro-carbon bond in α-position of carbonyl chloride by transfer of two electrons from the cathode. The anion formed can follow two different routes, either elimination of a chloride anion leading to phenylketene, or reaction with another molecule of starting material through an anionic pathway. In order to determine the right route to explain the electrogenerated products we performed two cathodic reductions of the substrate in the presence of an excess of two different reagents: methyl chloroformate and cyclopentadiene. In the first case the reaction did not undergo any change, but in the second case the reaction led to a mixture (90:10) of 7-endo- and 7-exo-phenylbicyclo[3.2.0]hept-2-en-6-one formed by [2+2] cycloadition between phenylketene and cyclopentadiene.[10]

It is certain that depending on the generation rate of phenylketene, the nature of the products was determined. When the ketene was generated at low velocity, at lower current density, the acylation reaction was favourable. However the fast generation of phenylketene, at higher current density, led to the trimer compounds as the major



Scheme 1

products. Polarographic analysis of **4** showed that it was not possible to reduce **4** to **3** under our cathodic conditions. In conclusion we can affirm that when the reaction is carried out at higher current density the major product was the α-pyranone **(1)** although which was less stable than its γ-isomer. On the other hand when the reaction was carried out at lower current density the α-isomer **(1)** initially formed underwent isomerization to the γ form **(3)** catalyzed by the catholyte's basic character.

EXPERIMENTAL SECTION

Electrolysis was carried out using an Amel potentiostat Model 552 with an electronic integrator Amel Model 721. Mass spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett-Packard Model 5988A mass-selective detector equipped with a Hewlett-packard ms Chem Station. Ir spectra were obtained, as dispersion in KBr, on a Perkin-Elmer Model 583 spectrophotometer. H-Nmr (300 MHz) and ^{13}C-nmr (75.4 MHz) spectra were recorded on a Varian-Unity 300 apparatus with TMS (^{1}H) or deuteriochloroform (^{13}C) as internal standard. Melting points were determined on a Reichter Thermovar microhot stage apparatus and were uncorrected.

General electrolysis procedure. Electroreductions were performed in a concentric cell with two compartments separated by a glass frit diaphragm of medium porosity and under constant cathodic potential of -0.9 V vs SCE in dry CH_2Cl_2 - anhydrous Et_4N^+ Cl^- (0.3 M at high and 0.15 M at low current density); 50 ml and 10 ml of this solution were placed into the cathodic and anodic compartments respectively and an argon atmosphere was used. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred and the temperature was kept at 20 °C by external cooling.

Electrochemical synthesis of 6-benzyl-4-oxo-3,5-diphenyl-4H-pyran-2-yl phenylacetate (4).

Distilled 2-chloro-2-phenylacetyl chloride (0.94 g, 5 mmol) was electrolyzed at the current density of 7 mA/cm^2 until current consumption was 2 F mol^{-1}. By removing the solvent under reduced pressure a yellow solid was obtained which was extracted with ether (50 ml) twice and water (50 ml) once in a separation funnel. The ethereal phase was dried (over anhydrous $MgSO_4$) and chromatographed over silicagel (CH_2Cl_2 as eluent). 6-Benzyl-4-oxo-3,5-diphenyl-4H-pyran-2-yl phenylacetate **(4)** was obtained (0.24 g, 40%), mp 86-88°C (from ethanol). Its purity was checked by hplc: ODS-Hypersil (5μ) 200x4.6, eluent MeOH - H_2O (8:2), uv detection 236 nm, flow rate 0.3 ml/min, R_t= 29 min. Ms (m/z) 472 (M+, 2%), 354 (M^+ - Ph-CH=C=O, 20), 263 (6), 236 (10), 178 (7), 118 (12), 91 (100). Ir (υ, cm^{-1}) 3060, 3030, 2925, 1770 s, 1718 vs, 1639, 1601, 1131 s, 1097 s. Uv (λ, nm) (ether) 222, 236, 316. ^{1}H-Nmr (δ, ppm) 3.14 (2H ,s ,CH_2), 3.75 (2H ,s ,CH_2) and 6.66-7.45 (20H, m, 4 x Ph). ^{13}C-Nmr (δ, ppm) 37.51 (CH_2, pyr), 40.02 (CH_2, ester), 116.63 (C_5), 117.40 (C_3), 127.0, 128.11, 128.36, 128.53, 128.57, 128.60, 128.78, 128.97, 129.48, 130.87, 131.72, 135.58 (4 x Ph), 158.11 (CO, ester), 160.30 (C_6), 162.42 (CO, pyr), 167.30 (C_2).

Electrochemical synthesis of 6-benzyl-4-hydroxy-3,5-diphenyl-2H-pyran-2-one (1).

Distilled 2-chloro-2-phenylacetyl chloride (0.94 g, 5 mmol) was electrolyzed at the current density of 15 mA/cm^2. After consuming 2 F mol^{-1} the crude reaction product obtained after stripping the solvent to dryness under reduced pressure was washed with ether (50 ml) in an ultrasonic bath leaving a white dust in the bottom of the flask. Then both the solid and ethereal phases were placed in a separation funnel with 50 ml of water.

The interphase afforded a white solid which was washed with cold MeOH. The ethereal phase was dried over anhydrous $MgSO_4$ and after several hours the ether was stripped to dryness under reduced pressure. Addition of cold MeOH (5 ml) afforded the same white solid (mp 79-80 °C, from cyclohexane). This product was identified as 6-benzyl-4-hydroxy-3,5-diphenyl-2H-pyran-2-one **(1)** (0.20 g, 34%). Ms (m/z) 354 (M^+, 10%), 263 (9), 236 (16), 178 (9), 145 (34), 118 (15), 91 (100). Uv (λ, nm) (ether) 226, 250. Ir (υ, cm^{-1}) 3415 br (OH), 1756 vs (CO), 1665 w, 1600 w , 1177 s, 1077 s , 695 w. ^{1}H-Nmr (δ, ppm) 3.35 (2H, br, CH_2), 5.38 (1H, br, exchangeable, OH) and 6.97 - 7.80 (15H, m, 3 x Ph).

The methanolic phase after removing the solvent under reduced pressure was redissolved in ether and extracted with 5% NaOH. Acidification of this alkaline solution afforded 6-benzyl-2-hydroxy-3,5-diphenyl-4H-pyran-4 - one **(3)** (0.165 g, 28%), mp 169-170°C (from benzene). Uv (λ, nm) (ether) 222, 240, 308. Ir (υ, cm^{-1}) 3500, 3030, 1677 vs, 1640 s, 1556, 1492, 1392, 1260, 1210, 1154, 1008, 970, 750, 700. Ms (m/z) 354 (M^+, 74%), 326 (19), 263 (15), 236 (16), 207 (46), 178 (49), 145 (13), 118 (27), 91 (100). ^{1}H-Nmr (δ, ppm) 3.72 (2H, s, CH_2), 6.06 (1H, br, exchangeable, OH) and 7.14-7.49 (15H, m, Ph). ^{13}C-Nmr (δ, ppm) 37.55 (CH_2), 104.23 (C_3), 114.40 (C_5), 127.0, 128.51, 128.64, 128.80, 128.95, 129.02, 129.13, 130.02, 130.55, 130.76, 135.72 (3 x Ph), 160.41 (C_6), 162.14 (C_2), 162.97 (CO).

Electroreduction in the presence of cyclopentadiene.

Distilled 2-chloro-2-phenylacetyl chloride (0.94 g, 5 mmol) was electrolyzed in the presence of an excess (6:1) of cyclopentadiene. The reaction product was extracted with ether (50 ml) twice and water (50 ml) in a separation funnel. The ethereal phase was dried over anhydrous $MgSO_4$ and chromatographed over silicagel (CH_2Cl_2 as eluent). A mixture (90:10 by ^{1}H-nmr) of 7-endo and 7-exo-phenylbicyclo[3.2.0]hept-2-en-6-one[10] (0,23 g, 25%) was obtained. Ms (the same in both cases) (m/z) 184 (M^+, 7%), 155 (13), 141 (12), 128 (16), 118 (100), 91 (86). Ir (υ, cm^{-1}) C=O 1768 vs. ^{1}H-Nmr (important assignments) (δ, ppm) 3.89 (2H, m, H-C_1 and H-C_5, endo), 4.03 (2H, m, H-C_1 and H-C_5, exo), 4.73 (1H, dd, J = 7 and 4 Hz, H-C_7, endo), 4.90 (1H, m, H-C_7, exo), 5.46 (1H, dm, J = 5.6 Hz, H-C_3 or H-C_2, endo), 5.75 (1H, m, H-C_3 or H-C_2, exo), 5.80 (1H, dm, J = 5.6 Hz, H-C_2 or H-C_3, endo), 5.96 (1H, m, H-C_2 or H-C_3, exo).

Chemical preparation of 6-benzyl-2-methoxy-3,5-diphenyl-4H-pyran-4-one (6). 0.30 mmol, (42 mg) of methyl iodide were added to a solution of 0.2 mmol (70 mg) of **3** in 20 ml of dry dichloromethane which contained 0.4 mmol of anhydrous K_2CO_3 and a catalytic amount of $Et_4N^+Cl^-$. After 5 h with a strong magnetical stirring at room temperature the crude mixture was washed with aq. 5% $NaHCO_3$ and purified by column chromatography. 6-Benzyl-2-methoxy-3,5-diphenyl-4H-pyran-4-one (**6**) was obtained (74 mg, 80%), mp 130-131 °C. Ir (υ, cm^{-1}) 3058, 2930, 1710 vs (CO), 1634 s, 1598, 1550 vs, 1492 s, 1354 vs, 1212, 1134 s, 964 s, 760 s, 702 vs. ^{1}H-Nmr (δ, ppm) 3.21 (3H, s, CH_3), 3.71 (2H, s, CH_2) and 7.16-7.45 (15H, m, 3 x Ph). ^{13}C-Nmr (δ, ppm) 37.15 (CH_2), 60.55 (CH_3), 109.93 (C_3), 116.85 (C_5), 126.41, 126.60, 127.38, 127.49, 127.67, 127.84, 127.98, 128.18, 128.28, 128.52, 128.86, 130.20, 130.36, 131.87, 132.06, 135.83 (3 x Ph), 159.41 (C_6), 163.83 (CO), 166.28 (C_2). Uv (λ, nm) (EtOH) 218, 232, 306. Ms (m/z) 368 (M^+, 40%), 340 (37), 250 (23), 221 (100), 189 (19) , 178 (57), 104 (61), 91 (78).

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