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GENERAL ROUTE AND MECHANISM OF THE REARRANGEMENT OF THE 4-SUBSTITUTED 5-HYDROXY-3-OXOCYCLOPENTENES INTO THE 2-SUBSTITUTED ANALOGS[a]

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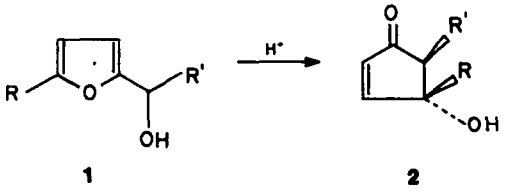
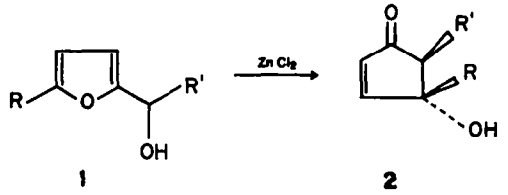
Abstract—A general method of synthesis of hydroxycyclopentenones of type **6** starting from the isomeric compound **2** is described. This conversion is shown to occur through an alumina-catalyzed process of intramolecular hydration.

In a previous paper we reported a new and general method of synthesis of 3-oxocyclopentenes **2** by molecular rearrangement of suitable 2-furylcarbinols **1**, catalyzed by acids or by zinc chloride[1] (Chart 1). The reaction was shown to proceed in a stereospecific manner yielding only one enantiomeric pair, characterized by the trans relationship of the OH group at 5 and the side chain at 4.



1 **2**

2a: R = H, R' = phenyl
2b: R = H, R' = n-hexyl
2c: R = H, R' = methyl
2d: R = H, R' = t-butyl-heptanoate



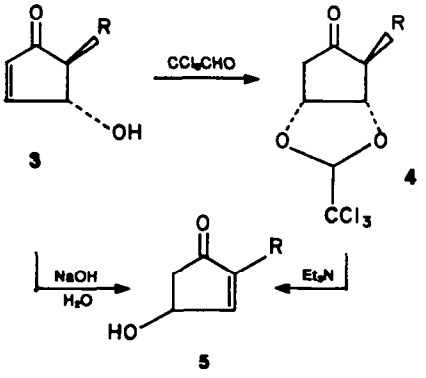
1 **2**

2e: R = Me, R' = Allyl
2f: R = Me, R' = n-Bu
2g: R = Me, R' = cyclohexyl
2h: R = Me, R' = phenyl
2i: R = Me, R' = 2-thienyl
2j: R = Me, R' = *p*-tolyl

Chart 1.

The compounds **2** are very useful especially as they can isomerise into 3 - oxocyclopentene - 5 - hydroxy - 2 - derivatives, particularly interesting for the prostaglandin and pyrethrolones synthesis.[2] In fact, recently, Stork *et al.* described a method for this conversion via the formation of the chloralhemiacetal **4**, which by treatment with triethylamine, yielded the compound **5** in high yield.

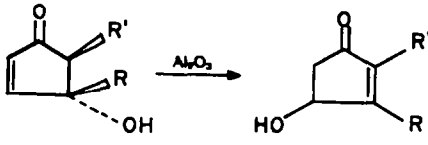
This procedure represented an effective alternative to the known synthetic route involving an hydration-dehydration sequence by treatment of **3** with dilute base: in fact, in this case the compound **5** was obtained in only a fair yield since the *trans* relationship of 4 and 5 substituents did not allow a relatively high rate of hydration.[2]



3 **4** **5**

In this paper[b] we wish to show that the direct conversion of the compounds **2** into 2-substituted 5-hydroxy-3-oxocyclopentenes **6** in a simple and convenient manner is achieved via an intramolecular migration of the alcoholic function.

In fact, after the adsorption of the compounds **2** on neutral or basic alumina for different periods, the subsequent elution gave high yields of **6**, free of the starting materials (Table 1).



2a–j **6a–j**

All the new products showed spectral data in complete agreement with these reported for similar compounds;[3] e.g. **6a**: IR spectrum (film, ν_{max} cm^{-1}): 3590, 3400, 1710, 1600. ^{1}H-NMR spectrum (CCl_4, δ): 7.58 (m, 2H, aromatic protons), 7.51 (d, 1 H, 1-H; J = 3 Hz), 7.32 (m, 3 H, aromatic protons), 4.93 (m, 1 H, 5-H), 3.20 (broad s, 1 H, –OH), 2.91 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 6 Hz), 2.40 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 2 Hz).

The reaction mechanism could not be explained in terms of a two-step sequence including the addition of a

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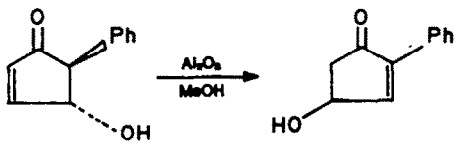
[b]A preliminary communication was published by us.[3]

Table 1.

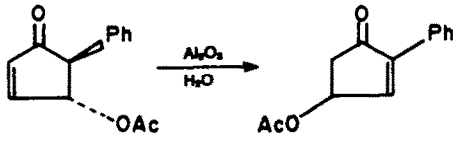
Starting compounds	Alumina	Reaction time/h	Products	Yield% *
2a	neutral	8	6a	90
2b	basic	30	6b	95
2c	basic	16	6c	85
2d	basic	16	6d	95
2e	neutral	24	6e	95
2f	basic	48	6f	95
2g	basic	48	6g	93
2h	neutral	7	6h	92
2i	neutral	3	6i	93
2j	neutral	8	6j	92

* All yields refer to isolated, chromatographically pure products.

nucleophilic reagent and the following elimination of a leaving group: in fact **2a**, after adsorption on alumina, deactivated with methanol, under anhydrous conditions, turned completely into the isomeric 3-oxocyclopentene **6a**. Furthermore, by the usual treatment, the acetoxy-derivative **7** rapidly isomerised to compound **8**.[c]



2a



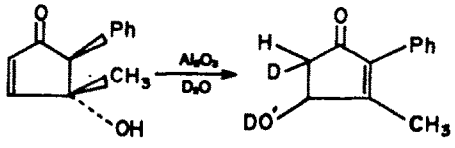
7 **8**

[c] These results completely exclude a mechanism via dehydration-hydration, with the initial formation of a cyclopentadienone intermediates and the subsequent addition of water to give the more stable α-β unsaturated ketone.

[d] The possibility that the rearrangement occurs via the formation of 2-substituted 3-methyl-3,4-epoxycyclopentanones was excluded since these compounds were never isolated.

[e] Recently this type of conversion was performed in a buffer solution at pH 8.5; the yields were fair, but no mechanism was proposed.[5]

The mechanism was demonstrated carrying out the rearrangement of **2h** on neutral alumina, deactivated with D_2O. In fact, the isolated product **9** was characterized by the presence of one D atom at 4, as shown by the spectroscopic data (^{1}H-NMR and MS).

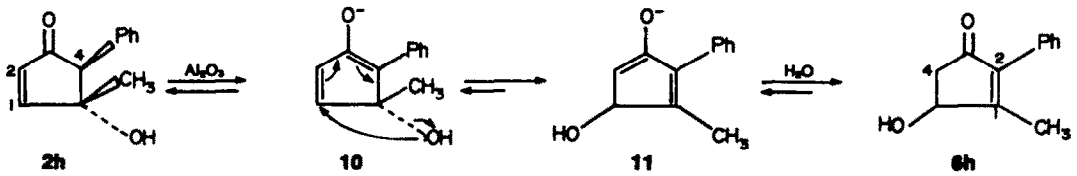


2h **9**

This result was in agreement with the proposed pathway (Scheme 1).

The slow step was the formation of the enolate **10**, which rapidly rearranged into the isomeric, thermodynamically more stable, enolate **11**[4] by migration of the alcoholic function.[d] Furthermore, this mechanism could explain the greater reactivity of the compounds **2** with an aromatic substituent at 4: in fact, in these derivatives the rate of the slow step, the formation of the enolate **10**, was remarkably enhanced by the more acidic nature of the proton at 4 and, therefore, rather mild conditions were sufficient. On the contrary, when R' was an aliphatic group, the lower mobility of the proton at 4 required both the employment of basic Al_2O_3 and longer times of adsorption.

The routes at present employed can be conveniently replaced by the described method, since it allows a rapid conversion of 4-substituted 5-hydroxy-3-oxocyclopentenes into the 2-substituted analogs using a simple and cheap procedure.[e]



2h **10** **11** **6h**

Scheme 1.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. ^{1}H-NMR spectra were taken with a Jeol 60 HL spectrometer and with a Perkin-Elmer R 32 spectrometer using usually CCl_4 or $CDCl_3$ solns with TMS as an internal standard. IR spectra were taken with a Perkin-Elmer 257 spectrometer. Mass spectra were obtained with an AEI MS-12 spectrometer at 70 eV, by using direct insertion at source temp. of 150°. Commercial Merck silica gel and Woelm alumina were used for column chromatography. Merck precoated silica gel plates were used in tlc. The chromatograms were detected by spraying with 5N H_2SO_4 and heating at 110° for 10 min.

2-Phenyl-5-hydroxy-3-oxocyclopentene **6a**. After adsorption of 500 mg of **2b**[6] on alumina (10 g, basic, Brockmann grade III) for 8 hr, elution with 4:1 C_6H_6/Et_2O gave 450 mg of pure **6a**, $C_{11}H_{10}O_2$, (90%), plates from hexane, m.p. 58–59°. (Found: C, 76.01; H, 5.90. Calc. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79%). MS, *m/e*: 174 (M^+). For IR and ^{1}H-NMR data, see the initial section.

2-n-Hexyl-5-hydroxy-3-oxocyclopentene **6b**. After the adsorption of 500 mg of **2b**[6] on alumina (10 g, basic, Bromann grade III) for 30 hr, elution with 4:1 C_6H_6/Et_2O gave 475 mg of pure, oily **6b**, $C_{11}H_{18}O_2$, (95%). (Found: C, 72.33; H, 10.05. Calc. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%). IR spectrum (film, ν_{max}, cm^{-1}): 3400, 1710, 1635. ^{1}H NMR spectrum ($CDCl_3$, δ): 7.14 (m, 1 H, 1-H), 4.90 (m, 1 H, 5-H), 3.30 (broad s, 1 H, –OH), 2.80 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 6 Hz), 2.28 (dd, 1H, 4-H, J_1 = 18 Hz, J_2 = 2 Hz), 2.14 (m, 2H, allylic $-CH_2-$), 1.30 (sharp s, 8 H, 4 $-CH_2-$), 0.86 (t, 3H, $-CH_3$) MS, *m/e*: 182 (M^+).

2-Methyl-5-hydroxy-3-oxocyclopentene **6c**. After the adsorption of 500 mg of **2c**[6] on alumina (10 g, basic, Brockmann grade III) for 16 hr, elution with 4:1 C_6H_6/Et_2O gave 425 mg of pure oily **6c**, $C_6H_8O_2$, (85%). (Found: C, 64.11; H, 7.15. Calc. for $C_6H_8O_2$: C, 64.27; H, 7.19%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1710, 1640. ^{1}H NMR spectrum ($CDCl_3$, δ): 7.22 (m, 1 H, 1-H), 4.90 (m, 1 H, 5-H), 3.40 (broad s, 1 H, –OH), 2.82 (dd, 1 H, 4-H, J_1 = 18 Hz, J = 6 Hz), 2.24 (dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 2 Hz), 1.83 (d, 3 H, 2-CH_3, J = 1 Hz). MS, *m/e*: 112 (M^+).

t - Butyl - 5 - hydroxy - 3 - oxo - 2 - cyclopentene - heptanoate **6d**. After the adsorption of 500 mg of **2d**[7] on alumina (10 g, basic, Brockmann grade III) for 16 hr, elution with 4:1 C_6H_6/Et_2O yielded 475 mg of pure **6d**, $C_{16}H_{26}O_4$, as very dense oil (95%). (Found: C, 67.90; H, 9.41. Calc. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28%). IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 3610, 1735–1710, 1640. ^{1}H NMR spectrum (CCl_4, δ): 7.05 (m, 1 H, 1-H), 4.85 (m, 1 H, 5-H), 4.20 (m, 1 H, –OH), 2.70 (dd, 1 H, 4-H; J_1 = 16 Hz, J_2 = 6 Hz), 2.30–2.00 (m, 5 H, 4-H, the allylic $-CH_2-$, and the $-CH_2-\alpha$ to the ester function). MS, *m/e*: 282 (M^+).

Allethrolone **6e**. After adsorption of 500 mg of **2e**[1] on alumina (10 g, neutral, Brockmann grade III) for 24 hr, elution with 1:1 C_6H_6/Et_2O gave 475 mg of pure, oily **6e**, $C_5H_{12}O_2$, (95%). (Found: C, 70.85; H, 7.90. Calc. for $C_5H_{12}O_2$: 71.03; H, 7.95%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1695, 1640–1635. ^{1}H NMR spectrum (CCl_4, δ): 5.65 (complex m, 1 H, $-CH_2-CH=CH_aH_b$), 5.02 (m, 1 H, $-CH_2CH=CH_aH_b$), 4.81 (m, 1 H, $-CH_2-CH=CH_aH_b$), 4.57 (m, 1 H, 5-H), 3.75 (broad s, 1 H, –OH), 2.85 (d, 2 H, $-CH_2-CH=CH_aH_b$), 2.65 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 6 Hz), 2.15 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 3 Hz), 2.05 (s, 3 H, 1-Me). MS, *m/e*: 152 (M^+).

2 - n - Butyl - 5 - hydroxy - 1 - methyl - 3 - oxocyclopentene **6f**. After the adsorption of 500 mg of **2f**[1] on alumina (10 g, basic, Brockmann grade III) for 18 hr, elution with C_6H_6/Et_2O 1:1 yielded 478 mg of pure, oily **6f**, $C_{10}H_{16}O_2$, (95%). (Found: C, 71.31; H, 9.68. Calc. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1690, 1643. ^{1}H NMR spectrum (CCl_4, δ): 4.62 (m, 1 H, 5-H) 3.95 (broad s, 1 H, –OH), 2.67 (dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 6 Hz), 2.12 (partially visible dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 2.2 Hz), 2.07 (s, 3H, 1-CH_3), 1.35 (m, 6 H, 3 $-CH_2-$), 0.92 (t, 3 H, $-CH_2-CH_3$, J = 6 Hz). MS, *m/e*: 168 (M^+).

2 - cyclohexyl - 5 - hydroxy - 1 - methyl - 3 - oxocyclopentene **6g**. After the adsorption of 500 mg of **2g**[1] on alumina (10 g, basic, Brockmann grade III) for 48 hr, elution with 1:1 C_6H_6/Et_2O gave 465 mg of pure **6g**, $C_{12}H_{18}O_2$, as very dense oil (93%). (Found: C, 74.28; H, 9.24. Calc. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%). IR spectrum (film, ν_{max} cm^{-1}): 3400, 1685, 1638. ^{1}H NMR spectrum (CCl_4, δ): 4.50 (m, 1 H, 5-H), 3.32 (broad s, 1 H, –OH), 2.60 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 6 Hz), 2.12 (not completely visible dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 2.2 Hz), 2.07 (s, 3 H, 1-CH_3). MS, *m/e*: 194 (M^+).

2 - Phenyl - 5 - hydroxy - 1 - methyl - 3 - oxocyclopentene **6h**. After the adsorption of 500 mg of **2h**[1] on alumina (10 g, neutral, Brockmann grade III) for 7 hr, elution with 1:1 C_6H_6/Et_2O gave 460 mg of pure **6h**, $C_{12}H_{12}O_2$, (92%), plates from hexane, m.p. 102–104°. (Found: C, 76.42; H, 6.61. Calc. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43%). IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 3590, 3400, 1699, 1643, 1602. ^{1}H NMR spectrum (CCl_4, δ): 7.28 (m, 5 H, aromatic protons), 4.75 (m, 1 H, 5-H), 3.50 (s, 1 H, –OH), 2.85 (dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 6 Hz), 2.30 (not completely visible dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 2.2 Hz), 2.13 (s, 3 H, 1-CH_3). MS, *m/e*: 188 (M^+).

2 - (2 - Thienyl) - 5 - hydroxy - 1 - methyl - 3 - oxocyclopentene **6i**. After the adsorption of 500 mg of **2i**[1] on alumina (10 g, neutral, Brockmann grade III) for 3 hr, elution with 1:1 C_6H_6/Et_2O gave 465 mg of pure **6i**, $C_{10}H_{10}O_2S$, (93%), needles from hexane, m.p. 89–90°. IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 3590, 3400, 1695, 1622. ^{1}H NMR spectrum (CCl_4, δ): 7.15 (m, 3 H, aromatic protons), 4.67 (m, 1 H, 5-H), 3.41 (s, 1 H, –OH), 2.87 (dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 6 Hz), 2.35 (partially visible dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 2.2 Hz), 2.30 (s, 3 H, 1-CH_3). MS *m/e*: 194.25 (M^+).

2 - p - Tolyl - 5 - hydroxy - 1 - methyl - 3 - oxocyclopentene **6j**. After the adsorption of 500 mg of **2j**[1] on alumina (10 g, neutral, Brockmann grade III) for 8 hr, elution with C_6H_6/Et_2O 1:1 yielded 460 mg of pure **6j**, $C_{13}H_{14}O_2$, (92%), prisms from hexane, m.p. 86–87°. (Found: C, 77.35; H, 6.96. Calc. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%). IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 3600, 3400, 1700, 1643, 1612. ^{1}H NMR spectrum (CCl_4, δ): 7.14 (s, 4 H, aromatic protons), 4.70 (m, 1 H, 5-H), 3.12 (s, 1 H, –OH), 2.82 (dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 6 Hz), 2.35 (dd, 1 H, 4-H, J_1 = 18 Hz, J_2 = 3 Hz), 2.31 (s, 3 H, 1-CH_3), 2.12 (s, 3H, p-CH_3). MS, *m/e*: 202 (M^+).

Rearrangement of **2a** *on* Al_2O_3/MeOH. After the adsorption of 100 mg of **2a** on dry alumina (3 g, neutral, deactivated with 0.3 ml of MeOH) for 7 hr, elution with 1:1 C_6H_6/Et_2O under anhyd conditions yielded 89 mg of a compound identical with an authentic sample of **6a**, on the basis of the spectroscopic (IR and ^{1}H NMR) and physical data (m.p.).

4 - Phenyl - 5 - acetoxy - 3 - oxocyclopentene **7**. 200 mg of **2a** were treated with 2 ml Ac_2O and 2 ml pyridine at room temp. for 7 hr. Then the usual isolation procedure gave 240 mg of crude product which was chromatographed on SiO_2 very rapidly. The elution with 95:5 C_6H_6/Et_2O yielded 150 mg pure **7**, $C_{13}H_{12}O_3$, as a very dense oil (60%). (Found: C, 72.04; H, 5.75. Calc. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%). IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 1720, 1600. ^{1}H NMR spectrum (CCl_4, δ): 7.57 (dd, 1 H, 1-H, J_1 = 6 Hz, J_2 = 3 Hz), 7.20 (m, 5 H, aromatic protons), 6.32 (dd, 1 H, 2-H, J_1 = 6 Hz, J_2 = 1.5 Hz), 5.80 (m, 1 H, 5-H), 3.47 (d, 1 H, 4-H, J = 3 Hz), 2.03 (s, 3 H, $-OCOCH_3$). MS, *m/e*: 216 (M^+).

2 - Phenyl - 5 - acetoxy - 3 - oxocyclopentene **8**. After the adsorption of 100 mg of **7** on alumina (3 g, neutral, Brockmann grade III) for 1 hr, elution with 95:5 C_6H_6/Et_2O gave 91 mg of pure **8**, $C_{13}H_{12}O_3$, as a very dense oil (91%). (Found: C, 72.31; H, 5.78. Calc. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%). IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 1720, 1600. ^{1}H NMR spectrum (CCl_4, δ): 7.58 (m, H, aromatic protons), 7.51 (d, 1 H, 1-H, J = 3 Hz), 7.32 (m, 3 H, aromatic protons), 5.73 (m, 1 H, 5-H), 2.94 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 6 Hz), 2.40 (dd, 1 H, 4-H; J_1 = 18 Hz, J_2 = 2 Hz), 2.0 (S, 3 H, $-OCOCH_3$). MS, *m/e*: 216 (M^+).

2 - Phenyl - 5 - hydroxy - 1 - methyl - 4 - d - 3 - oxocyclopentene **9**. After the adsorption of 100 mg of **2h** on alumina (3 g, neutral, deactivated with 0.2 ml of D_2O) for 6 hr, elution with 1:1 C_6H_6/Et_2O gave 91 mg pure **9**, $C_{12}H_{11}O_2D$, (91%), plates from hexane, m.p. 104–108°. IR spectrum (1% $CHCl_3$, ν_{max} cm^{-1}): 3600, 3400, 1690, 1640, 1600. ^{1}H NMR spectrum (CCl_4, δ): 7.36 (m, 5 H, aromatic protons), 4.72 (m, 1 H, 5-H), 2.55 (dd, 1 H, 4-H, J_1 = 6 Hz, J_2 = 2 Hz), 2.15 (s, 3 H, 1-CH_3). MS, *m/e*: 189 (M^+).

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