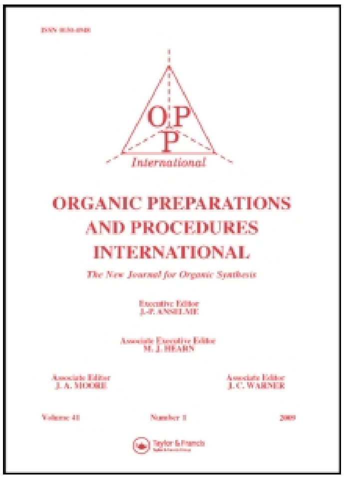

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A CONVENIENT PREPARATION OF *cis*-DIHYDROIONONE

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A CONVENIENT PREPARATION OF *cis*-DIHYDROIONONE

Submitted (5/14/80)

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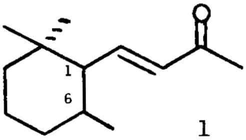
The recent, increased attention in the chemopreventive role of retinoids in the development of cancers of the epithelial tissues,[1] has prompted interest in syntheses of radiolabelled retinoic acid, its analogues and metabolites. For a synthesis of *cis*-5,6-dihydroretinoic acid $[10\text{-}^{3}\text{H}]$, large quantities of a precursor, *cis*-dihydroionone (1), were required. An obvious and inviting approach from the standpoint of simplicity and cost appeared to be the selective reduction of the



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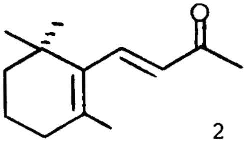

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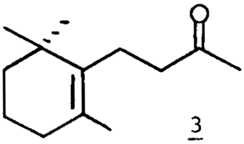

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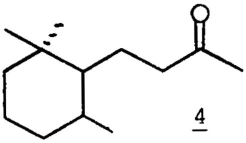

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ring double-bond of β-ionone (2). Although numerous methods to accomplish the reduction of 2 to 3 in good to excellent yield have been reported,[2] the only report[3] for the direct[4] conversion of 2 to 1, by hydrogenation with Raney nickel, yields mixture of 1 and 3 in unspecified proportions. Products 1 and 3 apparently were separated as their semicarbazones by repeated recrystallizations, but the procedure is tedious; neither the yield, purity nor a complete characterization of 1 was reported. We now disclose an exceedingly simple, moderately selective reduction of 2 to 1 together with a facile purification of 1 on a multigram scale via preparative HPLC, and spectral data consonant with the structure of 1.

EXPERIMENTAL

Both ^{1}H and ^{13}C NMR spectra were obtained on a Bruker WP-200-mHz instrument. Chemical shift values are expressed in parts per million downfield from internal $(CH_3)_4Si$. The IR spectrum was measured neat on salt plates using a Perkin-Elmer 283 spectrophotometer. The high resolution mass spectrum was performed by Shrader Analytical Laboratories, Detroit, Michigan and the elemental analysis was performed by Galbraith Laboratories, Knoxville, Tennessee.

cis-Dihydroionone (1).- A solution of 4.81 g (25 mmol) of β-ionone (Aldrich) in 75 ml of ethanol with 95 mg of 5% Pd/C was stirred under an atmosphere of hydrogen for 0.5 hr. resulting in an uptake of 616 ml (27.5 mmol) of hydrogen. The reaction mixture was filtered through Celite and concentrated under reduced pressure to a mobile oil (4.85 g, 99.7%) consisting of 1 (70%) and 4 (30%)[5] as determined by normal phase HPLC eluted with hexane: ethyl acetate (99:1) at 2 ml/min with refractive index detection. In this analytical HPLC, baseline separation was achieved between 4 (retention time ≈ 11 min) and 1 (retention time = 13 min), and no β-ionone (2) (retention time = 15 min) was detected. The entire mixture (4.85 g) of 1 and 4 was injected onto a Waters Preparative 500 HPLC fitted with two normal phase columns in tandem eluted with hexane: ethyl acetate (99:1) at 150 ml/min with refractive index detection. Well-defined (although not baseline) peak separation was observed for 1 and 4. The eluent between 30 and 40 minutes (total volume - 1500 ml) was collected. Concentration of the collected eluent under reduced pressure yielded 1.94 g (40%) of 1 as a mobile oil[6] in 98% purity as ascertained by analytical normal phase HPLC.[7]

^{1}H NMR($CDCl_3$): δ 6.85 (dd, 1, J = 10.86, 15.81 Hz, side chain C_4H), 6.05 (d, 1, J = 15.81 Hz, side chain C_3H), 2.25 (s, 3, $COCH_3$), 2.00 (m, 1 ring C_6H), 1.90 (dd, 1, J = 4.03, 10.86 Hz, ring C_1H), 1.70-0.85 (m,6), 1.05 (s, 3), 0.75 (s,3), 0.72 (d, 3, J = 6.59 Hz, ring C_6 methyl); partial ^{13}C NMR($CDCl_3$): δ 197.58 (s, side chain C_2), 147.27 (d, side chain C_4), 133.38 (d, side chain C_3), 54.89 (d, ring C_1); IR(film): 2980, 2930, 2875, 1680, 1625, 1455 cm^{-1}; MS: 194.1664 (Calcd 194.1669).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41.
Found: C, 80.59; H, 11.46.

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4. The literature also contains a successful indirect conversion of 2 to 1 via an intermediate ketal of 2 [P. Bachli and H. Schinz, Helv. Chim. Acta, 34, 1160 (1951)]. As in the case of the procedure in reference 3, this indirect preparation of 1 yields a mixture of dihydro products in undisclosed proportions, requires tedious purification techniques, and lacks yield, purity data or a complete characterization of 1. An unsuccessful attempt to prepare 1 from 4 [L. Columbi, A. Bosshard, H. Schinz, and C. F. Seidel, Helv. Chim. Acta, 34, 265 (1951)] has also been documented.

5. Compound 4 gave IR and ^{1}H NMR spectra in full accord with the proposed structure: IR(film): 1715 cm^{-1} (C=O); ^{1}H NMR($CDCl_3$): δ 2.40 (t, 2, J = 6.85 Hz, $C\underline{H}_2COCH3$), 2.13

(s, 3, $COCH_3$).

6. The cis axial-equatorial relationship for the hydrogens at the 1 and 6 positions of purified 1 was confirmed by the magnitude of their coupling constant (J = 4.03 Hz) as ascertained by double resonance experiments. Composed of 13 sharp lines, the ^{13}C NMR of 1 is also in harmony with the presence of a single stereoisomer. We are assuming that the bulky 3-buten-2-one side chain of 1 occupies an equatorial ring position, thereby precluding the possibility of a trans equatorial-equatorial relationship for the 1 and 6 ring position protons of 1.
7. This yield of pure 1 represents a 57% recovery of the available 1 in the mixture. We have found that a less conservative collection of 1 by HPLC seriously compromises its purity.

A CONVENIENT PREPARATION OF α,α-DIPHENYLACETOPHENONE

Submitted by (1/13/79)

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Although several mechanistic studies and synthetic applications of alkali aromatic ketyls[1-4] have been recently published, there have been no further study of the reaction of phenyllithium with carbon monoxide since the work of White-