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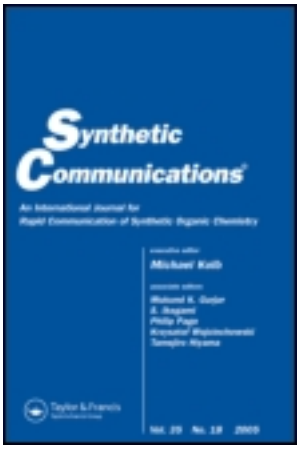

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Thionyl Chloride-pyridine Mediated Rearrangement. Synthesis of Potential Intermediates for (+) and (±)-Occidol

Ajoy K. Banerjee [a] & William Vera [a]
[a] Centre de Química , IVIC , Apartado 21827, Caracas, 1020-A, Venezuela
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THIONYL CHLORIDE-PYRIDINE MEDIATED REARRANGEMENT. SYNTHESIS OF POTENTIAL INTERMEDIATES FOR (+) AND (±)-OCCIDOL.

Ajoy K. Banerjee* and William Vera

Centro de Química, IVIC, Apartado 21827, Caracas 1020-A, Venezuela

Abstract - Thionyl chloride-pyridine mediated rearrangement of cylohexadienyl alcohols (2) and (8) has provided hyposantonin (3) and tetrahydronaphthalene (9), respectively, which in turn have served as potential intermediates for the synthesis of optically active and racemic occidol (6), respectively.

Our previous works[1,2] have demonstrated that several tertiary alcohols undergo a variety of interesting rearrangements with thionyl chloride and pyridine. These observations led us to study the behavior of the below mentioned cyclohexadienyl alcohols with thionyl chloride and pyridine. The discussion of the results obtained is the topic of the present paper.

The already reported alcohol (2)[3] from α-santonin (1) was selected as reference material for our study. The alcohol (2), on treatment with thionyl chloride and pyridine for 24 hr, underwent rearrangement yielding the hyposantonin (3)[4] in 43% yield. Though an authentinc specimen of hyposantonin (3) could not be obtained for comparison of the melting point its spectroscopic data provided convincing evidence in support of the structure of the hyposantonin (3). The present transformation can be

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*To whom correspondence should be addressed

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explained by assuming the formation of the intermediate (A). The methyl migration of (A) which accompanies the elimination of the chlorosulfide (-OSOCl) would probably lead the formation of the intermediate (B) that rearranges to hyposantonin (3).

Alkaline hydrolysis of hyposantonin (3) followed by oxidation with Jones reagent[5] at 0°C afforded keto-acid (4) whose transformation to hyposantanous acid (5) was realized by Clemmemsen reduction.[6] The transformation of hyposantonin (3) to acid (5) by reduction with zinc dust and acetic acid[7] was not satisfactory. The spectroscopic data nicely matched with the assigned structure (5). As the transformation of the hyposantanous acid (5) to (+)-occidol (6) has already been reported,[4] the present approach constitutes a new route towards the synthesis of (+)-occidol (6).

The aromatization of the cyclohexadienyl alcohol has also been utilized for the synthesis of a potential intermediate for racemic occidol (6). The dienone (7), prepared by the published procedure,[8] on reduction with sodium borohydride and cerium chloride yielded the alcohol (8) which on treatment with thionyl chloride and pyridine underwent aromatization by the above mentioned path affording tetrahydronaphthalene (9) in 35% yield. This, on alkaline hydrolysis, gave the alcohol (10) whose transformation to the already reported[9] dimethyl α-tetralone (11) in satisfactory yield, was achieved by oxidation with Jones reagent.[5] Though its authentic specimen was not available for direct comparison, its spectroscopic data provided strong evidence in favor of the assigned structure. As this tetralone (11) was utilized by HO[10] in the synthesis of racemic occidol (6), the present approach offers an alternative path to α-tetralone (11) for its transformation to (±)-occidol.

To the best of our knowledge this is the first example of the rearrangement of cyclohexadienyl alcohols, effected by thionyl chloride and pyridine, that occurs with aromatization and methyl migration. The present approach for the conversion of santonin (1) to hyposantonin (3) appears to be more convenient than the published procedure.[4] In addition the experimental procedure for the synthesis of tetralone (11) seems less complicated than the literature.[9] procedure. Moreover, it is necessary to report that the above mentioned method of aromatization will be very useful for the synthesis of potential intermediates for aromatic sesquiterpenes like platphyllide[11] and rishitinol.[12]

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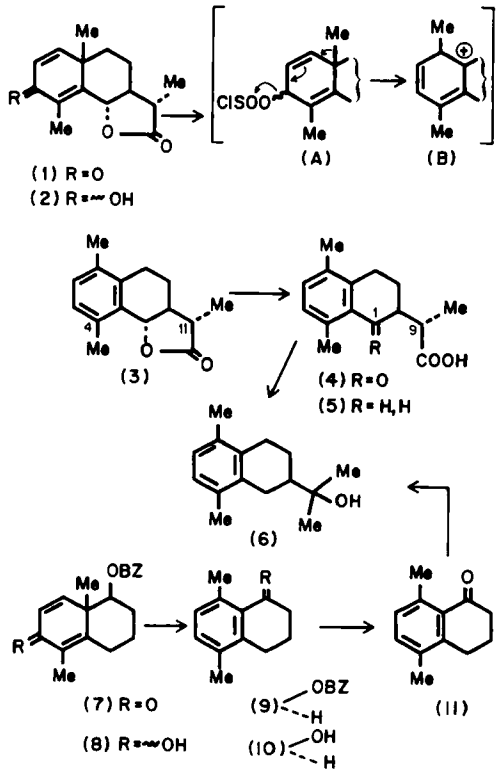

EXPERIMENTAL SECTION[2]

Hyposantonin (3) - To a solution of the alcohol (2) (2.12 g) in dry pyridine (20 ml) was added freshly distilled thionyl chloride (2 ml) and stirred at room temperature for 24 hr. Work-up followed by chromatographic purification on silica gel (eluant: hexane-diethyl ether, 8:2) afforded hyposantonin (3) (842 mg, 43%); mp. 150-151°C (ether-hexane) (lit.[13] 152-153°C); $[\alpha]_D$ +31.9° (benzene) [lit.[13] 32.7°C (benzene)]; m/z 230 (M^+); ν_{max} 1772 cm^{-1} (CO); δ 1.23 (3H, d, J=6 Hz, 11-Me), 2.17 (3H, s), 2.43 (3H, s) (1,4-Me) and 6.95 (2H, bs, aromatic protons) (Found: C, 78.15; H, 7.84. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%).

Hyposantanous acid (5) - To a solution of hyposantonin (3) (2.12 g) in methanol (20 ml) was added an aqueous solution of sodium hydroxide (10 ml, 5%), heated under reflux for 2 hr, diluted with water and

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extracted with chloroform. The aqueous layer was cooled to 0°C and acidified with hydrochloric acid (4 ml); work-up afforded an oily material (1.13 g); ν_{max} 1710 (CO) and 3365 cm^{-1} (OH). This was dissolved in acetone (10 ml) and treated with Jones reagent (2 ml). The resulting product on passing over a column of silica gel (eluant: hexane-diethyl ether, 2:8) yielded the keto-acid (4) (1.08 g), a very viscous material, m/z 246 (M^+); ν_{max} 1687 (CO); δ 1.18 (3H, d, J=9 Hz, 9-Me), 2.23 (3H, s), 2.55 (3H, s) (5,8-Me) and 6.85 (2H, s, aromatic protons). No attempt was made to crystallize the acid.

The keto-acid (4) (1.02 g) was heated under reflux for 6 hr with amalgamated zinc (3 g), water (3 ml), toluene (6 ml) and hydrochloric acid (2 ml). Work-up followed by chromatographic purification over silica gel (eluant: hexane-diethyl ether, 3:7) gave hyposantanous acid (5) (672 mg, 31% from hyposantonin); mp. 89-90°C (from ether-hexane) (lit.[4] mp. 91-92°C); $[\alpha]_D$ + 62° (ethanol) (lit.[4] + 64); m/z 232 (M^+); ν_{max} 1704 (CO) and 2300-3400 cm^{-1} (acid OH); δ 1.21 (3H, d, J=6 Hz, 9-Me), 2.12 (6H, s, 5,8-Me), 6.75 (2H, s, aromatic protons) and 10.21 (1H, bs, acid OH) (Found: C, 77.32; H, 8.32. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

1,4-Dimethyl--5-benzoyl-5,6,7,8-tetrahydronaphthalene (9) - To a solution of the dienone (7) (1.78 g) and $CeCl_3$, 6 H_2O (2.26 g) in ethanol (100 ml), cooled to 0°C was added sodium borohydride (1.10 g) in portion-wise within 20 min. The reaction mixture was stirred for 30 min and diluted with water. Work-up afforded alcohol (8) (1.50 g, 83%); m/z 298 (M^+), 176 (M^+-$PhCO_2H$) and 158 (M-$PhCO_2H$-H_2O); ν_{max} 1710 (CO) and 3418 cm^{-1} (OH). The alcohol (8) without further purification was immediately utilized for the next step.

To a solution of the alcohol (8) (1.50 g) in pyridine (30 ml) was added freshly distilled thionyl chloride (2 ml) and stirred at room temperature for 18 hr. Work-up followed by chromatographic purification on silica gel (eluant: hexane-diethyl ether 8:2) yielded the tetrahydronaphthalene (9) (490 mg, 35%); m/z 280 (M^+) and 158 (M^+-PhCOOH); ν_{max} 1715 cm^{-1} (CO); δ 2.28 (s, 6H, 1,5-Me), 6.83 (s, 2H, aromatic protons) and 7.37-8.15 (m, 5H, aromatic protons) (Found: C, 81.16; H, 7.12. $C_{19}H_{20}O_2$ requires C, 81.39; H, 7.19%).

1,4-Dimethyl-5β-hydroxy-5,6,7,8-tetrahydronaphthalene (10) - To a solution of tetrahydronaphthalene (9) (480 mg) in ethanol (10 ml) was

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added an aqueous solution of sodium hydroxide (10 ml, 1N) and heated under reflux for 6 hr. Work-up followed by chromatographic purification (eluant hexane-diethyl ether, 3:7) yielded the alcohol (10) (170 mg, 57%);m/z 176 (M^+) and 158 (M^+-H_2O); ν_{max} 3425 cm^{-1} (OH); δ 2.31 (bs, 6H, 1,4-Me), 3.35 (m, 1H, CHOH) and 6.85 (bs, 2H, aromatic protons) (Found: C, 81.65; H, 9.08. Calc. for $C_{12}H_{16}O$ requires C, 81.77; H, 9.15%).

1,4-Dimethyl-α-tetralone (11) - To the alcohol (10) (160 mg) in acetone (3 ml) at 0°C was added Jones reagent (0.5 ml). Work-up and chromatographic purification (eluant hexane:diethyl ether, 4:6) yielded the α-tetralone (11) (110 mg, 70%) mp. 31-32°C (from light petroleum) (lit.[9] mp. 33°C); m/z 174 (M^+); ν_{max} 1710 (CO); δ 2.33 (bs. 6H, 1,4-Me) and 6.93 (bs, 2H, aromatic protons) (Found: C, 82.67; H, 8.05; $C_{12}H_{14}O$ requires C, 82.72; H, 8.10%).

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