2,6-DIHYDROXY-4-PYRROLIDINYL-ACETOPHENONE AND ITS COMPLEX WITH PYRROLIDINE[a]

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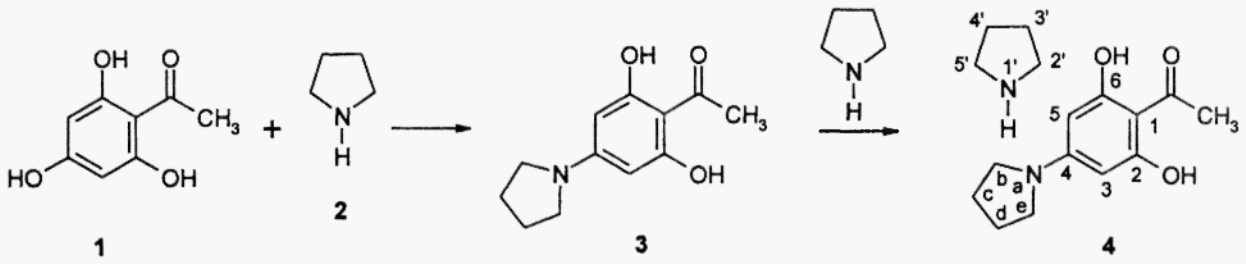
Abstract - The synthesis of 2,6-dihydroxy-4-pyrrolidinyl-acetophenone (**3**), characterized earlier as an oil, has been simplified and improved substantially leading to **3** in crystalline form. Compound **3** tends to form a 1:1 molar complex with pyrrolidine; it could be utilized to produce the novel spiro derivative **6**.

Introduction

We have recently been intending to utilize, as a starting material in various synthetic projects, 2,6-dihydroxy-4-pyrrolidinyl-acetophenone (**3**) whose synthesis had previously been described by ApSimon et al.[1] In their approach 2,4,6-trihydroxy-acetophenone (**1**) (0.537 mmol in its hydrate form) was allowed to react with a large molar excess (11.98 mmol) of pyrrolidine (**2**) in toluene for three days at 40 °C. Subsequently the solvent was removed on the rotoevaporator, the residue was dissolved in CH_2Cl_2 and passed through Florisil, then eluted with more CH_2Cl_2. After removal of the solvent and purification by thick layer chromatography, **3** was obtained as an oil in 37 % yield and was characterized by IR, ^1H NMR and MS. Here we wish to note that by using a simpler approach the synthetically useful starting material **3** can be obtained in much higher yield and in crystalline form.

[a] This paper is dedicated to Prof. András Messmer on the occasion of his 80th birthday.

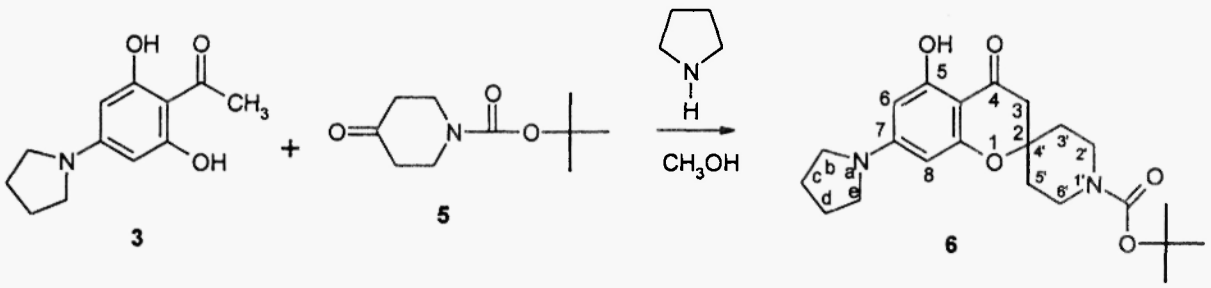


Results

We effected the above reaction by using **1** and **2** in an equimolar ratio in methanol under reflux for 6 hrs, during which part of the final compound **3** precipitated in crystalline form, then after cooling pure **3** was obtained in 77 % yield (see experimental section). We have also established that **3** forms a loose complex (**4**) with pyrrolidine, which was obtained from **3** by using another molar equivalent of pyrrolidine. This complex cannot be characterized as a salt as based on the fact that in **4** the ^{1}H and ^{13}C NMR chemical shifts due to the non-covalently bonded pyrrolidine fall between those of pyrrolidine base and pyrrolidine perchlorate, with somewhat more likeness to the former (see experimental section).

We had no intention to work with a larger molar excess of pyrrolidine.

In order to synthetically utilize 2,6-dihydroxy-4-pyrrolidinyl-acetophenone, we allowed **3** to react with the piperidone derivative **5**, which gave the spiro compound **6**.



Experimental

2,6-Dihydroxy-4-pyrrolidinyl-acetophenone (**3**). 2,4,6-trihydroxyacetophenone monohydrate (**1**) (9.3 g, 0.05 mol) was suspended in methanol (35 ml) to which pyrrolidine (**2**) (4.25 ml, 51 mmol) was added. The mixture was stirred and refluxed for 6 hrs; precipitation had already become substantial after the first hour. The substance was left to stand in the refrigerator overnight. After filtration the residue was washed with methanol (10 ml) to give **3** (8.55 g, 77.27%), mp

210-211 °C; IR (KBr, cm^{-1}): 3337 (b, OH), 1648 (C=O); ^1H NMR: 1.92 (m, 4H, H_2-c,d); 2.50 (s, 3H, COMe); 3.24 (m, 4H, H_2-b,e); 5.53 (s, 2H, H-3,5); 12.21 (br s, 2H, OH); ^{13}C NMR: 24.8 (C-c,d); 31.7 (CO<u>Me</u>); 47.0 (C-b,e); 90.2 (C-3,5); 101.3 (C-1); 152.7 (C-4); 163.6 (C-2,6); 200.1 (<u>C</u>OMe); MS (EI) m/z (rel. %): 221 (57), 206 (100), 192 (8), 178 (10), 164 (5), 150 (5). *Anal.* Calcd for: $C_{12}H_{15}NO_3$: N 6.33. Found: N 6.27.

2,6-Dihydroxy-4-pyrrolidinyl-acetophenone - pyrrolidine complex (4). A mixture of compound 3 (2.21 g, 10 mmol) and pyrrolidine (0.85 ml, 10 mmol) was refluxed in methanol until most of 3 had dissolved. After cooling the substance completely solidified during precipitation. After having let it stand in the refrigerator overnight, the substance was filtered and washed with methanol (3 ml) to give 3 (2.41 g), mp 155 °C (melts) which did not change after crystallization from ethanol; IR (KBr, cm^{-1}): 300-1900 (b, NH); 1616 (C=O); ^1H NMR: 1.62 (m, 4H, H_2-3',4'), 1.90 (m, 4H, H_2-c,d), 2.53 (s, 3H, COMe), 2.77 (m, 4H, H_2-2',5'); 3.21 (m, 4H, H_2-b,e), 5.44 (s, 2H, H-3,5), 8.88 (br s, 2H, OH); ^{13}C NMR: 24.8 (C-3',4',c,d), 31.5 (CO<u>Me</u>), 45.9 (C-2',5'), 46.9 (C-b,e), 90.0 (C-3,5), 102.5 (C-1), 152.9 (C-4), 165.4 (C-2,6), 199.9 (<u>C</u>OMe); MS (EI) m/z (rel. %): 221 (53), 206 (100), 192 (7), 178 (9), 164 (4), 150 (4). *Anal.* Calcd for: $C_{16}H_{24}N_2O_3$: N 9.58. Found: N 9.44.

In the absence of any adequate literature data, the NMR spectra of pyrrolidine base and pyrrolidine perchlorate, the latter prepared according to reference 2, were also recorded for the sake of comparison. Pyrrolidine base: ^1H NMR: 1.55 (m, 4H, H_2-3',4'), 2.68 (m, 4H, H_2-2',5'); ^{13}C NMR: 25.2 (C-3',4'), 46.5 (C-2',5'). Pyrrolidine perchlorate: ^1H NMR: 1.85 (m, 4H, H_2-3',4'), 3.11 (m, 4H, H_2-2',5'); ^{13}C NMR: 23.6 (C-3',4'), 45.0 (C-2',5').

1'-butoxycarbonyl-5-hydroxy-7-pyrrolidinyl-spiro[2H-1-benzopyrane2,4'piperidine]-4(3H)one (6). Compound **3** (2.21 g, 0.01 mol) and N-Boc-4-piperidone (**5**) (2.0g, ~0.01 mol) were suspended in methanol (5 ml) to which pyrrolidine (**2**) (0.85 ml, ~0.01 mol) was added. Following dissolution of the solid compounds precipitation occurred during reflux, which was continued for 12 hrs while monitoring the reaction by TLC. After having left the substance to stand in the refrigerator overnight we obtained compound 6 (2.52 g, 62.61%), mp 215-218 °C (decomposes); the melting point remained unchanged after crystallization from acetonitrile; IR (KBr, cm^{-1}): 1686, 1656 (C=O) 1609, 874 (Ar), 1219 (Ar-O-C), 1156 (CO-O-C); ^1H NMR: 1.46 [s, 9H, $C(CH_3)_3$]; 1.58 (m, 2H, H_{2ax}-3',5'); 2.00 (m, 2H, H_{2eq}-3',5'); 2.02 (m, 4H, H_2-c,d); 2.60 (s, 2H, H_2-3); 3.22 (m, 2H, H_{2ax}-2',6'); 3.34 (m, 4H, H_2-b,e); 3.85 (m, 2H, H_{2eq}-2',6'); 5.63 (d, 1H, H-8); 5.64 (d, 1H, H-6); 12.15 (s, 1H, OH); MS (EI) m/z (rel. %): 402 (18) M, 329 (12), 258 (17), 206 (27), 57 (100). *Anal.* Calcd for: $C_{22}H_{30}N2O_5$: N 6.96. Found: N 7.0.

General: Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1000 spectrophotometer. All ^1H and ^{13}C NMR spectra were recorded on a Varian ^{UNITY}*INOVA* 300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) with internal deuterium lock in DMSO-d_6 at ambient temperature. Chemical shifts are given relative to δ_{TMS}=0.00 ppm. ^1H and ^{13}C chemical shift assignments were verified by a concerted use of standard high-field two-dimensional (2D) NMR methods: (NOESY, HSQC, HMBC). All pulse programs were run by using the standard spectrometer software package and utilizing its pulsed field gradient facility. MS spectra were taken on a VG-TRIO-2 (EI, 70 eV) spectrometer.

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References

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