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A CONVENIENT SYNTHESIS OF 8-[METHOXY OR BENZYLOXY] - 1,2- DIHYDRO -5- HYDROXY - 2 - QUINOLONE.

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ABSTRACT: 8-[methoxy or benzyloxy] -1,2-dihydro- 5-hydroxy- 2-quinolinones were prepared in good yield with selective deprotection during cyclization .

1,2-dihydro-5-hydroxy-8-methoxy-2-quinolinone or its 1,2,3,4-tetrahydro analogue are important heterocyclic ring systems in the cardiovascular area [1,2]. During the investigations of compounds possessing such heterocycles[3], we required a general and high-yielding method for the synthesis of **3**. Several routes toward the preparation of these compounds have been described in the literature. The majority of these methods involve the preparation of 1,2-dihydro-5,8-dihydroxy-2-quinolinone[4,5,6] as an intermediate. However selective methylation or benzylation of the 8 position have proved to be unsatisfactory in terms of yield and difficulty of purification.

In order to overcome these drawbacks we initially decided to use a 2-alkyloxy-3,3- dimethoxy propanilide having a hydroxy function protected in the 5 position by a benzyl group then to deprotect it by conventional manner after cyclization.

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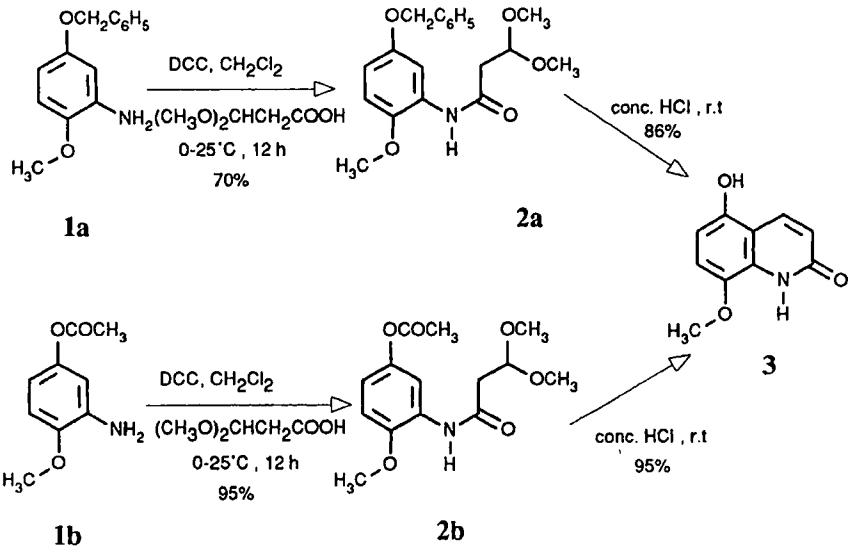

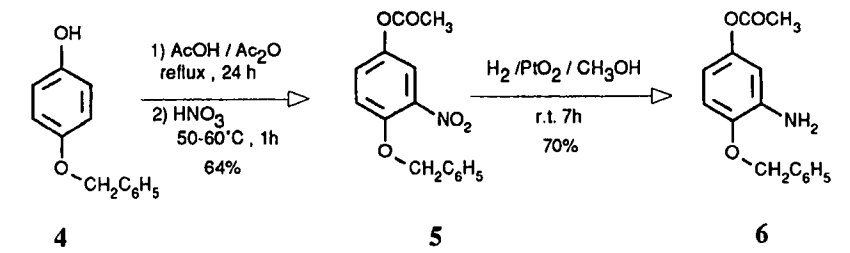

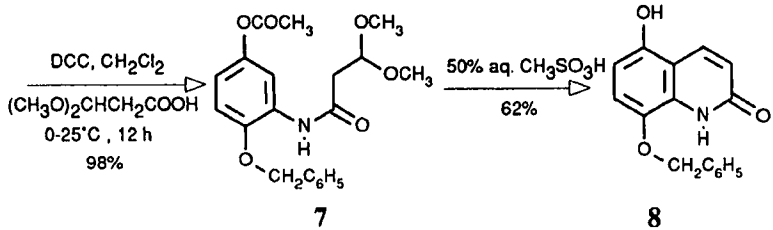

2-methoxy-5-benzyloxy-aniline[7] **1a** was condensed with 3,3- dimethoxy - propionic acid in a 70 % yield to give **2a** .

Attempted cyclization of **2a** in sulfuric acid as reported for analogous reactions[4] was unfruitful. However we were able to obtain **3** in an excellent yield in hydrochloric acid (cyclization with subsequent surprising debenzylation in position 5). This approach was slightly improved by the replacement of the benzyl group by an acetyl group allowing the preparation of **3** in only 2 steps from **1b**[8].

With the aim of preparing directly the 8-benzyloxy analogue, 4-benzyloxy-phenol **4** was converted to the 3-nitro-4-benzyloxy-phenyl acetate **5** in 64% yield by nitration in a mixture of acetic acid : acetic anhydride then hydrogenation over platinium oxide afforded the corresponding 3-amino-4-benzyloxy - phenyl acetate **6** in 70% yield which was condensed with 3,3-dimethoxy- propionic acid in a 98% yield to give **7** .

Attempted ring closure of **7** in hydrochloric acid failed mainly due to O-deprotection at both the 5 and 8 positions. We achieved the desired cyclization using a 1:1 mixture of methane sulfonic acid and water. This protection on the 8 position allows to functionalyze the 5 position and could be removed by hydrogenolyse . This preparation of **8** is an important improvement over the previously reported synthesis of the cardiovascular drug 8-hydroxy-carteolol[5,9].

EXPERIMENTAL SECTION

All melting points are uncorrected.^{1}H-NMR spectra were recorded on a AC Brucker spectrometer at 200MHz. Starting materials and reagents were of commercial quality , purchased from Aldrich Chemical Co.

3-nitro-4-benzyloxy-phenyl acetate **5** : to a solution of **4** (0.25 mol) in 150 mL of acetic acid was added dropwise 100mL of Ac_2O and the mixture refluxed during 24 h . To this solution , at room temperature , was slowly added HNO_3 (11.5 mL, 0.27 mol, d=1.52) with stirring . At the end of the addition the temperature was maintained between 50-60°C for 1h . The mixture was cooled

to 0°C and diisopropyl oxide (200 mL) was added . The precipitated product was filtered and dried to give **5** in 64% yield.

5 : mp 99°C.^{1}H-NMR ($CDCl_3$/TMS): δ ppm : 2.30 (s, 3H, $COCH_3$); 5.20 (s, 2H, $C_6H_5CH_2$); 7.10 (d, 1H, *J*=8.9, H_{arom}); 7.30 (dd, 1H, *J*=8.9,2.8, H_{arom}); 7.35-7.50 (m, 5H, C_6H_5); 7.72 (d, 1H, *J*=2.8, H_{arom}).

3-amino-4-benzyloxy-phenyl-acetate **6** : mixture of **5** (0.33 mol) in 400 mL of MeOH containing catalytic amount of PtO_2 was hydrogenated at room temperature for 7 h .Filtration on Celite then evaporation of the solvent gave a residue which was dissolved in 200 mL of CH_2Cl_2 and washed with 100 mL of O.5 N aq.Na OH. The organic layer was dried (Na_2SO_4) then evaporated to dryness to give **6** in 70% yield.

6 : mp 72-74°C.^{1}H-NMR ($CDCl_3$/TMS): δ ppm : 2.30 (s, 3H, $COCH_3$); 3.85 (br s, 2H, NH_2); 5.09 (s, 2H, $C_6H_5CH_2$); 6.35-6.50 (m, 2H, H_{arom}),6.80 (d, 1H, *J*=10, H_{arom}); 7.25-7.50 (m, 5H, C_6H_5).

5-benzyloxy-2-methoxy-3',3'-dimethoxy propanilide **2a** *and 4-alkyloxy- 3-(3,3-dimethoxypropanamido) phenyl acetate* **2b - 7** : solution of **1a, 1b or 6** (0.037 mol) and 3,3-dimethoxypropanoic acid (4.96g, 0.037mol) in 40 ml of CH_2Cl_2 was treated dropwise at 0°C with a solution of DCC (7.63g, 0.037mol) in 20 mL of CH_2Cl_2 . After stirring for 12h, the mixture was refluxed for 1.5h ,the insoluble material removed by filtration and the organic layer washed with 20 mL 1N aq. HCl , dried (Na_2SO_4), filtered and evaporated to yield a product which was crystallized (**2 b,7**) or chromatographied (**2a**) .

2a :(yield: 70%) mp 105°C (Flash-chromatography AcOEt/Heptane 1:4).
^{1}H-NMR ($CDCl_3$/TMS): δ ppm: 2.75 (d, 2H, $COCH_2$); 3.20 (s, 6H, OCH_3); 3.90 (s, 3H, OCH_3); 4.65 (t, 1H, $C\underline{H}(OCH_3)_2$); 5.10 (s, 2H, $C_6H_5C\underline{H}_2$); 6.70 (dd, 1H, *J*=9, 3, H_{arom}); 6.90 (d, 1H, *J*=9, H_{arom}); 7.35-7.50 (m, 5H, C_6H_5); 8.25 (d, 1H, *J*=3, H_{arom}); 8.90 (s, 1H, NH).

2b :(yield: 95%) mp 78°C.^{1}H-NMR ($CDCl_3$/TMS): δ ppm: 2.31 (s, 3H, $COCH_3$); 2.75 (d, 2H, *J*=5.2, $COCH_2$); 3.46 (s, 6H, OCH_3);3.92 (s, 3H, OCH_3); 4.76 (t, *J*=5.2, 1H, $C\underline{H}(OCH_3)_2$); 6.75 (dd, 1H, *J*=8.9, 2.7, H_{arom}); 6.87 (d, 1H, *J*=8.9, H_{arom}); 8.21 (d, 1H, *J*=2.7, H_{arom}); 8.78 (s, 1H, NH).

7 :(yield= 98%) mp 91°C (AcOEt/Pentane).^{1}H-NMR ($CDCl_3$/TMS): δ = 2.26 (s, 3H, $COCH_3$); 2.69 (d, 2H, *J*=5.2, $COCH_2$); 3.20 (s, 6H, OCH_3); 4.64 (t, 1H, *J*=5.2 $C\underline{H}(OCH_3)_2$); 5.07 (s, 2H, $C_6H_5C\underline{H}_2$); 6.74 (dd, 1H, *J*=8.9, 2.7, H_{arom}); 6.92 (d, 1H, *J*=8.9, H_{arom}); 7.30-7.50 (m, 5H, C_6H_5); 8.24 (d, 1H, *J*=2.7, H_{arom}); 8.88 (s, 1H, NH).

1,2-dihydro-5-hydroxy-8-methoxy-2-quinolinone **3** : to 30 mL of concentrated HCl was added portionwise **2a** or **2b** (0.026 mol). After stirring for 1h under nitrogen , the precipitate was filtered and washed with 100ml of H_2O then dried to give **3** ;

3 from 2a: (yield= 86%) mp 236°C.

3 from 2b: (yield= 95%) mp 235°C.

^{1}H-NMR (DMSO/TMS): δ ppm: 3.80 (s, 3H, OCH_3); 6.45 (d, 1H, *J*=9.6 H-3); 6.55 (d, 1H, *J*=8.6, H_{arom}); 7.00 (d, 1H, *J*=8.6, H_{arom}); 8.00 (d, 1H, *J*=9.6, H-4); 9.90 (s, 1H, NH); 10.70 (s, 1H, OH). *Anal.* cald for $C_{10}H_9NO_3$: C 62.82;H 4.74; N 7.32 ; found C 62.78;H 4.77;N 7.27.

8-benzyloxy-1,2-dihydro-5-hydroxy-2-quinolinone **8** : to 200 mL of 50% aq. CH_3SO_3H was added portionwise **7** (9.33g, 0.026 mol). After stirring for 1h under nitrogen , the mixture was poured into cold water and the precipitate filtered and crystallized from EtOH/ diisopropylether to give **8** in 62% yield .

8 : mp 212°C.^{1}H-NMR (DMSO/TMS): δ ppm: 5.15 (s, 2H, $C_6H_5C\underline{H}_2$); 6.41 (d, 1H, *J*=9.5, H-3); 6.46 (d, 1H, *J*=8.5, H_{arom});7.03 (d, 1H, *J*=8.5, H_{arom}); 7.22-7.64 (m, 5H, C_6H_5); 8.00 (d, 1H, *J*=9.5, H_{arom}); 9.93 (s, 1H, NH);10.60 (s, 1H, OH). *Anal.* cald for $C_{16}H_{13}NO_3$: C 71.90;H 4.90;N 5.24; found C 71.85;H 4.93; N 5.22.

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