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# New Synthesis of 4,4'-Diethylaminoethoxyhexestrol dihydrochloride (Coralgil) and scaling up to multi-grams scale

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## Abstract

We report here new preparation with significant yield improvement of title compound. For this purpose the preparation of 4,4'-diethylaminoethoxyhexestrol dihydrochloride under different reported and analogue conditions have been tried. The optimized synthesis of Coralgil is reported. The synthesis was also scaled up to multi-grams for chemo-genomics study.

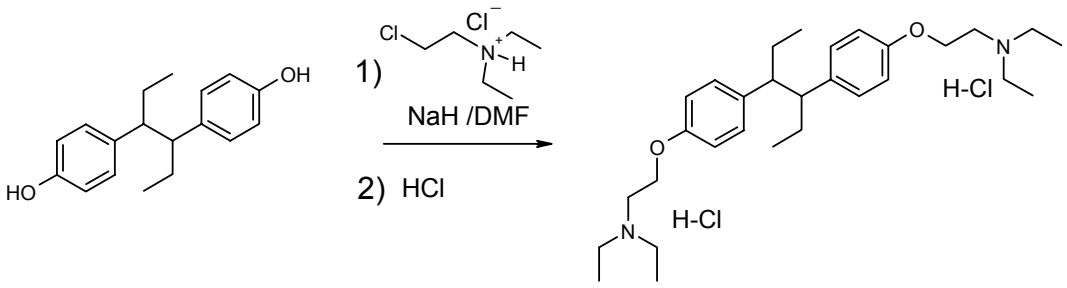
## Introduction

The bis-diethylaminoethylether of hexestrol (with commertial names: Altelide; Carifolmin; Coragil; Coralgil; Coralgina; Coralgyl; Coronastin; Diaethiphenum; Diethylphen; Dolgin; Etafen; Etaphen; Koralgil; MG 345; Trimanil; Trimanyl, has been prescribed as a Vasodilator) has been shown to be hypocholesteremic by inhibiting the reduction of desmosterol to cholesterol.[1] The hypocholesteremic activity of the title compound in man has been reported[2] and its mode of action confirmed.[3] The histopatological features of non-alcoholic steatohepatitis were described in patients taking 4,4'-diethylaminoethxyhexestrol.[4,5] The administration of 4,4'-diethylamino-ethoxyhexestrol dihydrochloride increases free cholesterol and total phospholipids in the liver. Phospholipid analysis showed marked increases in lysobisphos-phatidic acid and phosphatidylinositol in liver.

As the title compound is not commercially available we needed to prepare it in the context of joint collaboration in the chemo-genomics project DrugMatrix. We report here new preparation with significant yield improvement of title compound and scaling up it to 25 grams scale.

## Results and Discussion

For optimization of the synthesis of Coralgil the preparation of 4,4'-diethylaminoethoxyhexestrol dihydrochloride under different reported and analogue conditions have been tried. According to the Hughes *et al.* method,[1] the reaction using sodium ethoxide in toluene gave 46% yield, and there is no yield improvement using sodium methoxide in ethanol and toluene.[6] The preparation with $K_2CO_3$ in acetone[7] or DMF[8] gave similar results. We prepared the title compound by treating hexestrol with NaH in DMF to afford the sodium phenolate which was reacted with diethylaminoethylchloride hydrochloride followed by treatment with ethereal HCl in 85% overall yield, which is similar to the Ezquerra *et al.* method in preparation of [2-(3-Benzyl-3*H*-benzoimidazol-5-yloxy)-ethyl]-dimethyl-amine.[9]




Scheme 1

## EXPERIMENTAL

Melting points were measured on a Kofler micro hot stage. NMR-spectra were recorded on a Bruker AC-200 in CDCl3. Thin layer chromatography (TLC) was performed on pre-coated plates (Merck TLC aluminum sheets silica 60 F254) with detection by UV light or with phosphomolybdic acid in aqueous EtOH by heating. For reaction monitoring and quality (purity)

control of the product a Waters 996 HPLC system, that included Waters 600-MS pumps, an autosampler (Waters 712 WISP), and Waters 996 photodiode array UV detector was used. The separations were carried out using a Chromolith Performance reversed phase analytical column (E. Merck, 100 × 4.6 mm) at 25 °C and a mobile phase from (A) 0.1% TFA in 97:3 water/MeCN and (B) 0.1% TFA in MeCN (all solvents were HPLC grade, Fisher and Merck; TFA was analytical reagent grade, ROTH). The following gradients were applied at a flow rate of 3 mL/min: linear increase from solution 3% B to 60% solution B in 8 min, hold at 60% solution B for 2 min.

## Preparation of 4,4'-diethylaminoethoxyhexestrol dihydrochloride

To a suspension of NaH (9 g, ~50% in mineral oil, ~190 mmol) in dry DMF (250 mL), hexestrol (13.6 g, 50 mmol) was added and the mixture heated up to 90ºC for 30 min. under argon. Then a solution of diethylaminoethylchloride hydrochloride (20 g, 116 mmol) in dry DMF (100 mL) was added dropwise and the reaction followed by TLC. After 2 hours no starting material was detectable. Water (20 mL) was added to the reaction mixture and all volatiles evaporated in vacuo. The residue was extracted using diethyl ether (3×200 mL) and the combined organic phase washed with water and brine, dried over $MgSO_4$, filtered and the solvent evaporated in vacuo.[2] The resulting oil was dissolved in dry ethanol and the solution added dropwise to cold dry diethyl ether saturated with HCl (500 mL) and kept in the refrigerator overnight to get crude crystalline 4,4'-diethylaminoethoxyhexestrol dihydrochloride (21.8 g). The product was re-crystallized from ethyl acetate and ethanol to yield a first fraction of 19.6 g (72%, >99% HPLC purity). Further workup of the mother liquor resulted in a total product of 85%. Mp: 225.5°C (Lit. 223-226°C), Anal. Calcd. ($C_{30}H_{48}N_2O_2$ .2 HCl) C, 66.53%, H, 9.30%, N, 5.17%, Cl, 13.09%; Found: C, 65.55, H, 9.64, N, 5.07, Cl, 12.61. $^1$H NMR (DMSO-$d_6$) δ 0.38 (t, 6H), 1.24 (t, 16H), 2.54 (b, 2H), 3.21 (q, 8H), 3.45 (b, 4H), 4.28 (b, 4H), 7.09 (dd, 8H). $^{13}$C NMR (DMSO-$d_6$) δ 8.2, 11.8, 26.8, 47.4, 50.1, 52.3, 61.8, 65.0, 114.3, 129.1, 137.2, 155.4.

## CONCLUSION

This report shows the advantage of changing the base in the Coralgil preparation that NaH in DMF afford the sodium phenolate which reacts readily with diethylaminoethylchloride hydrochloride with 85% overall isolated yield.

## References & Notes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10. An analytical sample of the free base was obtained by flash chromatography on silica (1:1, petrol /ethyl acetate). Mp: 47°C and the structure confirmed by NMR: $^{1}$H NMR ($CDCl_3$) δ 0.45 (t, 6H), 1.072 (t, 12H), 1.24 (m, 4H), 2.42 (m, 2H), 2.59 (q, 8H), 2.85 (t, 4H), 3.97 (t, 4H), 6.89 (dd, 8H).