an aquaretic atleast in rats, but enhances considerably ion excretion almost to an extent similar to that produced by furosemide.

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Synthesis of Propafenone, an Antiarrhythmic Agent

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Propafenone, an antiarrhythmic agent belonging to class I C was synthesized by two different methods starting from phenol. Method-1 involving initial formation of chalcone from o- hydroxyacetophenone was superior over methods-2 with respect to yield and reaction process. In method-2, the oxypropanolamine chain was first built and then aldol condensation was carried out.

ARRHYTHMIA refers to the abnormalities of heart rate and antiarrhythmic agents used in arrhythmias are classified on the basis of their mechanisms of action.[1] Class I drugs [eg. quinidine, procainamide, disopyramide (I A); lidocaine, tocainide, mexiletine (I B); ecainide, flecainide, propafenone (I C)] block voltage sensitive sodium channels. Class II drugs (eg. metoprolol) are β-adrenergic receptor blockers. Class III (eg. aminodarone) - drugs act mostly by blockage of K^+ channels, while class IV drugs (eg. Verapamil) block slow inward calcium channel.

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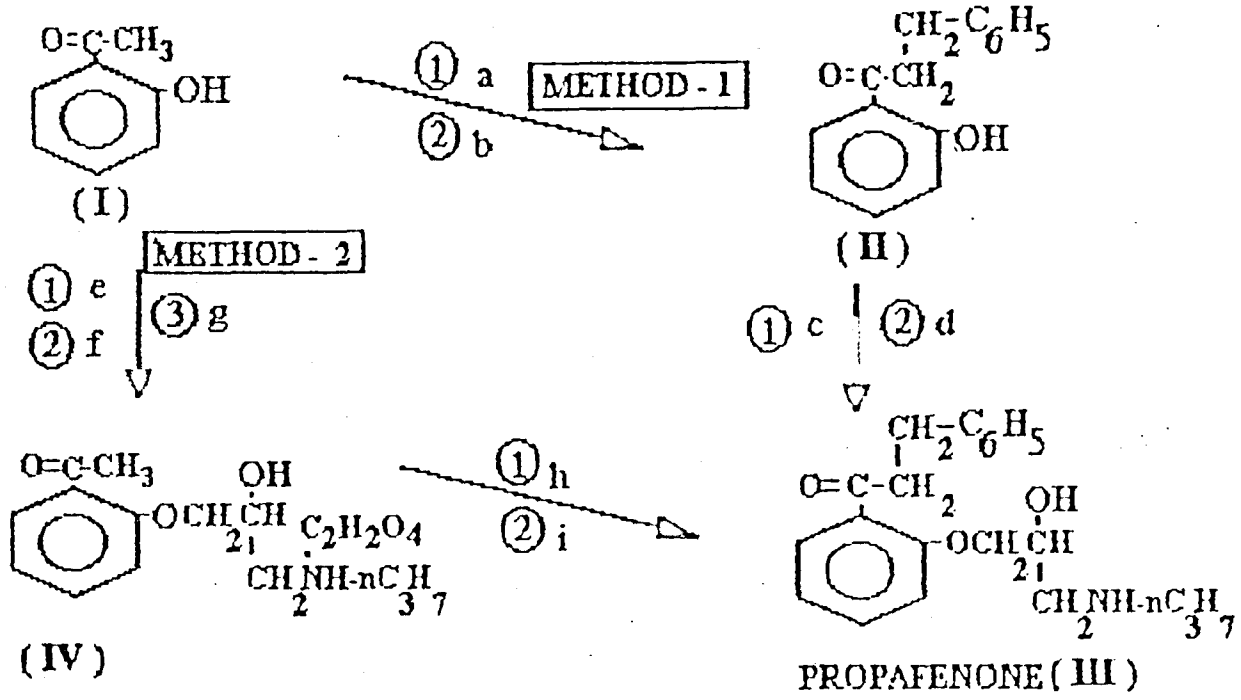
Class I C antiarrhythmic agents depress phase-O of cardiac action potential without any effect on repolarization of cardiac cells. Among class I C drugs propafenone alone does not cause depression of left ventricular function and hence is superior to the other drugs. It can be safely used in asthematic patients where β- blockers cause complications due to bronchospasm. Unlike the calcium channel blockers, propafenone does not cause hypotention[2].

Studies indicate that propafenone is comparable in efficacy or more effective than quinidine[3], mexiletine[3], tocainide[2], flecainide[2], metoprolol[4] and amiodarone[2], in preventing and abolishing both



a, h : C_6H_5CHO, NaOH, CH_3CHO; b, l : H_2, Pd/C, NaOH;
c, e : Epichlorohydrine, NaOH; d, f : $H_2NCH_2CH_2CH_3$, CH_3OH;
g : $C_2H_2O_4$, Alcohol.

(SCHEME)

supraventricular and ventricular arrhythmias. Propafenone is also effective in the management of tachycardia and Wolff-Parkinson-White Syndrome.

Propafenone was synthesized from 1-(2-hydroxyphenyl)-3-phenyl-1- propanone[5] and o-hydroxyacetophenone[6]. The present work aims to synthesize it from readily available and cheaper substrate and to optimize the various steps involved.

CHEMISTRY

Propafenone (III) was synthesized from o-hydroxyacetophenone (I) by two methods as shown in the Scheme. In method 1, 'I' was condensed with benzaldehyde to form a chalcone which on hydrogenation gave 'II'. Reaction of 'II' with epichlorohydrin in presence of alkali followed by aminolysis with n-propylamine gave propafenone. In the second method the oxypropanolamine chain was introduced first in 'I' followed by chalcone formation and hydrogenation. 'I' was prepared from phenol by Fries rearrangement of intermediate phenylacetate.

EXPERIMENTAL

Synthesis of *o*-hydroxyacetophenone (I)

Phenylacetate, 150 g (1.08 M), anhydrous aluminium chloride, 165 g (1.24 M) and 300 ml of chlorobenzene were refluxed for four hours with constant stirring. After removal of solvent, 900 ml of 10% hydrochloric acid was added to the reaction mixture and the product was separated by steam distillation, then dried and redistilled under reduced pressure. The yield obtained was 60 ml (67.0 g) {45%}, boiling at 90° (8 mm Hg pr.).

Synthesis of 1-(2-hydroxy phenyl)-3-phenyl-1-propanone (II)

To o-hydroxyacetophenone, 60 ml (0.48 M) and benzaldehyde 61.2 ml (0.6 M) in 720 ml of 96% aqueous methanol, sodium hydroxide (134.4 g) was added and the reaction mixture was stirred vigorously for thirty minutes when an orange red solution was obtained. Stirring was further continued for four hours to complete the reaction. Hydrochloric acid, (1N, 4.8 liters) was added to it when a precipitate of 1-(2-hydroxy phenyl)-3-phenyl-- prop-2-en-1-one was obtained, it was washed with water, dried and recrystallized from ethanol, yield-94.4 g (87%). Melting point 87°. The product was taken in ethanol and hydrogenated at 1 atm. pr. of H_2 at 55° in presence of Pd/C and 94 g of sodium hydroxide. After 48 h. the solution was filtered and neutralized with 25% aqueous hydrochloric acid (420 ml) and concentrated under vacuum. Addition of water and cooling in ice gave crystals of 'II'. M.P. 31°. Yield - 66.4 g (69%), [I.R. (KBr) (cm^{-1} 3396 (O-H, phenolic), 3028, 2926 (C-H), 1639 (C=O)].

Synthesis of propafenone (III)

Compound 'II', 66.4 g (0.31 M) was refluxed with 200 g (2.17 M) of epichlorohydrin and 12.4 g (0.31 M) of NaOH in 100 ml water for five hours. The oily layer in the reaction mixture was separated, and excess of epichlorohydrin was removed from it under vacuum, the resulting yellow mass solidified on cooling, but did not crystallize. Yield - 77.00 g (88%). The product was then reluxed for three hours with 133.4 g (1.92 M) of n- propylamine in 90 ml methanol. The excess of n-propylamine and methanol were evaporated and the residue was treated with 100 ml of 1 M aqueous hydrochloric acid and the solution refluxed for one hour. After cooling the crystals of propafenone hydrochloride were obtained. The product was filtered and washed with cold water and recrystallized from a mixture of acetone and methanol (8:2 v/v), yielding 88.1 g (93.00 %) of propafenone hydrochloride melting at 173° [I.R. (KBr) (cm^{-1}) 3422 (N-H and O-H-alcoholic), 2970, 2783 (C-H), 1662 (C=O), 1240 (Ar-O, ether), 1032, 1186 (Alkyl-O, ether), 60 MHz ^1H NMR ($CDCl_3$) δ 7- 7.5 (m 9H arom, H), δ 4.4 (1H NH), δ 4-4.2 (m 3H O-CH_2, O-CH), δ 3.25 (m 4H CH_2-N-CH_2), δ 3 (m 4H CH_2-CH_2), δ 1.2 (m 5H CH_2-CH_3)].

RESULTS AND DISCUSSION

Propafenone was synthesized by two different methods and method-I gave higher yield of propafenone hydrochloride (50% starting from o-hydroxyacetophenone). Fries rearrangement of phenylacetate was optimized with a view to enhance the yield of o- hydroxyacetophenone and chlorobenzene was found to a better solvent when compared with the commonly used ones. Similarly, yield was maximized during Aldol condensation by using seven moles of base and 1.2 liters of solvent for each mole of 'I'.

Propafenone was prepared from phenol in the present work while literature methods have employed intermediates generated at the end of second and fourth steps and hence no additional conclusions can be drawn by comparing with literature methods.

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