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STUDY ON PHYSIOLOGICALLY ACTIVE SECONDARY AMINES, -β (0-METHOXYPHENYl)-ISOPROPYL-N-METHYLAMINE: AN OVERVIEW

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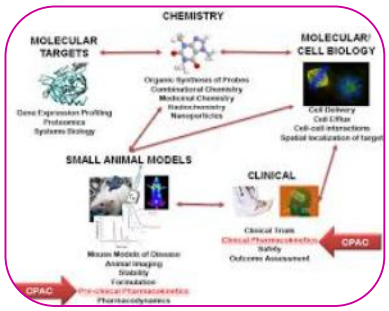
ABSTRACT

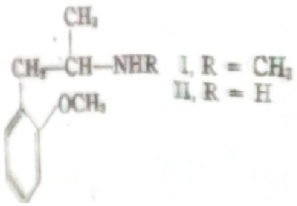
In this paper, fourteen secondary amines related to β- (0-methoxyphenyl) - isopropyl-N- methylamin (Orthoxine) (have been prepared. Some of these have been separated into their diasterieoisomeric forms, and one into its optical isomers. Several of these compounds possess a high order of bronchodilator and/or local anesthetic activity as indicated by pharmacological and preliminary clinical studies. An improved method is described for the preparation of aralkyl alkyl ketones by condensing an arylaldehyde with the requisite nitroparaffin in toluene using an azeotropic distillation procedure to force the reaction to completion, followed by a two-phase reductive hydrolysis.



KEY WORDS: *optical isomers , pharmacological and preliminary clinical studies.*

INTRODUCTION :

Recent studies have been directed toward the separation of the various pharmacological activities of sympathomimetic amines with the objective of preparing bronchodilator compounds which possessed the desirable properties of ephedrine or epinephrine but lacked the normally attendant undesirable side effects such as pressure and central nervous system stimulating properties. Considerable progress in this direction was realized with the finding that β-(o-methoxyphenyl)- isopropyle-N-methylamine'[1-6]



METHODOLOGY AND DISCUSSION

(I) possessed promising oral bronchodilator activity without exhibiting any significant effect on the blood pressure or central nervous system. Since that time work has continued on the investigation of related compounds, and the present paper reports a number of secondary amines structurally related to I.

Efforts to prepare I by catalytic hydrogenation of β-(o-methoxyphenyl)- β-hydroxyisopropyl-N-methylamine by the method of Rosenmund and Karg were not successful. Synthesis through the intermediate o-methoxyphenyl acetone was studied in some detail. Preparation of this ketone from o-propenylanisole *via* the corresponding glycol resulted in relatively low yields of the desired ketone and, moreover, the process was cumbersome. The most satisfactory procedure involved the condensation of -anisaldehyde with nitrothane in toluene, with concomitant removal of water, azeotropically, to complete the reaction. This was followed by a two- phase chemical reductive hydrolysis to the desired o-methoxyphenyl acetone. The latter was then subjected to reductive amination with methanolic methylamine. Using a variety of amines a series of related secondary amines was prepared as shown in Table-I.

In order to prepare a number of longer chain secondary alkylamines a variety of methods were studied for the preparation of β- (o-methoxyphenyl)- isoprolylamine (11) from the corresponding substituted phynylacetone. Catalytic hydrogenation of the oxime using Adams platinum oxide or Raney nickel in the presence of ammonia gave a yield of 73% of the desired compound (11). When omethoxyphenylacetone was subjected to the Leuckart reaction following the procedure of Crossley and Moore, 18 the primary amine (11) was fomed in a 58% yield. Attempts at catalytic debenzylation of β-(o-methoxyphenyl) - Isopropyl-N-benzylamine using palladium-charcoal have been unsuccessful. In this connection it is interesting that similar debenxylation attempts with the corresponding dibenzylamine caused the removal of only one benzyl group. When the procedure of Alexander and Misegadeslg was used, in which ammonium chloride was added to the ketone- ammonia mixture to decrease secondary amine formation, there was obtained a mixture of 40% of primary amine and 13% of secondary amine. This secondary amine, bis- [β-(o-methoxyphenyl) - Isopropyl] - amine, could be obtained in good yield from o-methoxyphenyl acetone by reductive amination with either β-(o-methoxyphenyl) - Isopropylamine or half a molecular equivalent of alcoholic ammonia. It was isolated in two diastereoisomeric modifications, one of which crystallized during filtration from the catalyst and subsequent solvent removal. This appeared to be a solvated form of the free base, from which the alcohol could be removed by warming in vacuo or even by exposing to the air. The hydrochloride of this latter diastereoisomer was extremely insoluble in water and a number of salts were prepared in an effort to increase its solubility. The lactate was found to be about seventeen times as soluble as the hydrochloride.

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