IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 13, Issue 10 Ser. II (October. 2020), PP 13-19
www.iosrjournals.org

Study of Antihypertensive drugs: Pharmacological classification and its mechanism of action

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Abstract: *The current study depicts that the even slight presence of easily oxidizable substance like thio-urea, ascorbic acid, hydrazine, alcohols etc. interfere in the estimation. In such case higher recovery was obtained because the compound reacts with the reagent. Therefore, the presence of such substances was avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.*

Background*: The antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure). Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensive, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium chamiel blockers, the beta blockers, and the angiotensin II receptor antagonists or ARBS. Several class of antihypertensives differ in their side effects profile, ability to prevent endpoints, and the cost. The choice of more expensive agents, where cheaper ones would be equally effective, may have negative impacts on national healthcare budgets. As of 2009, the best available evidence favors the thiazide diuretics as the first-line treatment of choice for high blood.*

Materials and Methods*: An aliquot containing l-5mg of the sample was taken in a l00mL stoppered conical flask and 5mL of 0.02NNCS reagent, prepared in hydrochloric acid and 5mL of 4N hydrochloric acid was added to it. The reaction mixture was shaken thoroughly and allowed to react for l5minutes at room temperature (25-300C). After the reaction was over 5mL of 5% potassium iodide was added to it. Contents were shaken thoroughly and allowed to react for a minute. The unconsumed NCS was determined iodometrically. A blank experiment was also run under identical conditions using all the reagents except sample. The amount of NCS consumed for the sample was calculated with the difference in the volumes of sodium thiosulphate solution for blank and actual experiments. The recovery of the sample was calculated with the amount of NCS consumed for the sample. For every sample percentage error, standard deviation and relative standard deviation were calculated.*

Results*: Atenolol there is a side chain attached to hydroxy group and phenolic nucleus is a part of acetamide molecule. Phenolic nucleus has two ortho positions available for electrophilic substitution. One other ortho position is more reactive as compared to other one which is near amide group. Therefore, the preferred position gets chlorinated. Side chain other than the amide group has got. One secondary hydroxyl group, therefore it may get oxidized to a carbonyl group. On the basis of these assumptions, reaction products has been proposed.*

Conclusion: *The current study depicts that the even slight presence of easily oxidizable substance like thio-urea, ascorbic acid, hydrazine, alcohols etc. interfere in the estimation. In such case higher recovery was obtained because the compound reacts with the reagent. Therefore, the presence of such substances was avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.*

Key Word*: Antihypertensive drugs, Pharmacological classification*

Date of Submission: 30-09-2020 Date of Acceptance: 13-10-2020

I. Introduction

The antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure). Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensive, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium chamielblockers, the beta blockers, and the angiotensin II receptor antagonists or ARBS.Several class of antihypertensives differ in their side effects profile, ability to prevent endpoints, and the cost. The choice of

more expensive agents, where cheaper ones would be equally effective, may have negative impacts on national healthcare budgets. As of 2009, the best available evidence favors the thiazide diuretics as the first-line treatment of choice for high blood pressure when drugs are necessary. Some of the important antihypertensive drugs have been described below:Atenolol is 2-(4-{2-hydroxy-3-[(propan-2-yl) amino] propoxy} phenyl) acetamide. Atenolol is almost white powder and freely soluble in methanol and distilled water. It is a selective β_1 receptor antagonist, a drug belonging to the group of beta blockers, a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. Labetalol hydrochloride is 2-hydroxy -5- { 1 -hydroxy-2-[(4-phenylbutan-2-yl) amino] ethyl} benzamide hydrochloride. Labetalol hydrochloride is a white, odorless powder. The compound is less soluble in water and freely soluble in water ethanol mixture.It is a selective α-1 and non-selective β adrenergic blocker used to treat high blood pressure. Corvedilol is known as [3-(9H-carbazol-4-yloxy)-2-hydroxypropyl] [2-(2-methoxyphenoxy) ethyl] amine. Carvedilol is a nonselective beta-adrenergic blocking agent with alphal-blocking activity and is indicated for the treatment of hypertension and mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. Propranolol hydrochloride is [2-hydroxy-3-(naphthalen-l-yloxy) propyl] (propan-2-yl) amine hydrochloride. Propranolol hydrochloride is almost white powder. It is freely soluble in methanol and in mixture of ethanol and water.Metoprolol tartrate is known as {2-hydroxy-3-[4-(2-methoxyethyl) phenoxy] propyl} (propan-2-yl).Metoprolol tartrate is white crystalline odorless powder. Compound is soluble in methanol and ethanol-water mixture and partial soluble in pure water.

N-chlorosuccinimide (NCS) in acidic medium has been used for quantitative estimation of some antimalarials (Quinine, Amodiaquine, Santoquine, Cloroquine etc.) diuretics e.g. frusemide, chlorothiazide, and other organic compounds like phenols, carboxylic acids etc. Till now it has not been used for the determination of antihypertensive drugs like atenolol, labetalol hydrochloride, carvedilol, propranolol hydrochloride and metoprolol tartrate. This initiated me to undertake the present study. Available pharmaceutical preparations of the under study drugs have also been analyzed by proposed method. Effects of various variables such as temperature, concentration and volumes of acid and reagent, reaction time were studied. Simple and convenient method has been described for the micro scale determination of mentioned drugs in pure form and in their pharmaceutical preparations. In every case standard deviation (SD), relative standard deviation (RSD) / coefficient of variation (CV) and percentage error has been calculated.

II. Material and Methods

For testing the quantitative validity of reaction, atenolol was taken as the test sample. Different amount of sample (1-5mg) were allowed to react with varying concentrations of N-chlorosuccinimide (NCS) at room temperature (25-300C) for different time. The unconsumed NCS was back titrated iodometrically. A blank experiment was also run under identical conditions using all the reagents except the sample. The difference in volumes of sodium thiosulphate consumed for blank and actual experiments was used to calculate the amount of the sample present in a particular experiment. The Stoichiometry of the reaction was established for each sample of drug and a possible course of reaction was also suggested. On the basis of reaction conditions developed for atenolol, the determination of other compounds in pure form and in their pharmaceutical preparation were done.Study of the variables is performed. In order to develop suitable reaction condition for the determination of above antihypertensive drugs with NCS reagent, the effect of different variables was studied.Effect of the reaction time has been measured. Keeping the amount of atenolol and concentration of NCS reagent constant, the reaction time was varied from up to 1-30 minutes. Effect of concentration of hydrochloric acid has been measured. Keeping the reaction time, amount of atenolol and concentration of NCS (2x10-2) constant, the concentration of hydrochloric acid was varied from (1-7N) and the result were noted. Effect of the concentration of NCS has been measured. Keeping the reaction time, amount of atenolol and concentration of hydrochloric acid as constant, the effect of varying concentration of NCS was studied (Table-10). 1-5mg of the samples was allowed to react with 5mL of NCS of varying concentration (0.01-0.1N). The unconsumed NCS was back titrated iodometrically and the recovery of the sample was calculated.

Keeping all other conditions constant, the reaction temperature was varied from 5-400C and the recovery of atenolol was calculated (Table-12). It was observed that the reaction was completed within 15 minutes at room temperature (25-300C). The heating of the reaction mixture gives inaccurate results. It may be due to decomposition of reagent at high temperature. Although the reaction is completed at room temperature, but the experiments were also canied out at lower temperature up to 50C. In this case there is a decrease in recovery of the sample because ionization of reagent take more time or does not ionize hence reagent does not react properly at lower temperature. Thus for the detennination of atenolol a reaction temperature of 25-300C was maintained. Such experiments were carried out with all other samples and the recovery was noted. It was observed that the reaction at room temperature was suitable for all other antihypertensive drugs e.g. labetalol hydrochloride, carvedilol, propranolol hydrochloride and metoprolol tartrate in their pharmaceutical preparations.

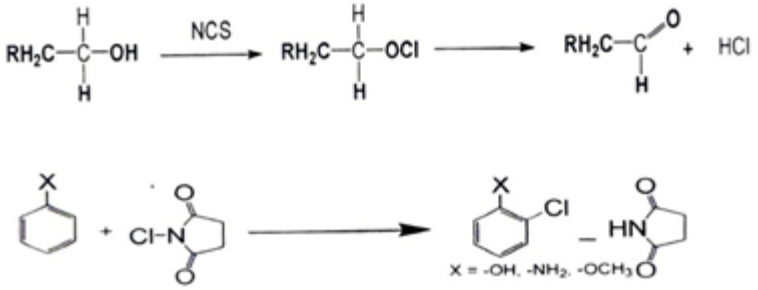
An aliquot containing l-5mg of the sample was taken in a l00mL stoppered conical flask and 5mL of 0.02NNCS reagent, prepared in hydrochloric acid and 5mL of 4N hydrochloric acid was added to it. The reaction mixture was shaken thoroughly and allowed to react for l5minutes at room temperature (25-300C). After the reaction was over 5mL of 5% potassium iodide was added to it. Contents were shaken thoroughly and allowed to react for a minute. The unconsumed NCS was determined iodometrically. A blank experiment was also run under identical conditions using all the reagents except sample. The amount of NCS consumed for the sample was calculated with the difference in the volumes of sodium thiosulphate solution for blank and actual experiments. The recovery of the sample was calculated with the amount of NCS consumed for the sample. For every sample percentage error, standard deviation and relative standard deviation were calculated.

III. Result and Discussion

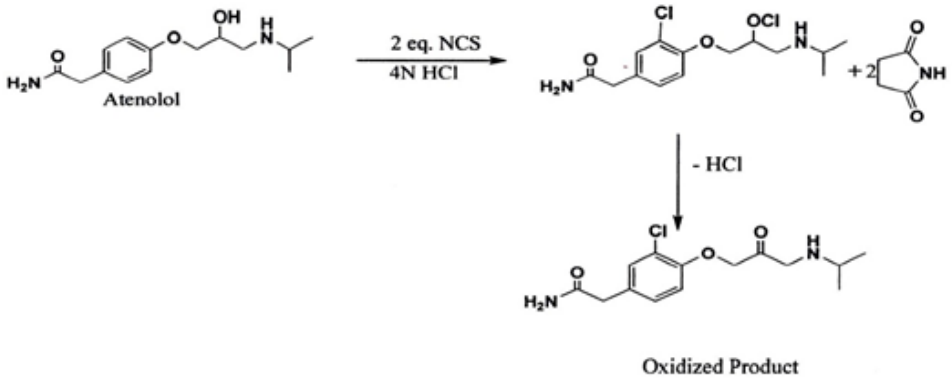
It has been mentioned (Table-2), that the stochiometric ratio between NCS reagent and antihypertensive drugs such as atenolol (112), labetalol hydrochloride (1:2), carvedilol (1:1), propranolol hydrochloride (1:1) and metoprolol tartrate (1:2) in pure form and in their pharmaceutical preparations is constant. This ratio does not change even under varying reaction conditions i.e., change in reaction time, concentration of reagent and reaction temperature etc. As described in the study of variation of the reaction (Table-3), a particular reaction time was needed for completion of the reaction and for concordant and accurate results. It varies from one compound to another. At a reaction time lesser than the described (Table-3), inaccurate results were obtained because of incomplete reaction. The increase in reaction time does not change percentage recovery of the sample because the reaction is completed at described time. Therefore, to avoid wastage of the reagent and time the estimations were done on the recommended conditions.

NCS is the main active agent, which reacts with antihypertensive drugs. As indicated in the (Table-11), that 5mL of 0.02NNCS was sufficient for all the samples for accurate results. Reaction was also carried out at lower and higher concentration at variable volumes of NCS. In this case, it was observed that the concentration and volume other than the prescribed under reaction conditions gives lesser recovery because of insufficient reagent. Higher concentration and volume do not give any improvement over the results. Therefore, prescribed concentration and volume (Table 8-9) of the NCS reagent was used. The effect of temperature (5-40^{0}C) has also been studied. It was observed that results improve with increase in reaction temperature. The best recovery was obtained at room temperature (25-30^{0}C). An increase in the reaction temperature above 25-30^{0}C gives inaccurate results (Table-l2). It happens due to decomposition of reagent at higher temperature. At a lower temperature upto50C it was observed that the reaction is very slow and needs more reaction time. It gives higher percentage error. It is because of less ionization of the reagent.

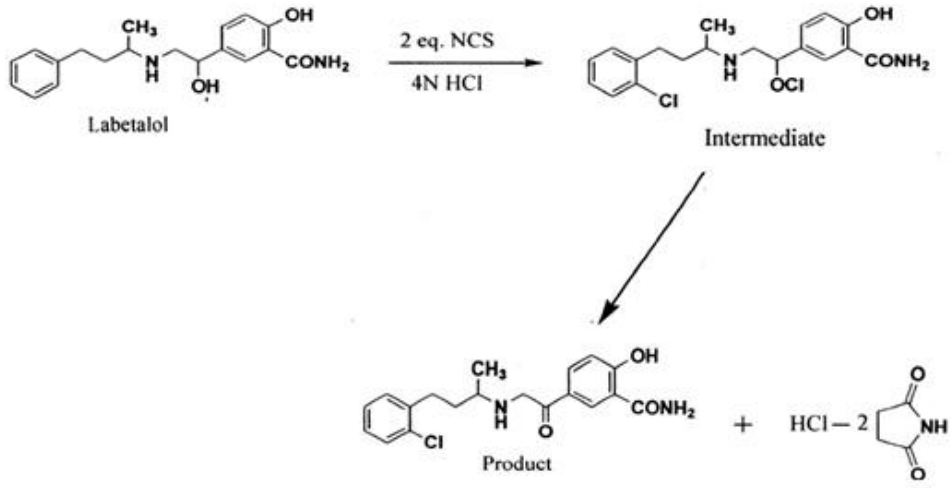
Possible course of reaction:On the basis of oxidation pattern of these compounds and literature available thefollowing course of reaction may be suggested for the reactions of NCS with each antihypertensive drug. **T**he oxidation of primary and secondary alcohols gives rise to carbonyl group. It has also been described there 61-68 that the reagent work as chlorinating agent, especially for activated benzene rings.



On the same basis a possible course of reaction has been proposed.In Atenolol there is a side chain attached to hydroxy group and phenolic nucleus is a part of acetamide molecule. Phenolic nucleus has two ortho positions available for electrophilic substitution. One other ortho position is more reactive as compared to other one which is near amide group. Therefore, the preferred position gets chlorinated. Side chain other than the amide group has got. One secondary hydroxyl group, therefore it may get oxidized to a carbonyl group. On the basis of these assumptions following reaction products has been proposed. Isolation of intermediate as well as final reaction products has not been possible, so this is only hypothetical approach

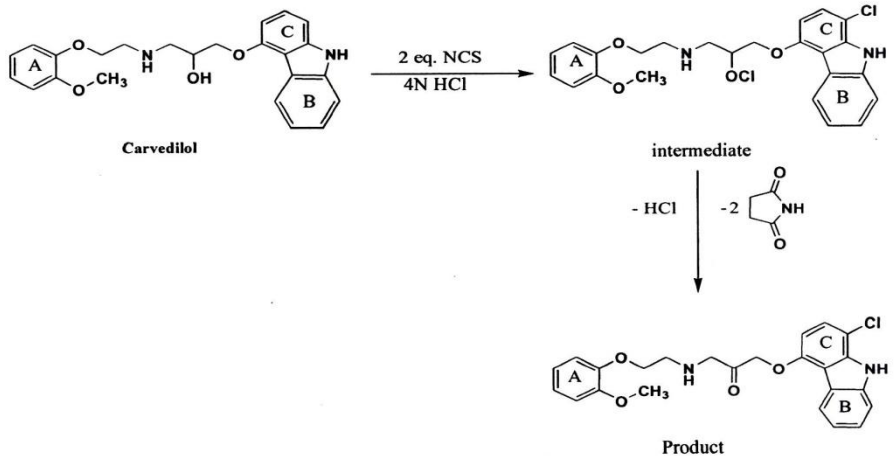


Labetalol hydrochloride has got more complicated structure involving two benzene rings of which one is having -$CONH_2$ and -OH group at vicinity and the other has a side chain. The -OH group is situated at para position and -$CONH_2$ at meta position to the substituted benzene ring. It is a phenylpropyl amine derivative of benzene. It reacts with two equivalents of NCS reagent. The sec. hydroxyl group is getting oxidized to carbonyl group and the benzene ring having a side chain is getting chlorinated at ortho position. On the basis of the nature of the compound and the reagent the final reaction product may be written as below.

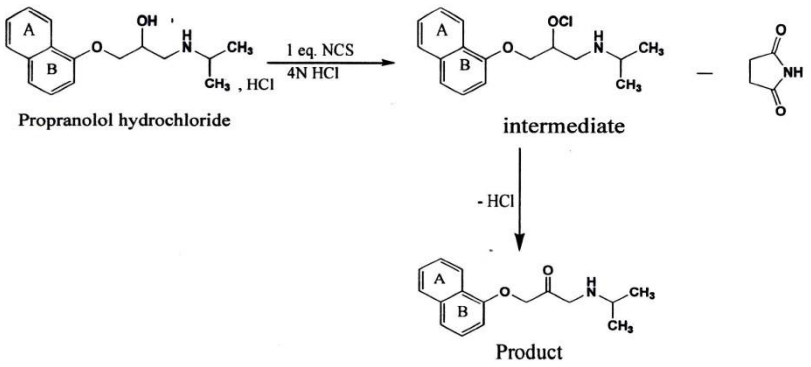


Carvedilol is a hetero cyclic derivative of indole. The molecule has different groups attached to side chain at aromatic ring A and C. Rings B and C are linked to each other by secondary amino group. Ring C is having a side chain attached to it through ether linkage. This side chain has a secondary hydroxy group, which is oxidized to ketonic group and ring C is having active position at ortho to amino group. On this basis following reaction product may be predicted.

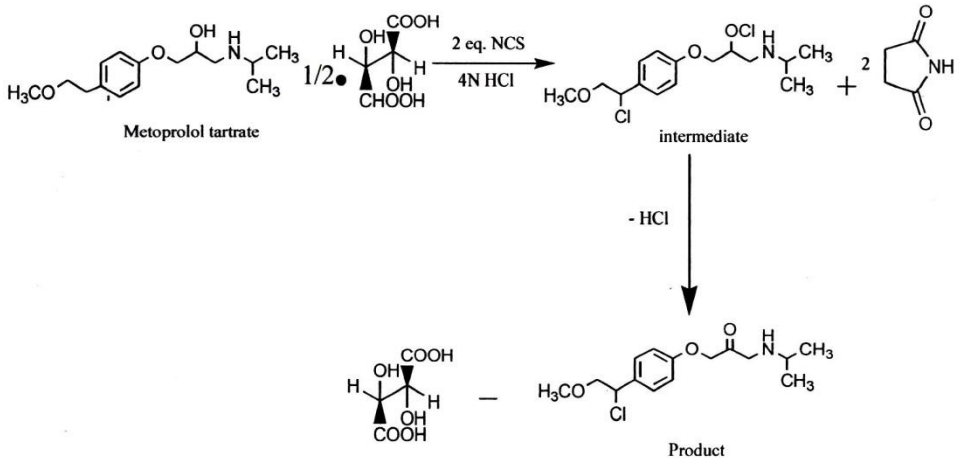
It also consumes two equivalents of NCS reagent, and oxidizes the secondary alcoholic group and chlorinated the ring C at ortho to amino group. The possible path of reaction may take place as follows:



Propranolol hydrochloride is a simple compound as compared to other compounds. lt has an aliphatic side chain attached to the ring B of naphthalene. One of the or-position of the naphthalene is substituted by a side chain through an ether linkage (ring B), and the other group is sterically hindered (ring A). Therefore, it will not react with NCS reagent. The only possibility is that the secondary hydroxyl group may be oxidized to keto group through intermediate step. Thus, the overall reaction product may be written as below:



Metoprolol tartrate is a complex compound existing as the salt of tartaric acid in which the acid part remains inactive in the estimation process. It is phenol derivative having a side chain which contains a secondary hydroxyl group and isopropyl group containing amino group. For reaction with NCS it is possible that the secondary -OH group may get oxidized to ketonic group. The para position of benzene ring has another side chain with ether link which is not as active as the ortho positions to the etheral side chain may get chlorinated. Metoprolol consumes two equivalents of NCS reagent in acidic medium. On this assumption the final product may be written as below:



In any one of the reaction products predicted for above compound no authentic proof has been given. I have not been able to located intermediate and the final reaction product. All the reactions are hypothetical based on stoichiometry and the reactions of the reagent.

IV. Conclusion

The current study depicts that the even slight presence of easily oxidizable substance like thio-urea, ascorbic acid, hydrazine, alcohols etc. interfere in the estimation. In such case higher recovery was obtained because the compound reacts with the reagent. Therefore, the presence of such substances was avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.

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Chandrashekhar Kr. Roy, et. al. "Study of Antihypertensive drugs: Pharmacological classification and its mechanism of action." *IOSR Journal of Applied Chemistry (IOSR-JAC),* 13(10), (2020): pp 13-19.