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Synthesis of Some New Compounds with Possible Oxytocic Activity

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Abstract

Oxytocics are drugs that stimulate uterine motility. Inspite of promoting the contractility of the uterus they hasten labor and are therefore useful clinically in the management of labor, particularly if they are selective for the uterus. Although oxytocics are occasionally used to induce labor at term or to complete a threatened abortion and to control hemorrhage during and following abortion, their principal use in obstetrics is to control postpartum hemorrhage.

Oxytocics are now used more or less routinely in the management of labor. They are administered in small dose to support the process of involution. during which uterus returns to its normal, nonpregnant condition. In case of delayed involution, which usually is associated with uterine atony, the stimulation of uterus by oxytocics is definitely helpful.

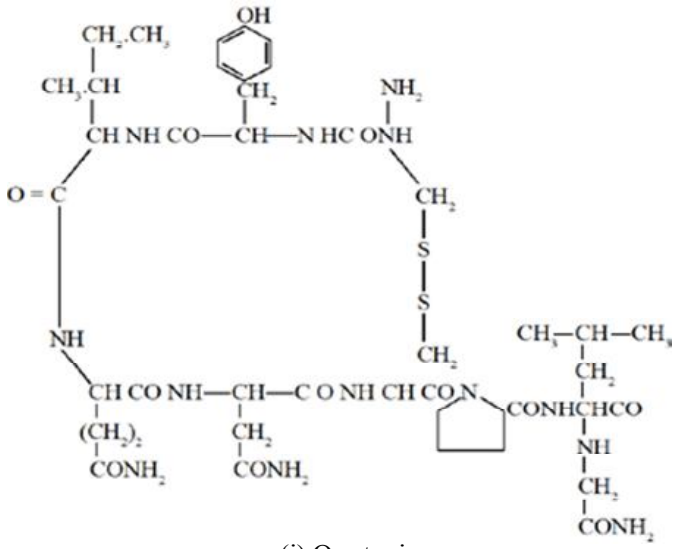
Compounds exhibiting pronounced oxytocic activity are quite varied in their chemical structure. The naturally occurring compounds include the hormones of posterior pituitary, oxytocin and vasopressin, the ergot alkaloid spartine. The synthetic substances comprise modified analogs of oxytocin and ergonovine, model compounds based on the structure of ergot alkaloids, certain derivatives of quinolizidine and some aminomethyl derivatives, besides there are number of botanical drugs and synthetic substances have been found to possess oxytocic activity.

Key words : Oxytocic activity, Alkaloids, Vasopressin, Spartine.

Introduction

The hypothalamus secretes a number polypeptide hormones, some of which are stored in the posterior part of pituitary. These are generally known as neurohypophysial extracts possess a number ofpharmacological properties. The strong effect neuro-hypophysial hormone upon the of uterine muscular contraction was first noted by Dale in 1906, using the uterus of the cat in early pregnancy and the milk-ejecting, or galactobolic, effect was recognized in 1910 by Ott and Scott[1].

Three biologically active octapeptides have been isolated from the mammalian posterior pituitary: Oxytocin (1), arginine vasopressin, from most mammals, and lysin-vasopressin from pigs. Another interesting analog, argine-vasotocin, occurs in nonmammalian vertebrates. Hormone oxytocin was synthesized by Vincent du Vigneaud[2].



(i) Oxytocin

Oxytocin contracts the uterus during the birthing process, thus perhaps helping expel the baby; also contracts myoepithelial cells in the breasts, there by expressing milk from the breasts when the baby suckles. Vasopressins is responsible for the elevation in blood pressure and antidiuretic properties. The effects of oxytocin and vasopressin on the uterus are quite complex.

Oxytocin is a hormone the secreted by neurohypophysis that specifically causes uterine contraction. There are four reasons for believing that oxytocin might be important in increasing the contractility of the uterus near term:-

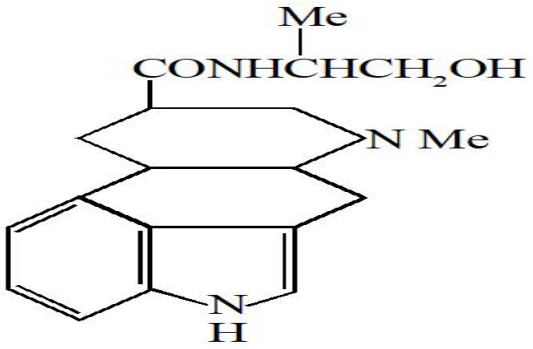
1. The uterus increases its responsiveness to a given dose of oxytocin during the latter few months of pregnancy.
2. The rate of oxytocin secretion by the neurohypophysis is considerably increased at the time of labor.
3. Though hypophysectomized animals and human beings can still deliver their young at term, labor is

prolonged.

4. Experiments in animals indicate that irritation or stretching of the uterus cervix, as occurs during labor, can cause a neurogenic reflex that causes the posterior pituitary gland to increase its secretion of oxytocin.

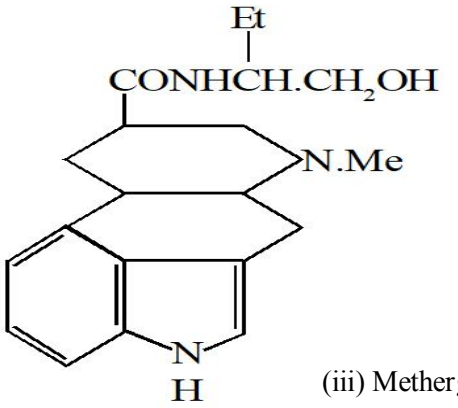
Ergot Alkaloid :

A large number of alkaloids also have been found to be uterine stimulants, only a few are useful therapeutically. Most of them, are unsatisfactory as oxytocics because they produce sufficiently pronounced side reactions, when administered in therapeutically effective doses. In addition to adrenergic blocking and hypotensive activities, ergot alkaloids possess few undesirable actions at effective dose levels. Of the two series of optically active isomeric alkaloids isolated from ergot, only the levorotatory ones are pharmacologically active. Although all of these have qualitatively similar effects on the uterus, ergonovine (ii) is the most potent and selective oxytocic agent among them. Its action is much more rapid and undesirable side actions, such as vasoconstriction and adrenergic blokade, are very rare at the effective dose level.



(ii) Ergonovine

Many derivatives of ergonovine have been prepared for desirable oxytocic effects. One of the newer oxytocic drugs is (±)-lysergic acid (±)-1-hydroxy-2-butylamide known as Methergine.

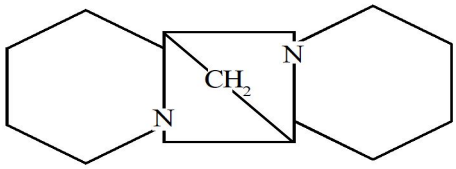


(iii) Methergine

A high oxytocic activity both in vivo and in vitro has been observed in a series of (+) lysergic acid cyclo-alkyl amides from propyl to heptyl.

Sparteine :

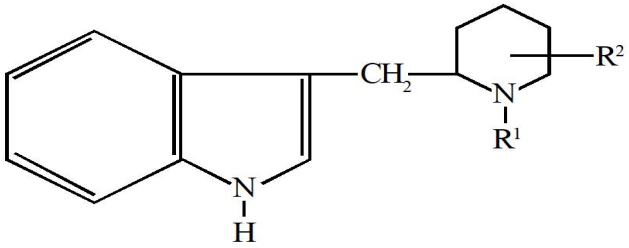
Sparteine (iv) is a naturally occurring alkaloid also has oxytocic action. Its oxytocic action was first observed by Tamba in 1921 and its structure was first proposed by Clemo and Raper and has been confirmed by the several total synthesis of the alkaloid. An elegant synthesis given by Leonard and Beyler.



(IV) Sparteine

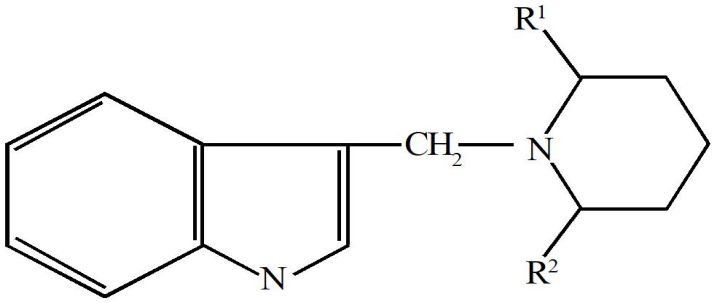
Indole Derivatives :

Alkerman and Veldstra 10 synthesized a number of compounds of the type (v) for evaluation as oxytocics. Measurement of the oxytocic activity of 10 members of this s11 in vitro on isolated guinea-pig uterus revealed that series (v) (R1 CH_3, R2 H) and its 5-ethylhomolog had high activity, which however, was not paralleled when it was examined in vivo on the intact rabbit uterus.



(V) Indole derivative
R^1 = H, Me; R^2= H, Me, COR

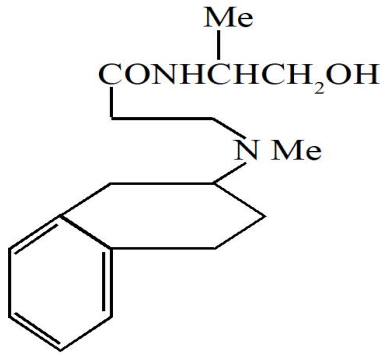
A series of 3-(piperidonomethyl) indoles (vi) show much higher in vitro, and in vivo activities.



(VI) 3-(Piperidonomethyl)indole derivative

Derivatives of 2-Aminotetrahydronaphthalene :

Bovet-Nitti and coworkers 14 observed that N-(2-tetrahydronapthyl)-N-methyl-B-alanyl-(1-hydroxy-2-propyl) amide (vii), possessed oxytocics activities.



(VII) N-(2-Tetrahydronaphthyl)-N-methyl-β-alanyl-(1-hydroxy-2-propyl) amide

They examined about 200 derivatives of 2-amino-tetrahydronaphthalene 15, many of which were based in an N-(2-tetrahydronaphthyl)-B-alanine structure as in (vii), the carbonyl of the B-alanyl group being part of esters and a variety of amides.

N. N-diethyl-N-2 (2-tetrahydronaphthyl) glycinamide (viii) was found highly activep16. Considerable activity was found among the substituted N-phenylglycinamides as well17. To a lesser extent oxytocic activity was also observed in alkylated glycinamides of the type N,N,N',N''-tetraalkylglycinamides, R_2 -NCH COR2 18.

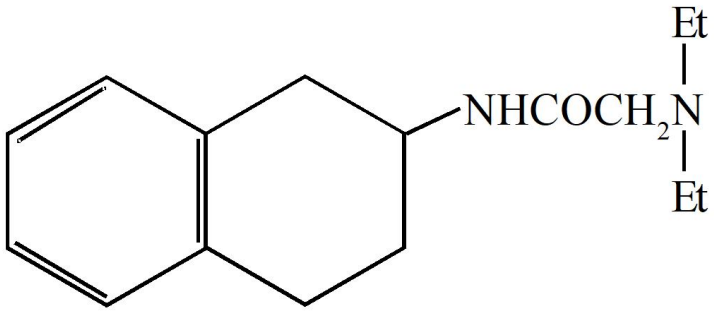
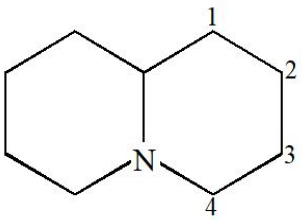


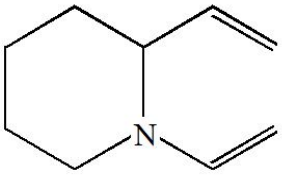
Fig. VIII N,N-Diethyl-N-(2-tetrahydronaphthyl)glycinamide

Quinolizidine Derivatives :

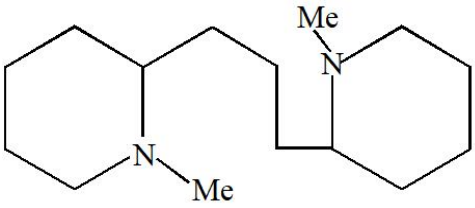
Ohki *et al.* examined quinolidine and its derivatives for oxytocic action. Quinolizidine (ix) was found to be 25 times more active-thansparteine, where as compound (x) and (xi) had almost no effect. The compound to show sparteinc like uterine contracting action, at least are quinolizidine nucleus was necessary.



(ix)



(x)



(xi)

3-butyl, 3-pentyl and 3-isopentyl derivatives of quinolizidine showed the highest activity with fewer side effects.

Aminomethyl derivaties of phenols :

Substituted amino methyl derivatives of various substituted phenols and naphthols (xii) possess very high activity in vitro when examined on guinea pig uterus.

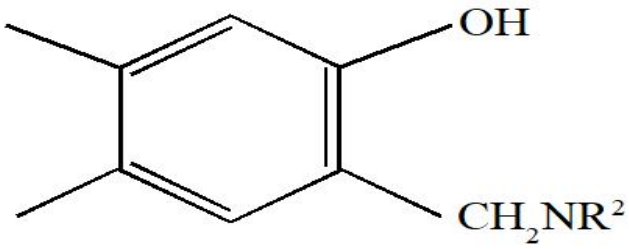


Fig. (xii) Aminomethyl phenol derivative

Galanty and Ervin have prepared compounds of the structure type (xiii) 20 and (xiv) 21. were found to possess useful uterotropic and antihypertensive activity.

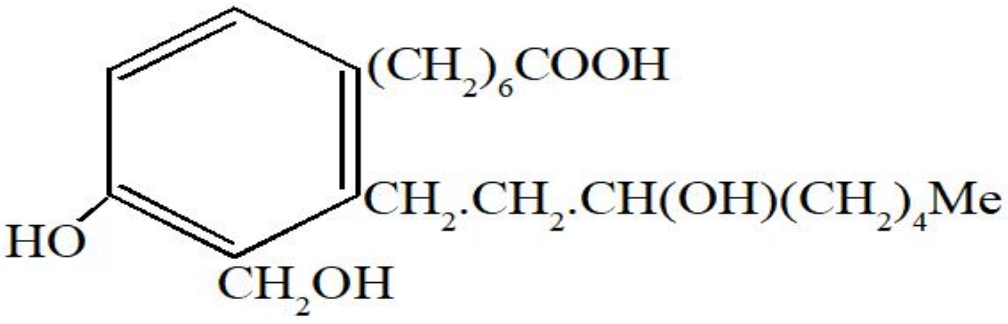


Fig. (xiii) Uterotropic phenol derivative

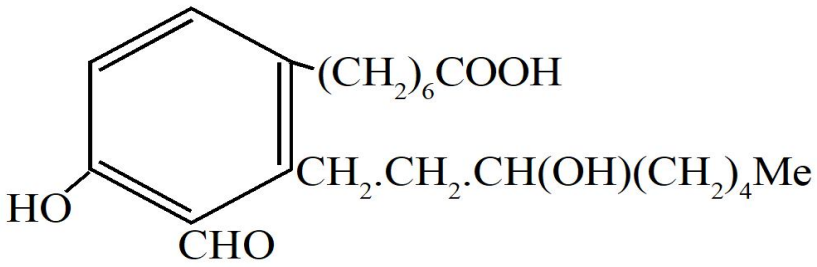
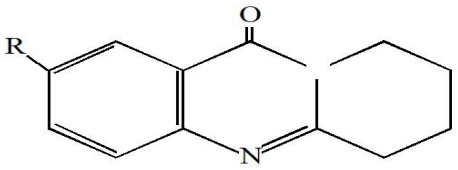


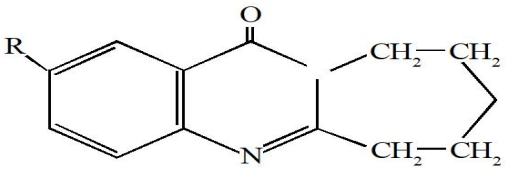
Fig. (XIV) Uterotropic phenol derivative

Lebi and Barth have prepared 1-penicillamine dacamino-6-carbaoxytocin(xv) and found that compound (R=H) possess high uterine stimulating activity.

Jain *et al* have synthesized the compounds of the structure type (xvi) and (xvii) and tested for uterotonic activity. All compounds were found to be inactive.



(xvi)



(xvii)

Zaitsev and uterotropic effects of Nesynov 24 ureas and have studied the thioureas in uterus preparation from pregnant and nonpregnant rats. Thiourea had a marked stimulating effect in both types of uteri. [4-(0-analog mthyl)-L-threonine) oxytocin, a new of neurohypophyseal oxytocin was synthesized and its uterotonic activity was 150 IU/mg in rats 25.

Nine oxytocin analogs containing mercapto acid or (1-mercapto) cyclohexyl carboxylic acid residues in position 1 and β homoamino acid residues [β-homotyrosine, homotyrosine-0-methyl ester, or β-homophenyl alanine) in poisition 2 was synthesized and some of their pharmacological potencies, as well as their binding affinity to the oxytocic receptor were determined.

Keeping in view the above mentioned facts it was thought worth while to direct investigation on the synthesis of alkylamine, arylaminopropionyl 2-aminotetraline and alkyl amino, arylaminobytryl 2-aminotetralin as potential oxytocics. The compounds to obtained have possibly all the structural requirements for the oxytocic activity.

The structure of these compounds have been established on the basis of their analytical results, i.r. spectra and the purity was checked by tlc.

Experimental

Uterine motility is controlled by a variety of biochemical and regulatory processes. Many drugs have the capacity to stimulate the smooth muscle of the uterus. However, only a few have effects that are sufficiently selective and predi table to justify their use as uterine stimulating (or

oxytocic) agents in obstetrical practice. These are oxytocin, certain of the prostaglandins, and the ergot alkaloids ergonovine and methylergonovine. There are so many compounds possess oxytocic activity varied in their has been reported that chemical structure. derivatives of indole, phenol, quinolizidine aminotetra-hydronaphthalene workers. It were some and 2-prepared by various
Keeping in view the above facts it was thought. worth while to prepare various compounds in the following two series, which may prove to be a fruitful oxytocics.

i) Alkylaryl amino propionyl-2-aminotetralin
ii) Alkyl arylamino butryl-2-amino-tetralin

The general sequence of the reaction may be depicted as follows-

Dimethylamine, diethylamine, dipropylamine, di-isopropylamine and morphalin were used in the condensation reaction. These compounds (iii) have been characterized on the basis of i.r. spectra, elemental analysis and the purity of compounds have also been checked by tlc.

Experimental

Preparation of 2-aminotetralin

A solution of 20 g (0.14 M) of B-naphthylamine in 250 cc of isoamyl alcohal (dried by distilling off a moist forerun) was heated to boiling. The boiling solution was poured in a stream through the separatory funnel into the flask upon the sodium and than washed with 50 cc of boiling amyl alcohol. A very voilent reaction was begin immediately which slow up after few minutes and then must be added by warming. The flame was so regulated that the reaction mixture, was always in boiling condition very vigorously till all the sodium was dissolved.

When all the sodium was completely dissolved the hot yellow solution was allowed to cool to about 100°C and then poured into 500 c.c. of cold water. The mixture was allowed to cool completely with frequent shaking and then the upper isoamyl alcohol layer was sepatated from the water layer which contains the principal portion of sodium hydroxide. The pure base was obtained by the removing excess of amyl alcohol.

Yield	70.02%	m.pt. 237°C
Anal found	N	9.48%
Col. for $C_{10}H_{13}N$	n	9.52%

The compound was characterized by infra red spectra. In i.r. spectrum the benzene ring has been characterized primarily by the bands at about 770 cm^{-1} and 3100-3450 cm corresponds to symmetric and asymmetric stretching vibrations of NH, group. The purity of compound was also checked by tlc.

Preparation of chloropropionyl-2-aminotetralin

Freshly distilled chloropropionylchloride (0.05 mole) in dry benzene was gradually added to

2-amino-tetralin dissolved in dry benzene containing potassium carbonate (50 gms) with constant stirring. The reaction mixture was fefluxed at 80°C for 6 hrs. Excess of benzene was distilled off and the residue was treated with sodium carbonate solution and washed with water to remove acid impurities. The product was recrystallised from chloroform.

Yield	68%	m.pt. 224°C
Anal found	N	5.86%
Calc. for $C_{13}H_{16}NOC1$	N	5.89%

Chlorobutryl-2-aminotetralin was also prepared data by the same procedure and the analytical data are given in Table 1.

Preparation of dimethylaminopropiony1-2-aminotetralin

Dimethyl amine (0.03 mole) in ether was gradually added to chloropropionyl-2-aminotetralin (0.01 mole) suspended in ether, and the reaction mixture was refluxed for 8 hrs. After the reaction excess of dimethyl amine and ether were removed. And the residue was washed with $NaHCO_3$ solution and water respectively. The dried product was recrystallised from MeOH.

Yield	70%	m.pt. 53 °C
Anal found	N	11.48%
Calc for $C_{15}H_{21}N_{20}$	N	11.43%

Similarly chloropropiony1-2-amino-tetralin was treated with different amines to give respective compounds and the results are tabulated in Table 2.

Preparation of diethylaminobutryl-2-aminotetralin :

To a solution of chlorobutryl-2- amino tetralin (0.01 mole), diethylamine (0.02 mole) suspended in ether was added gradually and the reaction mixture was refluxed for 8 hrs. After the reaction excess of diethylamine and ether were removed and residue was washed with $NaHCO_3$ to remove the acid impurities and finally with water. The product was recrystallized with MeOH.

Yield	63%	m.pt. 99-100°C
Anal found	N	9.81%
Calc for $C_{18}H_{21}N_{20}$	N	9.76%

Two bases so obtained by the similar reaction between chloroputryl-2-aminotetralin and different amines are summarized in table 3.

The amines used in the reaction are dimethylamine, diethylamine, dipropylamine, di-isopropylamine and morpholine.

Pharmacological Screening

In the present chapter, discussions have been made regarding the method used for determining the oxytocic activity and the pharmacological screening results of various compounds, synthesized in the investigation.

As the changes in methods of assessment or in the species of animals employed in the test can greatly influence the results, selection of a proper method is necessary for evaluating the biological or pharmacological activity of a particular oxytocic agent especially when comparison has to be done in a series of compounds.

All the compounds were used as free bases. They were suspended in propylene glycol ($CH_3CHOH.CH_2OH$) and diluted with distilled water to obtain required concentration (102M). Oxytocin injection, manufactured by Parke Davis diluted to (India) Ltd., was used as reference drug. Five units of oxytocin 5 ml with distilled water. Monothioglycerol, a antagonist, was used for confirmation of oxytocic activity of synthesized compounds.

Preparation of De Jalon solution

Solution was prepared by known procedure i.e. sodium chloride (NaCl, 9.0g), 10% of potassium chloride (KC1, 4.2 ml), glucose (0.5 g), sodiumbicarbonate ($NaHCO_3$ 0.5 g) and molar solution of calcium chloride ($CaCl_2$, 0.27 ml) were dissolved 1 lit. of distilled water. A mixture of oxygen and carbon dioxide continuously. (O_2 95% CO_2 5%) were aerated continuously.

The rat uterus preparation and procedure

The sensitivity of the uterus depends upon its condition. For this experiment young, virgin rats were used with 120-150 g weight. Three doses of Stilboestrol (0.1 mg/kg) were given 72 hrs, 48 hrs, 24 hrs, before, subcutaneously to bring the rate oestrus.

The animal was killed and the abdomen opened. The two horns of the uterus were dissected out and transferred into the dish containing De Jalon's solution. The two horn were separated out and freed from fat, and each was cut open longitudinally, so that the preparation was a sheet of muscle, instead of narrow tube. Each horn was further subdivide longitudinally and so obtain four pieces from one animal. A thread was attached at each end of piece (of uterus) and the preparation was mounted in De Jalon's solution which was aerated with oxygen and carbon dioxide. One thread was attached to a fixed pin and other to a lever fitted with a frontal-writing point as show in figure 1. The load on the lever was 1 gram and the magnification 20 mm. The volume of bath 20 ml and temperature usually 30±1°C which was regulated by a thermostat. After standardization the uterus, the fixed volume of the test compound (concentration 10-2 M) was poured into the bath and the response was recorded at kymograph with the help of Polyrite-8 followed by the response of oxytocin. Above mentioned procedure repeated for each compounds. Only three compounds (111, IV and VII) given the response.

Results

Alkyl arylaminopropionyl/butryl-2-aminotetralins were synthesized and screened for oxytocic activity. Out of ten compounds only three exhibited oxytocic activity. The screening results 1.e response are shown in Figure 2 to 4. Active test compounds have almost the same response in comparison to oxytocin.

Discussion

As mentioned earlier the compounds exhibiting oxytocic activity are not similar in their chemical structure. Dimethylamine, diethylamine, dipropylamine, isopropylamine and morpholine were used for condensation. Compounds (III), (IV) and (VII) were found to be active. From figure 2 and 3 it is clear that compound (III) and (IV) given more response in comparison to compound (VII). Increase in carbon atoms in intermediate alkyl chain did not affect the oxytocic activity except compound (VII).
The various compounds of test series did shown oxytocic activity except compound (III), (IV) and (VII).

In conclusion, it is evident from the results, of this study, that compound 111 (morpholinopropiony1-2-aminotetralin) and iv (diethylaminopropionyl-2-tetraline) have the satisfactory response.

Scope for Future Work :

The present investigation demonstrated that selected aminotetralin derivatives possess promising oxytocic activity. Further studies are required to establish their pharmacological potential through detailed dose–response investigations, receptor binding studies, and mechanistic evaluations. Structural modifications of the aminotetralin nucleus may lead to compounds with enhanced uterotonic activity and improved selectivity. In addition, comprehensive toxicity studies, pharmacokinetic profiling, and in vivo evaluation in suitable animal models are necessary before considering their possible therapeutic application as oxytocic agents.

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