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POTENTIAL ENERGY CALCULATIONS OF NALBUPHINE HYDROCHLORIDE

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Agonistic and antagonistic behaviour of some of the opioids led to the reassesment of the geometrical nature of bonding with the receptor surface. During the course of present work, potential energy calculations are carried out to find out the mode of binding and to examine the concept of bireceptor phenomenon. The structure of nalbuphine may be considered as a link between that of the pure antagonist naloxone and potent agonist morphine. Nalbuphine is a potentially analgesic exhibiting agonist properties. The allowed conformations are found to be at W_1 = 50° to 80° and 240° – 360° respectively. The remaining non allowed regions are found to be at W_1 = 0 to 30° and 120° to 360° and W_2 = 100° to 220°.

Key words: Nalbuphine, Opioids, Narcotics.

INTRODUCTION

Nalbuphine (N-cyclobutylmethyl-7, 8-dihydro 14-hydroxynonmorphine) crystallizes as the hydrochloride dihydrate in space group $P2_1\ 2_1\ 2_1$ with a = 11.576°A, b = 12.336°A, c = 14.658°A. z = 4 ($C_{21}H_{27}NO_4HCl\ 2H_2O$). Nalbuphine is structurally related to morphine, which is considered to exhibit agonist properties (Elliot *et al.* [2]. As an antagonist, it is four to five times as potent as morphine [3]. The dual behaviour of nalbuphine appears consistent with the two receptor theory proposed by Martin [4]. Nalbuphine structure may also be considered intermediate between that of pure antagonist naloxone [5] and as potent agonist of morphine [6].

Drug – receptor interaction constitute an important discipline in the field of bio-chemical activity. Opiate seemed to acqiure a key position both for the psychologists and pharmacologists in understanding the nature of personality disorganization and social set up of the addicts.

In order to trace the mode of action of narcotics, various studies are being carried out to assess the geometrical parameters of drugs with respect to receptor. The study of opiate receptor led to the exposition of a basic infra-structure in tracing the exact geometrical nature of the molecule in question. The drug of choice would impart its efficacy in exhibiting required analgesic activity or less side effects and addication liability. The agonistic and antagonistic behaviour of nalbuphine is of particular interest as it competes for the receptor with that of morphine and naloxone.

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The difference in the structure of nalbuphine and morphine is only cyclobutyl-methyl substitution on N, and by the -OH substitution at C_{14} and by hydrogenation of C_7-C_8 double bond. Generally, substitution of a larger group for the methyl group on the N of morphine (or similar agonist) tends to bring out antagonist activity [7].

Presence of the C_{14} -OH group appears in general to decrease disorienting side effects [8]. The absolute configurations of nalbuphine and morphine were believed to be same [9].

The crystal packing of the cations were determined by a complex hydrogen bonding net work involving H-bridges and the Cl^- anions. Although the nature of the forces acting between drug and receptor site had not been calculated. It was reported that hydrogen bonding might be playing significant role, as it was found that H_2O molecules and the Cl^- ion were forming an interface between the drug molecules to which they were connected. Hence such a drug receptor interface (DRI) may be well facilitated as drug-receptor interactions.

It was further reported that hydrogen bonding distances were agreed well with generally accepted average values [10] and were quiet closed with those in naloxone HCl. $2H_2O$ [5]. In naloxone, the Cl^- anion was more enclosed, being within H-bonding distances of O_1, O_5, O_6 and NH^+, while in nalbuphine the Cl^- was hydrogen bonded only to O_1 and O_3. In naloxone, O_3 being a keto oxygen did not participate in hydrogen bonding.

METHODS

The detailed mathematic calculations are given else where [11]. Nalbuphine is considered to be a potentially

useful analgesic which also exhibits agonist properties. The perspective view of nalbuphine is shown in Fig. 1. The coordinates of atoms C^{II}_{16}-C^{I}_{19}, C^{II}_{16}-C^{I}_{20}, C^{II}_{16}-C^{I}_{21} after rotation about the bonds C_{17}-C_{18} (w_1) and C_{17}-N(w_2) were evaluated.

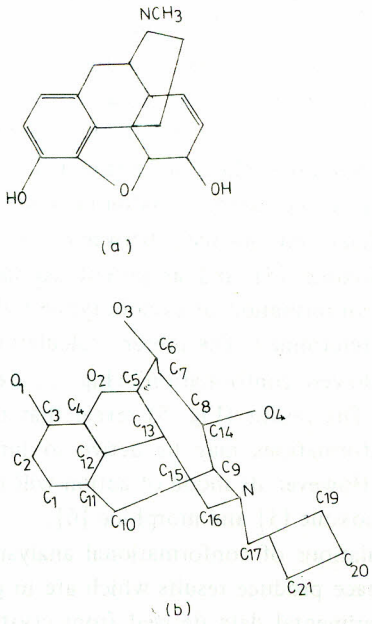

Fig. 1. (a) Structure of morphine; (b) Structure of nalbuphine.

RESULTS AND DISCUSSION

The contour maps for the pairs C^{II}_{16}-C^{I}_{19}, C^{II}_{16}-C^{I}_{20} and C^{II}_{20} and C^{II}_{16}-C^{I}_{21} are given in Fig. 2, 3 and 4 respectively.

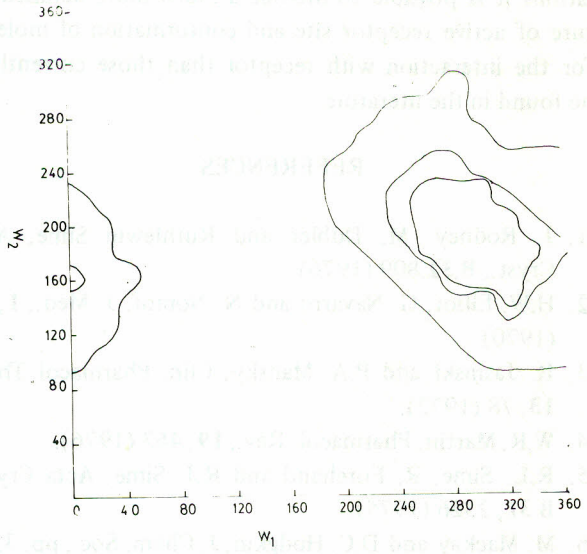

Fig. 2. Energy contours for the pair C^{II}_{16}-C^{I}_{19}. The units of energy are Kcal./mole.

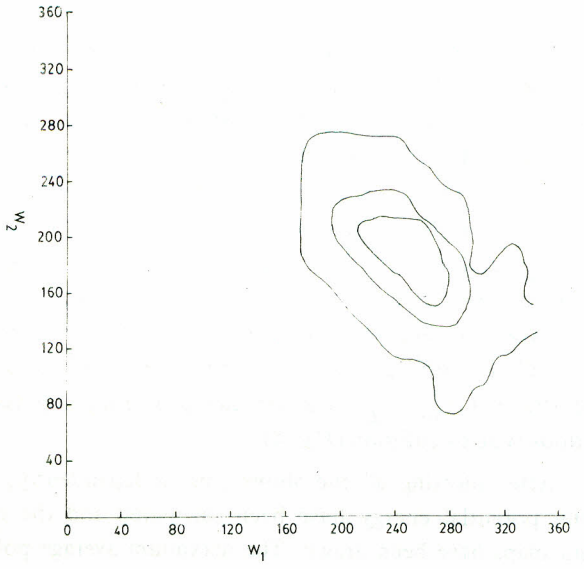

Fig. 3. Energy contours for the pair C^{II}_{16}-C^{I}_{20}. The units of energy are Kcal./mole.

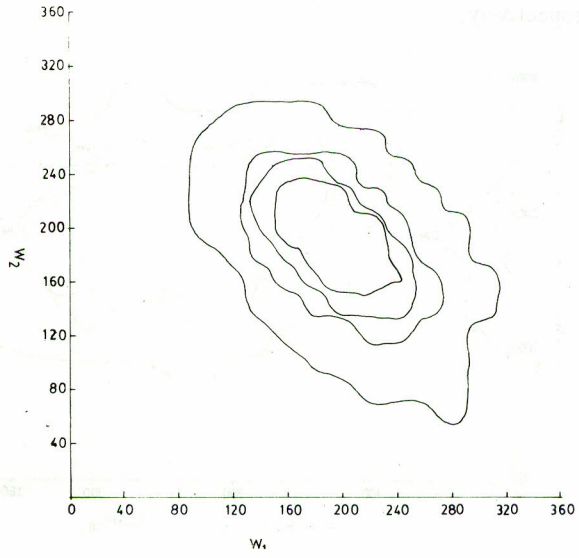

Fig. 4. Energy contours for the pair C^{II}_{16}-C^{I}_{21}. The units of energy are Kcal./mole.

C^{II}_{16}-C^{I}_{19} pair: The coordinates of atoms C^{II}_{16}, C^{I}_{19} after rotation about the bonds C_{17}-C_{18} and C_{17} – N were evaluated. The maximum potential energy was bound to be 15.7 K.Cal/mole ($w_1 = 280^o$ and $w_2 = 200^o$) for the pair C^{II}_{16}-C^{I}_{14} respectively. The allowed conformations are found to be at $w_1 = O^o - 360^o$ and $w_2 = O^o$ to 80^o, 240^o to 260^o while the region $w_2 = 100^o$ to 270^oshows the serious type of collisions (Fig. 2).

C^{II}_{16}-C^{I}_{20} pair: The maximum potential energy has been calculated as 10.5 K.cal/moles at $w_1 = 240^o$ and $w_2 = 180^o$. The region where allowed conformation occurs at

w_1 = 0^o to 160^o and 340^o to 360^o and w_2 = 0^o to 80^o and 300^o to 360^o for the pair C^{II}_{16}-C^{I}_{20}. The region w_1 = 180^o to 320^o and w_2 = 100^o to 280^o shows serious type of collisions and overlapping. (Fig. 3).

C^{II}_{16}-C^{I}_{21} pair : The coordinates of the atoms (C^{II}_{16}, C^{I}_{21}) have been evaluated after rotation about the bonds C_{17}-C_{18} and C_{17}-N. The maximum potential energy is calculated as 35.9 K.cal/moles (w_1 = 200^o and w_2 = 180^o). The maximum allowed conformations are found to be at w_1 = 0^o to 360^o and w_2 = 0^o to 60^o and 300^o to 360^o for the pair C^{II}_{16}-C^{I}_{22}. The remaining position represents serious type of collision (Fig. 4).

After plotting all the above pairs independently, the total potential energy have been calculated and the contour maps have been drawn. The maximum average potential energy is found to be 37.0 K.cal/moles at w_1 = 200^o and w_2 = 180^o (Fig. 5). The allowed conformation found at w_1 = 50^o to 90^o and w_2 = 0^o to 75^o, 320^o to 360^o respectively.

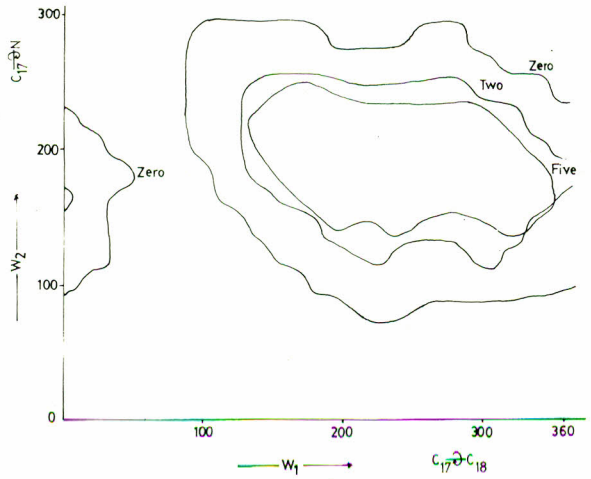

Fig. 5. Total energy contours for nalbuphine. The units of energy are Kcal./mole.

The study of potential energy with respect to narcotic analgesic compounds is important as it would be of great help in understanding the nature of the forces acting between drug and receptor surface.

The nature of the forces acting between drug and receptor site has not been established. It is likely that water and chloride ion can play important role as interface between drug and receptor. Chloride ion can form hydrogen bond with O_1 – H (drug) and O_3 – H (receptor). Water molecules can also form an interface between drug and receptor. Hence water molecules and chloride ions form an interface between drug and receptor. Therefore formation of this interface may fecilitate drug – receptor interaction.

A comparison of morphine and nalbuphine structures is given in Fig. 1. Nalbuphine is structurally related to morphine. There is a cyclobutylmethyl substitution on N, a OH substitution at C_{14} and hydrogenation of C_7 and C_8 double bond in the structure of nalbuphine. Electrostatic potential calculations [12] indicate that the morphine molecule is surrounded by a positive, or repulsive sheath except in the vicinity of the phenolic OH on carbon atom C_3 and the furan oxygen O. It is the regions of negative or attractive potential which are postulated to be responsible for binding to the receptor. Nalbuphine structure may also be considered intermediate between that of pure antagonist naloxone [5] and as potent agonist of morphine [6]. The conformation of cyclobutylmethyl in nalbuphine has been determined. The present calculations suggest very limited allowed conformations (Fig. 5, area outside zero contour). The results (Fig. 5) reveal that the molecule in these conformations may be active to interact with the receptor. However its mode of action will be intermediate that of naloxone [5] and morphine [6].

Calculations of conformational analysis for the molecule in space produce results which are in good agreement with experimental data derived from crystallographic studies [1]. If series of similar molecules with varying activities is studied from conformational point of view, it may be possible to define precise conformation of molecules which is essential for activity. For this type of work more detailed work will be required. These calculations can give information about non equilibrium conformational energies, electron densities as well as electrostatic maps. For such calculations it is possible to provide a much more detailed picture of active receptor site and conformation of molecule for the interaction with receptor than those currently to be found in the literature.

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