Pakistan J. Sci. Ind. Res., Vol. 31, No. 4, April 1988

CONFORMATIONAL STUDIES ON THE STRUCTURE OF 19-PROPYL THEVINOL HYDROBROMIDE

Zafar S. Saify* and M.A. Haleem

Department of Biochemistry, Facultry of Science, University of Karachi, Karachi-32

(Received March 20, 1986; revised April 7, 1988)

In order to assess the nature of drug-receptor interaction in case of opioid series 19-propyl thevinol hydrobromide is selected. Potential energy calculations are carried out by computer on the basis of coordinates obtained from X-ray diffraction studies. Potential energy calculations based on non-bonded interactions showed that there are only specific allowed conformations to enable the molecule to conform itself according to the requirement of receptor. As a result of this study, it is speculated that design of new analgetics and mapping of receptor would become more feasible.

Key words: Conformational studies, Drug receptor interaction, Propyl thevinol hydrobromide.

INTRODUCTION

Addiction to narcotics, sedatives and analgesic drugs has become a serious problems for the patients. Optiqates rank at the top among the drugs responsible for causing addiction and narcosis [1]. 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 constitutes a basic infra structure in tracing the exact geometrical nature of the molecule in question [2]. The drug of choice would impart its efficacy in exhibiting required analgesic activity or, less side effects and addiction liability [3]. Opiates can be classified into three categories i.e.,

(a) The fused ring opiates, for example, morphine and related derivatives;
(b) 4-phenyl piperidines such as pethidines and ketobemidones and
(c) Acyclics

All opiates appear to possess a basic nitrogen, an aromatio ring and at least one polar group having oxygen [4]. In order to assess the activity of opioids and conformation, potential energy of non-bonded interactions are calculated for the molecules [5,6] by Sord computer Mark M–68.

Method of calculation. Taking into consideration the rigid nature of structure of 19-propyl thevinol, the conformation of side chain

$$\begin{matrix} C_1 \\ \\ Me_{19} \end{matrix} \diagdown\!\!\diagup \; C_{19} - Pr_1 - Pr_2 - Pr_3$$

of the molecule (Fig. 1) is determined. The coordinate of the atoms Me_{19}, C_{19}, Pr_1, Pr_2, Pr_3, O_6 and Me_6 are redetermined by taking C_7 as origin. The coordinates Me_{19}, C_{19}, Pr_1, Pr_2, Pr_3, and O_{19} are rotated along the $C_7 - C_{19}$ bond at an interval of 10^o similar to the calculations as

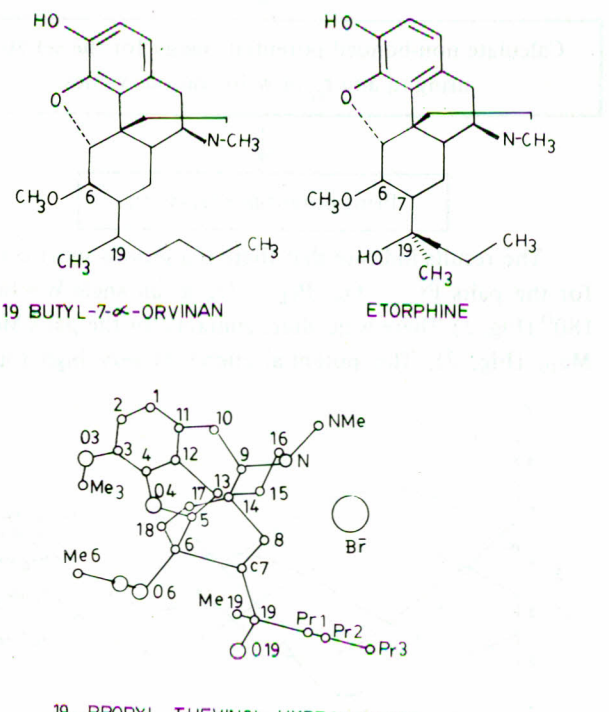

Fig. 1. Structure of 19 – butyl – 7 - α – orvinan, etorphine and hydromide.

*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi-32.

described elsewhere [7]. The Kitaigrodsky [8] potential energy function is used to calculate the non-bonding potential energy for the pairs O_6. . .Me_{19}, $O_6 - Pr_2$, $O_6 - Pr_3$, O_6. . .C_{19}, Me_6. . .Me_{19}, Me_6. . .O_{19}, $Me_6 - Pr_1$, $Me_6 - Pr_2$, Me_6. . .Pr_3, $O_6 - O_{19}$ and $O_6 - Pr_1$ according to the programme 1.

The detailed mathematical calculations are given elsewhere [7].

Programme 1

O

Read co-ordinates of atoms X_i, Y_i, Z_i

↓

Transfer the co-ordinates to origin C_7

↓

Calculate co-ordinates of the atoms after rotation (w) along the bond $C_7 - C_{19}$ except atoms i.e. O_6 and Me_6

↓

Calculate intermatomic distances rij of the atoms with O_6 and Me_6

↓

Calculate non-bonded potential energy for the set atoms using rij and r_0 of w for various values.

↓

Print potential energy, rij

The results indicate that there is a serious short contact for the pairs $Pr_2 - O_6$, $Pr_1 - O_6$ at an angle W = 80° to 180° (Fig. 2). There is no short contacts for the pairs $Me_6 - Me_{19}$ (Fig. 2). The potential energy is very high for the pair $O_6 - Pr_2$ and the structure in this conformation is not possible (Fig. 3). It is interesting to note that better H-bond can be formed between $O_6 - O_{19}$ at W = O and W = 350° – 360°. The hydrogen bond at W = O is 2.63A°, where at W = 350° – 360° is found to be in the region of 2.79A° – 2.63A°. The proper H-bond at W = 350° is 2.79 which is better as compared to W = 0 (2.63).

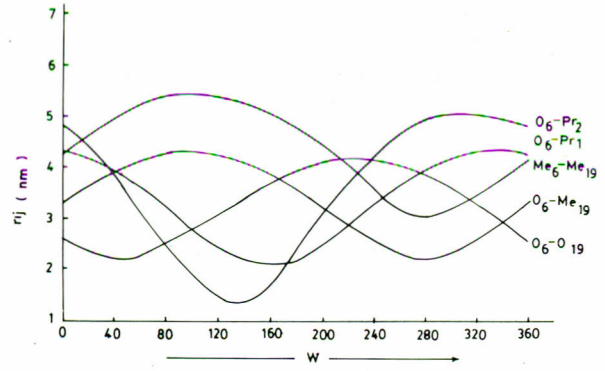

Fig. 2. Plot of r_{ij} (distance between ith and jth atom) versus W (angle of rotation about the bond C_7–C_{19}).

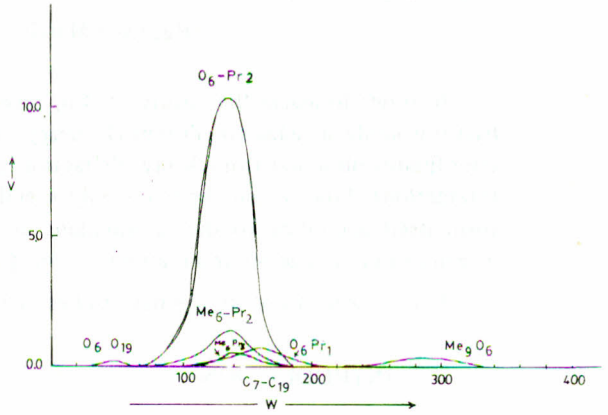

Fig. 3. Plot of conformational energy (V) versus W (W is the angle of rotation along the bond C_7–C_{19}) for the pairs O_6–O_{19}, O_6-Pr_2, Me_6–Pr_2, Me_6–Pr_3, O_6–Pr_1 and Me_6–O_6.

DISCUSSION

During the course of the present work, attempt is made to establish possible conformation of (19-propyl thevinol Hydrobromide) based on the X-ray crystallographic analysis. According to Becket's model of analgesic receptor [14], a flat aromatic surface, a quaternary carbon, and quaternary nitrogen atom suitably placed on a heterocyclic nucleus (Fig. 4) is necessary for a compound to exhibit analgesic activity. Morphine and codeine are

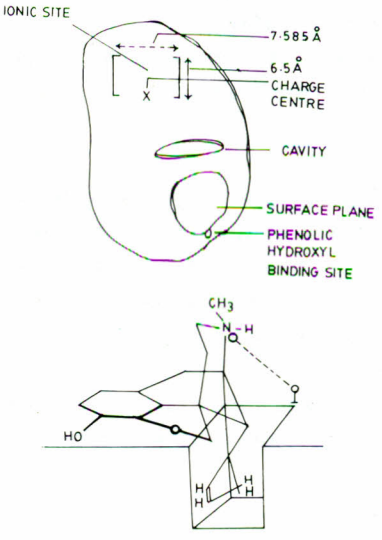

Fig. 4. Model of analgesic receptor.

supposed to interact with the receptor in specific conformation forms. The pattern of interaction determines the potency of analgesic activity. The special configuration of the molecule of 19-propyl thevinol as shown in Fig. 1, is similar to that of codeine and morphine.

In the side chain, the hydroxyl oxygen, O_{19}, is coplanar with O_6 and C_{19} and the methyl group Me_{19} is oriented toward the morphine ethenyl bridge. With the potential energy calculations a better activity is speculated between O_6 – O_{19}, the H-bond distance being 2.63.

Looking at the structure of eterphine and 19 butyl-7-orvinan which exhibited extremely high analgesic activity. It is expected that on the basis of potential energy calculations, of 19-propyl thevinol, the conformational adjustment of side chain, with respect to bond length, bond angles and oxygen-carbon relationship is of prime importance during an interaction with the receptor [12, 13].

CONCLUSION

Potential energy calculations would be a significant parameter to understand the nature of analgesic receptor. The determination of potential energy on related compounds to achieve a better mapping of drug-receptor interaction is being carried out.

REFERENCES

1. G.H. Loew and D.S. Berkowitz, J. Med. Chem., **18**, 656 (1975).
2. G.H. Loew, D.S. Berkowitz, H. Weinstein, and S. Srebrenik, *Molecular and Quantum Pharmacology*, (D. Reidel Publishing Co., Dordrecht, Holland, 1974), p. 355.
3. Z.S. Saify, Ph.D. Thesis, University of London (1971).
4. J.W. Lewis, K.W. Bentley and A. Gowan, Ann. Rev. Pharmacol., **11**, 241, (1971).
5. G.H. Loew and D.S. Berkowitz, J. Med. Chem., **22**, 603 (1979).
6. A.P. Feinberg and S.H. Cressel, Proc. Natl. Acad. Scl., U.S.A. **73**, 4215 (1976).
7. M.A. Haleem and Z.S. Saify, Pakistan J. Sc. Ind. Research, **19**, 294 (1986).
8. A.I. Kitaigorodsky, Tetrahedran **14**, 230 (1961).
9. J.H. Vanden Hende, and N.R. Nelson, J. Am. Chem. Soc., **89**, 12 (1967).
10. J.M. Lindsey and W.H. Barnes, Acta Cryst., **8**, 227 (1955).
11. M. Mackay and D.C. Hodgkin, J. Chem. Soc., 3261 (1955).
12. F.A. Gorin, T.M. Balasubramanian, (C.D. Barry, and G.R. Marshall, J. Supramol. Struct., **9**, 27 (1978).
13. P.S. Portoghese, J. Med. Chem., **8**, 609 (1965).
14. A.H. Beckett and A.F. Casy, J. Pharm, Pharmacol., **6**, 986 (1954).