Pakistan J. Sci. Ind. Res., Vol. 31, No. 10, October 1988

# POTENTIAL ENERGY CALCULATIONS OF METYRAPONE

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(Received January 20, 1987; revised October 13, 1988)

Metyrapone is one of the potent inhibitor of cytochrome p-450. The potential energy of non-bonded interaction is calculated for metyrapone. The possible allowed conformation is found to be in the region $W_1 = 30°$ to 85° and $W_2 = 0°$ to 90° and 200° to 360°.

*Key words:* Adrenaline, Noradrenaline, Tryptophan.

## INTRODUCTION

Metyrapone is a powerful inhibitor of certain cytochromes p-450 enzymes which are supposed to be involved in metabolic processes. This inhibitor (metyrapone) inhibits both the adrenal cytochrome p-450 catalysing 11-B-hydroxy action in steroid bio-synthesis and most microsomal cytochrome p-450 induced by pre-treatment [1, 2].

Testa and Jenner [3] found that cytochrome p-450 activity was induced by drugs, carcinogens, insecticides and other foreign compounds [5].

The metyrapone crystallizes in monoclinic system with unit cell dimensions a = 11.828 A°, b = 6.268 A°, c = 18.269 A°, β = 115.27° with space group $P2_1/c$. Mariam Rossi [4] studied the structure of metyrapone and proposed twisted butterfly conformation. The torsion angle about the $C_7$-$C_{10}$ bond to which the two 3-pyridyl groups were attached was found to be 59.4°. The van der waals surfaces for metyrapone, phenobarbital [6] and DDT [8] were also calculated [4] based on the crystallographic coordinates of each molecule by using Monte Carlo techniques [7]. The present work describes conformational analysis of metyrapone similar to other drugs [10-12].

## MATERIALS AND METHODS

The perspective view of metyrapone is shown in Fig. 1. The coordinates of atoms were evaluated after rotation about the bonds $C_{10}$-$C_7$ ($W_1$) and $C_{10}$-$C_{12}$ ($W_2$) for the pairs $C_8^I$-$C_{13}^{II}$, $C_8^I$-$C_{17}^{II}$, $C_9^I$-$C_{13}^{II}$ and $C_9^I$-$C_{17}^{II}$ respectively. (I and II represent first and second ring of the molecule).

The detailed mathematical calculations are given elsewhere [12]. Several programmes were written in basic language and sord computer (mark 68) was used throughout this work.

## RESULTS

The contour maps for the pairs $C_8^I$-$C_{13}^{II}$, $C_8^I$-$C_{17}^{II}$, $C_9^I$-$C_{13}^{II}$ and $C_9^I$-$C_{17}^{II}$ are given in Figs. 2, 3, 4, 5 respectively.

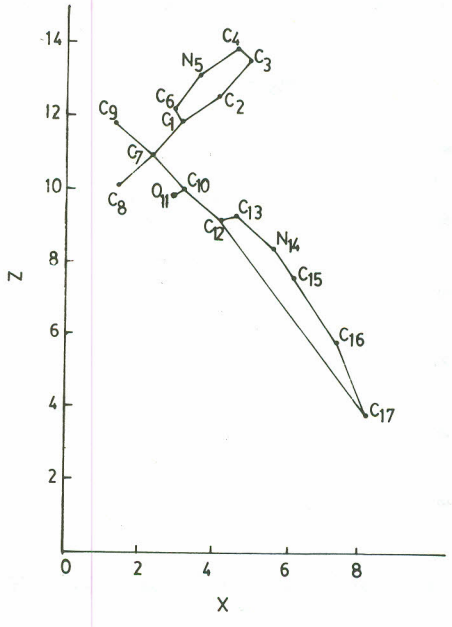


Fig. 1.

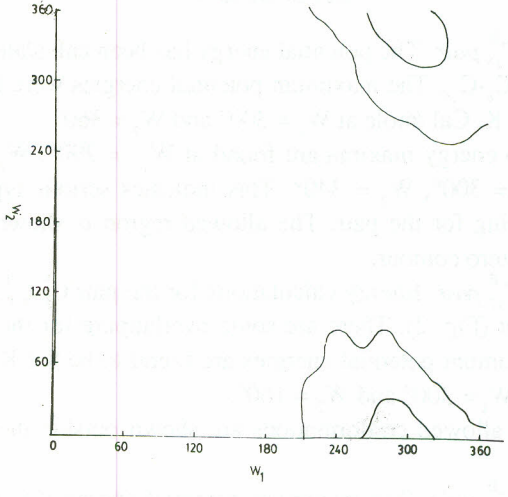


Fig. 2.

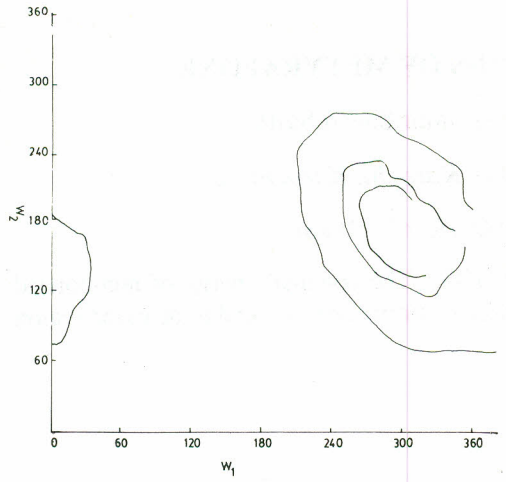


Fig. 3.

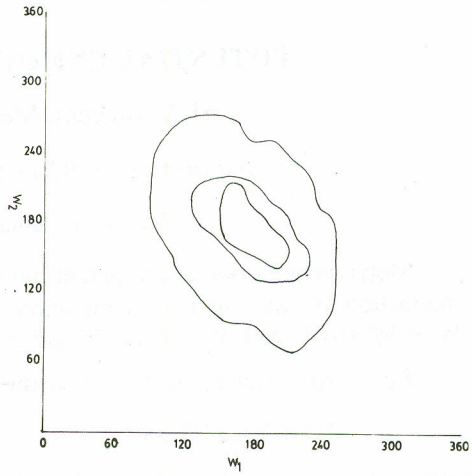


Fig. 5.

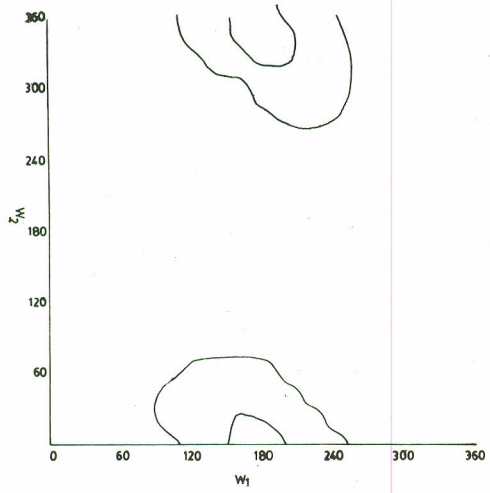


Fig. 4.

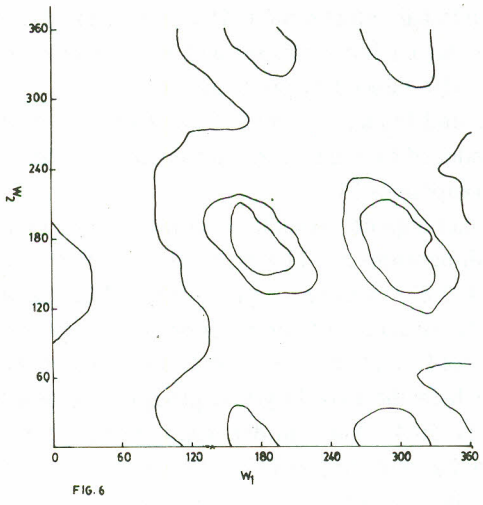


Fig. 6.

## DISCUSSION

*$C_8^I$-$C_{13}^{II}$ pair*. The potential energy has been calculated for the pair $C_8$-$C_{13}$. The maximum potential energies were found to be 3.9 K. Cal./mole at $W_1 = 300°$ and $W_2 = 360°$.

Two energy maxima are found at $W_1 = 290°$, $W_2 = 0°$ and $W_1 = 300°$, $W_2 = 340°$. This indicates serious type of overlapping for the pair. The allowed region is shown outside the zero contour.

*$C_8^I C_{17}^{II}$ pair*. Energy calculations for the pair $C_8^I$-$C_{17}^{II}$ indicates that (Fig. 2). There are some overlapping for the pair. The maximum potential energies are found to be 8.1 K.Cal./mole at $W_1 = 300°$ and $W_2 = 160°$.

The allowed conformations are shown outside the zero contour.

*$C_9^I$-$C_{13}^{II}$ pair*. The maximum potential energy was found to be 3.3 K. Cal./mole at $W_1 = 180°$ and $W_2 = 360°$. The area outside the zero contour represents allowed regions for this pair (Fig. 3).

*$C_9^I$-$C_{17}^{II}$ pair*. The maximum potential energy was found to be 6.3 K.Cal./mole at $W_1 = 180°$ and $W_2 = 180°$ for this pair Fig. 5). It is interesting to note that there is only one peak for this pair.

The total energy of the molecule is given in Fig. 6. The maximum potential energy is found to be 8.1 K.Cal./mole at $W_1 = 300°$ and $W_2 = 160°$.

The present calculations suggest steric interaction between ring connected to $C_7$-$C_{10}$ bond and methyl groups (Fig. 6). This type of steric interaction twists metyrapone. These interactions give "Twisted butterfly conformation". Mariam Rossi [4] suggested that interactions with the cryto-chrome p-450 PB active site can accomodate this spatial requirement. The present calculations indicates that the ring connected to $C_7$-$C_{10}$ bond is less flexible as compared to the

ring connected to $C_{10}$-$C_{12}$ (Fig. 6). Calculations of conformational analysis can give information about non equilibrium conformational energies, electron densities as well as electrostatic maps. It is likely to provide a much more detailed picture of active receptor site and conformation of molecule for the interaction with the receptor.

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