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Variations in the Physico-chemical Parameters of Some N-Methyl Substituted Barbiturate Derivatives

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The relative activity for the series of substituted barbituric acid derivatives show highly dependent lipophilic character. The increasing lipophilic character facilitate the movement of drug through lipophilic biophases and direct it on the sites of action.

Key Words: Barbiturate Derivatives, Dipole moment, Lipophilicity.

INTRODUCTION

The interactions of drugs with their biological counterparts are determined by inter moleculor forces. QSAR[1] studies are derived models for the correlation of biological activities with physico-chemical parameters. The different interactions between a ligand and its binding to protein crystallography-derived 3D structures are available. Molar refractivity is still the chameleon among the physico-chemical properties, despite its broad application in QSAR studies. It has been correlated with lipophilicity, with molar volume and with steric bulk[2]. Electronic properties[3] of molecules can be described by a wide variety of different parameters Hammet constants, field and resonance paparmeters (F and R), pK_a values, parameters derived moments hydrogen bonding parameters and parameters derived from quantum chemical calculations.

Keeping this QSAR studies in mind, the systematic investigation of various N-methyl substituted barbiturate derivatives have been subjected to a polarized continuums model (PCM) for evaluation of their physico-chemical parameters. The data thus obtained have been used to discuss the effect of substitutents on polarizability of the barbiturate aromatic ring and its possible dependence on the lipophilicity[4].

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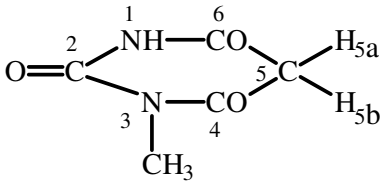
EXPERIMENTAL

Baeyer[5] detected barbituric acid in the course of an investigation of uric acid group. Since then 2500 derivatives have been synthesized, of these 50 compounds are of interest to the forensic scientist because they are clinically used.

Barbiturates are mainly termed as hypnosedatives under the psychoactive group of drugs. A sedative is a drug which is used to allay a patient and to make him drowsy without actually inducing sleep, where a hypnotic is a drug, which produces sleep.

As mentioned earlier barbituric acid (malonyl urea) result from the condensation of malonic acid and urea. The general strucutre formula of barbiturate molecules selected for the studies may be given as:



Serena Software[6] Version 5.13 based on evaluation of molecular mechanics energy (energy closely related to internal energy of molecule) and its breakup in to moleculer force fields *viz.*,

$$E_{MM} = E_{bn} + E_{an} + E_{vdw} + E_{tor} + E_{ch} + E_{misc}$$

The package provides a minimization of E_{MM}. Various possible conformations giving rise to the break up of the force field where E_{bn} corresponds the bond energy, E_{an} energy of angle, E_{vdw} correspond van derWall forces, E_{tor} torsion, E_{ch} charges and E_{misc} constitute the miscellaneous force other than mentioned above.

The package is able to produce window compatible output. The physicochemical properties calculated by the package include the dipole moments, van derWall forces, molar volume (Å), molar surface area and minimization energy, *etc*.

RESULTS AND DISCUSSION

As regards the effect of substituents on the hypnotic activities of the parent molecule and the possible role played by the substituents, a large amount of work has been conducted by Hansch *et al.*[7,8].

Keeping in view a detailed structure properties analysis of few 5a, 5b position substituted N-methyl derivatives of barbituric acid have been undertaken using computer aided drug designing and the PC-model logical calculations of molecular dynamics. Set of 5a, 5b disubstituants with 5a as alkyl, allyl and aryl with corresponding 5b positions substituted with alkyl, allyl and aryl groups have been selected for the present study.

TABLE-1
PC MODEL DATA
Variation in the E_{MM}, Dipole moment, VDW, Volume, Molar Surface Area and log P for the Substituted Barbiturates
Along with there Structural Formula the N-Methyl Barbiturate Substituted at R_{5a} and R_{5b}

Compd. No.	Name	R_3	R_{5a}	R_{5b}	E_{MM}	Dipole moment	VDW	Molar volume	Molar surface area	log P
I A	N-Methyl barbituric acid $C_5H_6N_2O_3$	CH_3	H	H	234.360	1.332	38.556	164	137.726	1.36
II A	N-Methyl-5-allyl barbituric acid	CH_3	C_3H_5	H	502.155	1.371	101.910	227	189.243	-
II B	N-Methyl-5-isopropyl barbituric acid	CH_3	H	$CH(CH_3)_2$	520.837	0.735	66.080	238	192.808	-
II AB	N-Methyl-5-allyl-5-isopropyl barbituric acid $C_{11}H_{16}N_2O_3$ (Narconumal)	CH_3	C_3H_5	$CH(CH_3)_2$	1301.006	4.629	290.310	285	219.732	1.15
III A	N-Methyl-5-(2-bromoallyl) barbituric acid	CH_3	C_3H_4Br	H	559.319	1.689	115.078	254	210.959	-
III B	N-methyl-5-isopropyl barbituric acid	CH_3	H	$CH(CH_3)_2$	520.837	0.735	66.080	238	192.808	-
III AB	N-methyl-5-(2-bromoallyl)-5-isopropyl barbituric acid $C_{11}H_{15}N_2O_3$ (Eunarcon)	CH_3	C_3H_4Br	$CH(CH_3)_2$	1113.057	3.066	248.446	317	252.030	1.16
IV A	N-methyl-5-ethyl barbituric acid	CH_3	C_2H_5	H	538.023	0.829	88.396	211	175.276	-
IV B	N-methyl-5-phenyl barbituric acid	CH_3	H	C_6H_5	767.620	0.913	187.306	291	237.328	-
IV AB	N-methyl-5-ethyl-5-phenyl barbituric acid $C_{13}H_{14}N_2O_3$ (Mebaral)	CH_3	C_2H_5	C_6H_5	682.616	1.403	161.270	312	243.809	1.42
V A	N-methyl-5-methyl barbituric acid	CH_3	CH_3	H	308.042	0.935	53.728	190	152.751	-
V B	N-methyl-5-(cyclohexen-1-yl) barbituric acid	CH_3	H	C_6H_5	631.344	1.207	112.999	284	223.153	-
V AB	5-(Cyclohexen-1-yl)-3,5-dimethyl barbituric acid $C_{12}H_{16}N_2O_3$ (Evipal)	CH_3	CH_3	C_6H_5	771.278	1.972	153.055	305	235.375	1.2

These values showed a variation with different substituents and the physico-chemical properties also changed in accordance with the substitution. The physiological activity of the drugs may directly be predicted using the physico-chemical properties.

The variations in the physco-chemical parameters have been showing the graphical representations as follows: Fig. 1A record the variation in the E_{MM} values, Fig. 1B record the variations in the dipole moment values, Fig. 1C record the variation in the van derWall forces where as Fig. 1D and 1E shows the variation in the molar volume and molar surface area.

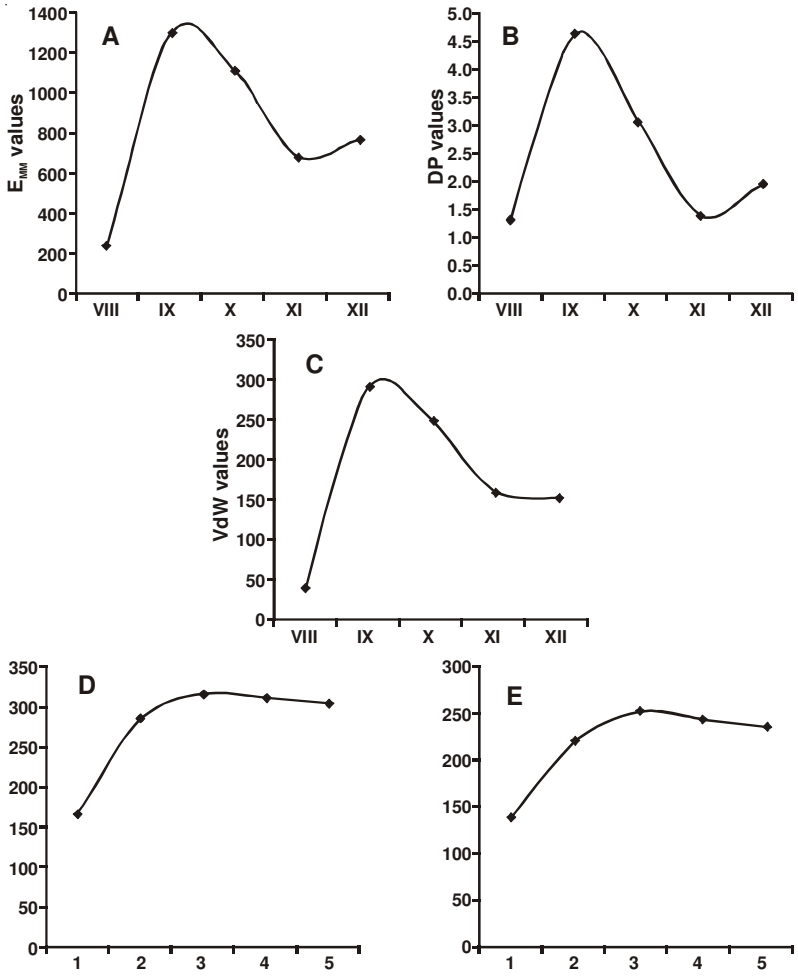


Fig. 1. Variation in the physico-chemical properties of 5a, 5b substituted derivatives of 3-methyl barbituric acid (A) E_{MM} (B) Dipole moment (C) van derWaals force (D) Molar volume (E) Molar surface area

According to the Hansch approach[7] the variation in the biological activity of the drug is a result of the decrease in mobility of drug through biological material. It has long been known that the relative activity of drugs in a series of structurally similar compounds are dependent of lipophillic character[8]. This lipophillic character has been examined using log P (lipophilicity/hydrophobicity) of the substituted molecules with the drug activity. The studies may justify the probable structural and dynamic parameters regulating hydrophobicity and their consequences and influence on the drug activity.

A comparison with N-methyl substituted barbiturates the observed sequence of hydrophobicity (reverse trend for lipophilicity) compound is interestingly.

al - ar > H - H > ak - ar > al - ak ≥ al - ak					with respect to substitution
VI	I	V	III	II	with respect to compounds
1.42	1.35	1.20	1.15	1.15	with respect to log P values

5a position allyl-alkyl substituted compounds have shown greater water solubility than the allyl-aryl compounds. This is again in accordance[9] with the difference in the π-density on the trienol ring in case of associated benzene, there by increasing the hydrophobicity or lipophilicity than the allyl-alkyl.

Amongest the N-methyl barbituric acid the observed sequence with respect to 5a and 5b positions have been found to be:

Al - Ak > H - H > AK - AK ≥ Al - Ak

The observed sequence for the overall susceptibility of 5b position over 5a (as constant) has been observed to be:

H - H > H - Ar > H - AK

These sequences are in agreement with the lipophilicity of the drug molecules.

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