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Variations in the Physico-chemical Parameters of Some 5a and 5b Substituted Barbiturate Derivatives

RAKESH RAY†, S. HARI KRISHNA, J.D. SHARMA† and S.N. LIMAYE*
Forensic Science and Chemistry, Dr. H.S. Gour University, Sagar-470 003, India
E-mail: snl222@yahoo.co.in

The barbiturates are therapeutically used as sedative, hyponotic, anaesthetic and anticonvulsant agents. The trienolmoiety and 5-substituents regulate the biological activity regarding the lypophilicity/hydrophobicity values of barbiturates against their physico-chemical properties.

Key Words: Barbiturates, Modelling, Hydrophobicity, Therapeutic.

INTRODUCTION

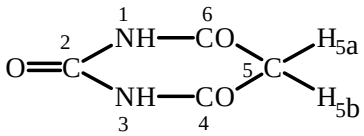
Barbiturates derived from barbituric acid (malonyl urea) resulted by the condensation of malonic acid and urea[1]. Several reports on the clinical and pharmacological evaluation of barbiturates are available in literature[2,3]. The important studies[4,5] on demethylation processes and their influence on the pharmacological effect of barbiturates are confirmed by the case of poisoning. It is necessary to know the metabolites accumulated, as a results of the permanent uses of large doses of barbiturates. Addicts prefer using the derivatives e.*g.*, phanodorn, medomin, amytal or seconal. The lethal doses for man have been reported[6]: Barbital 7-12 g, phenobarbital 4-5 g, merbal > 10 g; seconal 1.2 g, dial 2.4 g.

All the barbiturates have been observed to be more (or) less affected by body metabolism and are thus fundamentally different in their structures. In persuasion with the work performed in our laboratory the present attempt is to correlate the biological activities with a change in the molecular arrangement in barbiturates with respect to the physico-chemical properties acquired by the molecules.

†Department of Chemistry and Forensic Science, Dr. H.S. Gour University, Sagar-470 003, India.

EXPERIMENTAL

Barbiturate molecules selected for the studies are given under the general formula[7]:



Sarena software[8] PC-Model (version 5.13) package have been utilized to observe the physico-chemical properties of barbiturate (I) seconal (II) sigmadol (III) nembutal (IV) rutonal (V) darmavit (VI) and propanal (VII).

The package is able to produce window compatible output with the help of quantam chemistry program exchange (QCPE) version 5.04. The physico-chemical properties calculated by the package included: minimization energy, dipole moments, van derWall forces and molar volumes (A).

The data thus obtained have been used to discuss the effect of substituents on polarizability of the barbiturate aromatic ring and its possible dependence on the lipophilicity. Similar such reports are cited in literature[9,10].

RESULTS AND DISCUSSION

The present study is a statistical approach to derive a model molecule with respect to its substituents having greater stability, lesser strain and suitable biological activities.

Keeping in view a detailed structure properties analysis of few **5a**, **5b** position substituted 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**-disubstituents 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.

Fig. 1A record the variations 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 records the variation in the molar volume. The figures have been drawn to show that the different **5a**, **5b** substituted derivatives have specific effect on the physico-chemical properties and two compounds have shown similar values for any of the parameters. It is agreement that the structural feature is of greater importance in the case of present series of barbiturates.

The present work is a step ahead of Hansch hypothesis where the concentration dependence of drug activity has been examined[11] using log P (hydrophobicity/lipophilicity) of the substituted molecules with the drug activity. The present work, however, aims at stating the variation in molecular dynamics, dipole moments, the molar volume (parachore) and the van derWall interactions due to different substitutions at 5a, 5b- position of barbiturate derivatives.

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

Comp. No.	Name	R_{5a}	R_{5b}	E_{MM}	Dip moment	VDW	Molar volume	log P
I	Malonyglurea pyrimidinetrione (Barbiturate I)	H	H	119.644	1.816	14.580	131	1.35
II A	5-Allyl-barbituric acid	C_3H_5	H	383.235	1.300	77.382	198	–
II B	5-(1-methylbutyl) barbituric acid	H	C_5H_{11}	643.603	0.449	91.024	261	–
II AB	5-Allyl-5-5(-1methylbutyl) barbituric acid (Seconal II)	C_3H_5	C_5H_{11}	1422.949	4.672	305.427	312	2.15
III A	5-(-2 Bromoallyl) barbituric acid	C_3H_4Br	H	441.669	1.422	87.093	222	–
III B	5-(1-methyl butyl) barbituric acid	H	C_5H_{11}	643.606	0.449	91.024	261	–
III AB	5-(-2 Bromoallyl)-5-(1-methyl butyl) barbituric acid (Sigmodal III)	C_3H_4Br	C_5H_{11}	1417.842	4.539	310.412	336	2.15
IV A	5-Ethyl- barbituric acid	C_2H_5	H	421.197	1.565	61.606	180	–
IV B	5-(1-methyl butyl) barbituric acid	H	C_5H_{11}	643.606	0.449	91.024	261	–
IV AB	5-Ethyl-5-(1-methyl butyl) barbituric acid (Nembutal IV)	C_2H_5	C_5H_{11}	1420.723	4.629	290.310	301	1.95
V A	5-Methyl barbituric acid	CH_3	H	217.757	1.550	33.809	157	–
V B	5-Phenyl barbituric acid	H	C_6H_5	321.095	1.269	60.013	235	–
V AB	5-Methyl-5-phenyl barbituric acid (Rutonal V)	CH_3	C_6H_5	438.985	1.871	90.370	256	1.42
VI A	5-Furfuryl barbituric acid	C_4H_8O	H	173.575	1.692	31.889	207	–
VI B	5-Isopropyl barbituric acid	H	$CH(CH_3)_2$	439.082	0.461	58.944	206	–
VI AB	5-Furfuryl-5-isopropyl barbituric acid (Darmavit VI)	C_4H_8O	$CH(CH_3)_2$	2670.258	2.166	566.520	254	1.61
VII A	5-Propyl barbituric acid	C_3H_7	H	560.982	1.591	93.582	210	–
VII B	5-Propyl barbituric acid	H	C_3H_7	560.982	1.591	93.582	210	–
VII AB	5-,5-Dipropyl barbituric acid (Proponal VII)	C_3H_7	C_3H_7	1353.447	4.241	233.811	228	1.62

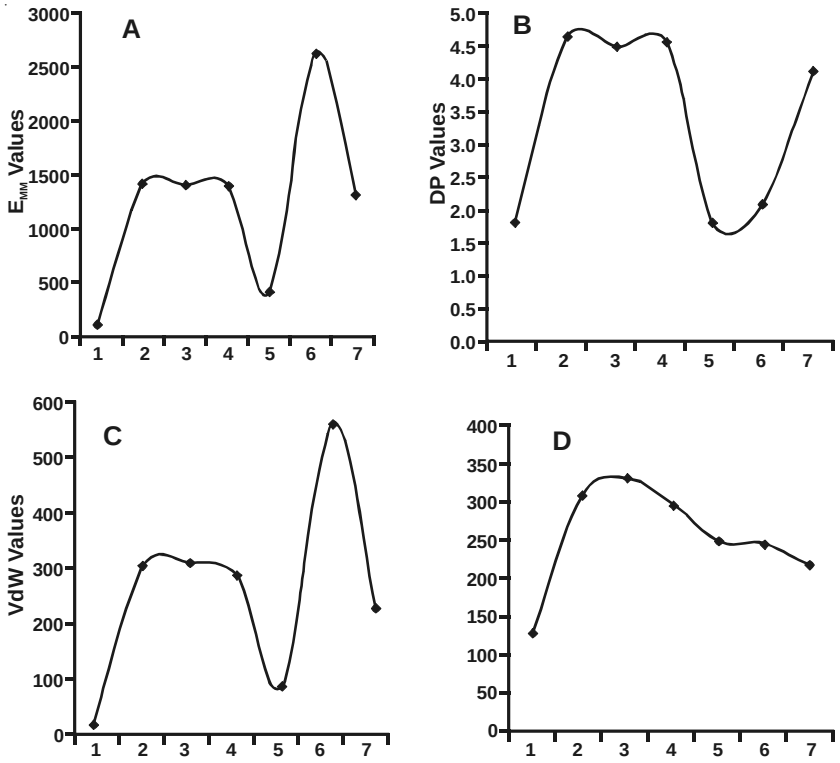


Fig. 1. Variation in the physico-chemical properties of **5a**, **5b** substituted derivatives of barbituric acid (A) E_{MM} (B) Dipole moment (C) van derWaals force and (D) Molar volume

log P is the lipophilicity[12] value (partition coefficient) for the barbituric acid derivatives obtained for the octanol water system. This lipophilicity of the compound is mainly responsible for the solubility of the drug molecule in the biological system. It may be stated that the physiological action of the drug is directly related to this lipophilicity value.

In the case of barbituric acid the lipophilicity for the compounds have been observed to be.

al - ak >	ak - ak ≥	ak - ak ≥	ak - ar >	H - H	with respect to substitution
VI	III	II	IV	I	with respect to compounds
2.15	1.95	1.62	1.42	1.35	with respect to log P values

Once again the H-H substituted molecules have shown a greater water solubility than the allyl-alkyl (al-ak) substitution[6].

To observe the overall suceptibility of the **5b**- with respect to **5a** some sequences has been observed keeping **5a** position constant.

H - H > H - ar > H - ak

The observed sequence, with respect to al, ak and ar groups at **5a** position keeping substitute at **5b** as constant is

Ar - H > Al - H > ak - H

Where as making substitutions in both **5a** and **5b** the observed sequence is

Al - ak > al - Al > Ar - Ak

An advanced explanation based on the Mopac (-Vector AM1/PM_3 calculations) - obtained for the compounds in being attempted.

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