A New Series of *N*-(3-phenyl-1,2,4-oxadiazol-5-yl)-alkylphthalimides. I.

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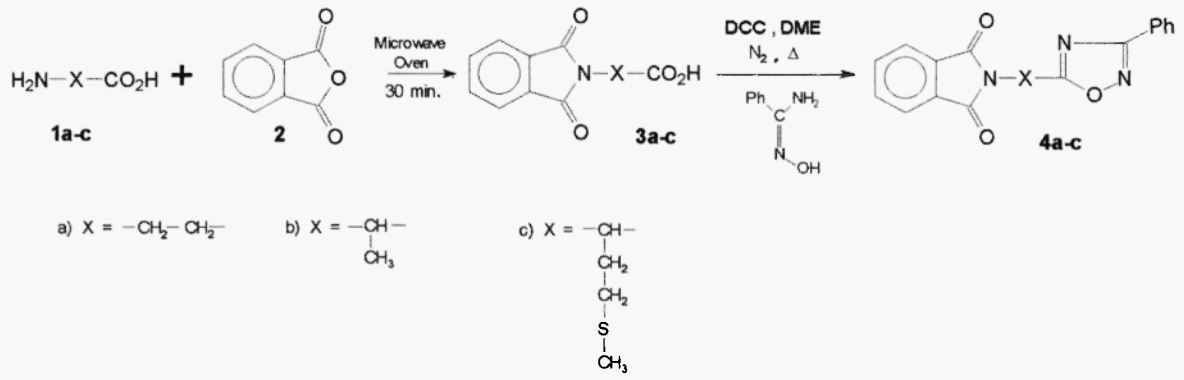
Abstract : Microwave induced reaction between aminoacids **1a-c** and phthalic anhydride **2** gave *N*-substituted phthalimide acids, **3a-c**.The condensation of the latter with benzamidoxime furnished oxadiazoles 4**a-c.** M.O. calculations of **4a-c** using semi-empirical AM1 method provided electronic parameters and other details.

INTRODUCTION. The biological activity of 3,5-disubstituted 1,2,4-oxadiazoles are well known (1). For example, they are anti-inflammatory (2), antiviral (3), fungicide (4) and herbicide (5). On the other hand, phthalimide derivatives possess antitumor (6), hipolipidemic (7-9) and antiviral (10) activities. Because of the importance of two functions, *viz.*, oxadiazole and phthalimide, we decided to synthesize phthalimide derivatives having 1,2,4-oxadiazol-5-yl alkyl group attached to nitrogen. The objective was to evaluate their pharmacological activities. To our knowledge, the literature does not record any such compound. This is for the first time we describe the synthesis and semiemperical molecular orbital calculations of the type AM1 of compounds **4a-c** (**scheme**).

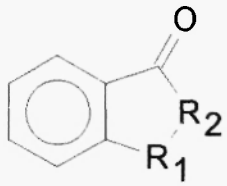


Scheme

SYNTHESIS. Phthalimide acids **3a-c** were obtained by heating phthalic anhydride **2** (7mmol) with appropriate amino acids **1a-c** (7mmol) using a domestic microwave oven. The yields were approximately 60% .These acids were prepared earlier by Billman and Harting (11). For synthesizing 3**b** and **3c,** DL-alanine and DL-methionine were employed. Treatment of acids **3a-c** (9.3mmol) with DCC (7.4mmol) in DME and benzamidoxime (9.3mmol) followed by heating gave oxadiazoles **4a-c** (12) in about 51% yield. The structures of these compounds were verified by infrared and ^{1}H-NMR spectra.

AM1 CALCULATIONS. Theoretical work on phathalimide and related compounds (Table I) were performed and correlated with hypolipidemic activity using LUMO energies and carbonyl group polarity by Ramos and Neto (13). These authors found a good correlation between experimental and theoretical work. These compounds have the ability to reduce triglyceride and cholesterol levels of serum in rats when a dose of 20 mg/kg/day is applied intraperitoneally. They found that a good correlation exists between the hypolipidemic activity and the two electronics parameters mentioned above. Other parameters were also obtained .

TABLE I - Phthalimide and related compounds (**7-9**).



compound	R_1	R_2	compound	R_1	R_2
I	CO	NH	V	CO	$CHCH_2CH_3$
II	CH_2	NH	VI	CO	CH_2
III	C=NH	NH	VII	C=NH	NCH_3
IV	NH	NH	VIII	CO	$CHCH_3$

We selected frontier orbital energies, dipole moments, heats of formation and total energy of the carbonyl group from the work of the previous authors (13). The comparative values of our work and those of the reported ones (13) are given in Table II. It is obvious that the E_{LUMO} values of our compounds are lower (-1.161 to -1.267 eV) compared to Ramos and Neto (13) (-1.128 to -0.345 eV). Further, the total charge on carbonyl groups is higher for our compounds (0.074 to 0.084 e.u.) than those reported earlier (0.011 to 0.065 e.u.). These observations suggest a better activity of compounds **4a-c**. With these results, we are optimist that the present phthalimides are potential candidates for testing the hypolipidemic activity.

TABLE II - Comparison of electronic parameters of **4a-c** with **I-VIII**.

Compound	ε_{LUMO} (eV)	ε_{HOMO} (eV)	$q_{C=O}$ (e.u.)	μ (D)	ΔH_f^o (Kcal)
4a	-1.161	-9.401	0.074	4.418	57.8
4b	-1.209	-9.437	0.083	3.129	62.6
4c	-1.267	-8.592	0.084	4.330	59.7
I	-1.128	-10.481	0.065	3.347	-26.1
II	-0.345	-9.727	0.014	3.854	5.4
III	-0.823	-9.998	0.049	1.755	26.9
IV	-0.589	-9.427	0.025	3.494	37.7
V	-0.911	-10.273	0.016	2.237	-12.9
VI	-0.983	-10.334	0.011	2.596	-34.6
VII	-0.789	-9.854	0.051	1.428	30.9
VIII	-0.921	-10.286	0.017	2.249	-13.2

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