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TETRAZINES AS POSSIBLE ANTIPARKINSONISM COMPOUNDS

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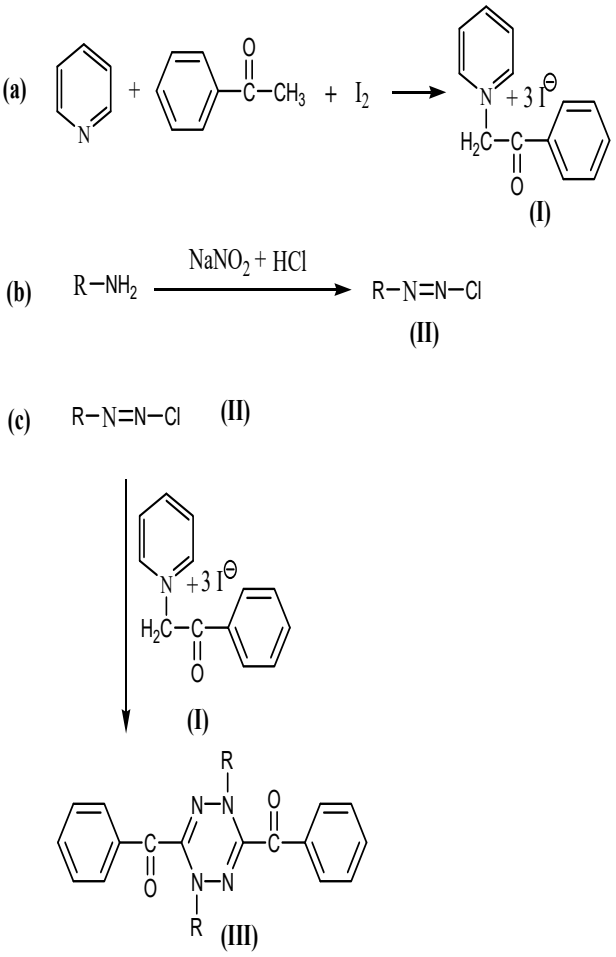
***Abstract*— Heating a mixture of pyridine, redistilled acetophenone and iodine yielded N-acetophenone pyridinium iodide (I) in excellent yield. Reaction of (I) with diazonium salts (II) in absolute ethanol afforded tetrazines (III) in the yields ranging from 35 to 45%. The target candidate molecules (III) were screened for their antiparkinsonism activity against oxotremorine induced tremor in albino mice of either sex. (Scheme)**



SCHEME

***Index Terms*— TETRAZINES, ANTIPARKINSONISM COMPOUNDS, Diazonium Salt.**

I. INTRODUCTION

Tetrazines have been less extensively studied against parkinsonism, however, there are some scattered reports which indicate the possibility of such compounds to be useful in this health area[1,2]. Triazines and tetrazines with suitable substituents viz; piperazine and quinazoline are very much beneficial in the treatment of tremors the main symptom of parkinsonism in man. The recommended doses are 25-50 mg or 25-100mg three times daily orally for adults. The antitremor actions of these drugs is ascribed to their oxotremolytic properties. Thus triazines and tetrazines markedly inhibit oxotremorine and clonidine induced tremors in rabbits, and parkinsonian tremors in human subjects[3]. This gave an impetus to the authors to undertake the synthesis of some 1,4-dihydro-1,2,4,5-tetrazines having thiadazole and quinazolone moieties with the expectation of getting more potent and therapeutically useful antiparkinsonian agents.

II. EXPERIMENTAL

N- Acetophenone pyridinium iodide (I)
The method followed by Gupta and Ojha[4] was followed.

1-Aryl-3-amino-6,8-dibromo/8-iodo-quinazolin(3H)4-ones
The procedure described by Filton and Smalley[5] was adopted.

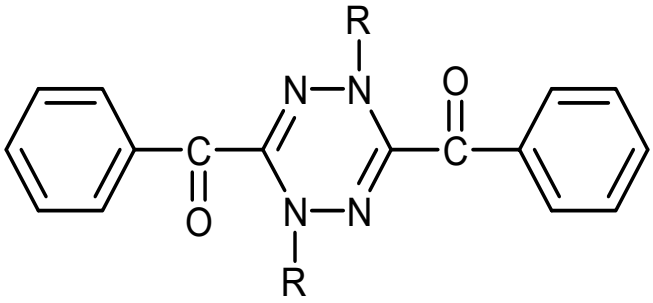
7-Amino-5-alkyl-1,3,4-thiadiazoles
The method of Funatsukuri and Cleda[6] was employed[7].

3,6-Dibenzoyl-1,4-di[7'-(5'-alkyl-1'3'4'-thiadiazolyl-2-phenyl-6,8-dibromo-4-oxo-quinazolinyl/2-phenyl-8-iodo-4-oxoquinazolinyl)]-1,4-dihydro-1,2,4-tetrazines (III)

A solution of sodium acetate (1.0g. in 25 ml of water) was added to the solution of N-acetophenone pyridinium iodide (0.01 mole in 100ml of ethanol). The mixture was cooled at 00C and stirred vigorously for 30 minutes. The dissolution of amino compounds was carried out separately. On complete dissolution a reddish yellow precipitate separated out and this diazotized material was added to the solution of N-acetophenone pyridinium iodide. The resultant reaction mixture was vigorously stirred mechanically for 1 hour and

subsequently kept in an ice-chest overnight. It was filtered off and washed repeatedly several times with cold water in order to remove adhered inorganic materials dried in vacuo. The tetrazines thus obtained, were recrystallized from methanol. The compounds of this category are listed in TABLE-I along with their characterization data.

TABLE-I



Characterization data of 3,6-Dibenzoyl-1,4-di[2'-(5'-alkyl-1'3'4'-thiadiazolyl-2-phenyl-6,8-dibromo-4-oxo-quinazolinyl/2-phenyl-8-iodo-4-oxoquinazolinyl)]-1,4-dihydro-1,2,4-tetrazines

Compd No.	R	m.p. (^{0}C)	yield	Molecular formula	Analysis Nitrogen %	
					Calcd.	found
1	5-propyl-1',3',4'-thiadiazolyl	180	40	$C_{26}H_{24}N_8O_2S_2$	20.58	20.24
2	5-butyl-1',3'4'-thiadiazolyl	200	35	$C_{28}H_{28}N_8O_2S_2$	19.58	19.44
3	2-phenyl-6,8-dibromo-4-oxo-quinazolinyl	210	35	$C_{44}H_{24}N_8O_4Br_2$	12.61	12.39
4	2-phenyl-8-iodo-4-oxo-quinazolinyl	215	37	$C_{44}H_{26}N_8O_4I_2$	12.39	12.35

The IR spectra of the above compounds exhibited characteristic bands in the region 1680±10 cm^{-1}, attributable to the —C(=O)— group.

III. ANTI OXOTREMORINE ACTIVITY

All the four compounds were screened for their antioxotremorine activity in albino mice of either sex weighing 20-25gms each.

METHOD[6,7]

The compounds under investigation were macerated with an equal quantity of gum acasia and suspended in distilled water. The animals were divided into groups. Each group consisted of two mice. After one hour of the administration of test compounds intraperitoneally, oxotremorine (which is the biological metabolite of tremorine and has been found several times more active and is a better choice as a tremorigenic agent because it eliminates the possibility that protective activity could be due to blockade of the metabolism of the parent substance) was injected to the mice. The maximum dose of oxotremorine to be injected was 5mg/kg., intraperitoneally. This dose of oxotremorine has been shown to produce tremors and salivation in untreated animals. Animals were examined ten minutes after oxotremorine injection for the occurrence of tremor and salivation. The animals were placed on their backs and hind limbs were observed for the presence or absence of tremors that occurred before whole body tremors became apparent. No attempt was made to grade their severity. Any dampness of the lips was taken to indicate the presence of salivation in the animals treated with oxotremorine.

IV. RESULT AND DISCUSSION

None of the four tetrazines evaluated for their antioxotremorine activity in the albino mice of either sex was found to exhibit any measurable degree of activity.

V. ACKNOWLEDGMENT

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