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SYNTHESIS AND SPECTRAL STUDIES OF NITROSOUREA DERIVATIVES OF 3-METHYL– 5/7-DICHLORO-4H-1,4-BENZOTHIAZINES AS POSSIBLE BIFUNCTIONAL ANTICANCER AGENTS

Rajni Gupta* and Archana Gupta

**Department of Chemistry, University of Rajasthan, Jaipur-302004, India*
Email: rajni187@yahoo.co.in

Department of Chemistry, University of Delhi, Delhi-110007, India
Email: gupta_archana18@yahoo.com

Abstract: The synthesis of of 3-methyl-5,7- dichloro-4- (N-propyl-N-nitrosoamido)- 2-substituted -4H-1,4-Benzothiazines by the isocyanation and successive nitrosation of 3-methyl -5,7- dichloro- 2-substituted -4H-1,4-Benzothiazines has been reported. The synthesized compounds have been characterized by their elemental analyses and spectral characteristics.

Introduction:

Analogous to phenothiazines, benzothiazines possesss a wide spectrum of biological activities[1]. Their several derivatives are in clinical use[2-7]. They exhibit significant anticancer activities[1], which are assigned due to their interaction with DNA by complexation.

Nitrosourea derivatives constitute an important class of anticancer agents and its several derivatives like MNNG, CNU, MNU, GANU, and CDL-7 etc. are clinically significant. They interact with DNA via alkylation [8-9]. However their clinical use is limited because of cumulative and delayed side effects exerted by these compounds. Bone marrow toxicity being dose limiting, therefore it is worthwhile to develop a new series of nitrosoureas with minimum toxicity and side effects. 4H-1, 4- Benzothiazines are much less toxic and therefore it is anticipated that their nitrosourea derivatives will be potent anticancer agents with minimum toxicity, side effects etc.

In 3-methyl-5,7-dichloro-2 substituted-4- (N-propyl-N-nitrosoamido) - 4H-1,4-Benzothiazines heterocyclic nitrogen with a side chain at 4-position constitutes N-nitrosourea linkage and possess both 1,4-benzothiazines nucleus and a nitrosourea moiety . They would show two fold interaction with DNA via complexation[10] as well as alkylation and will constitute bifunctional anticancer agents.

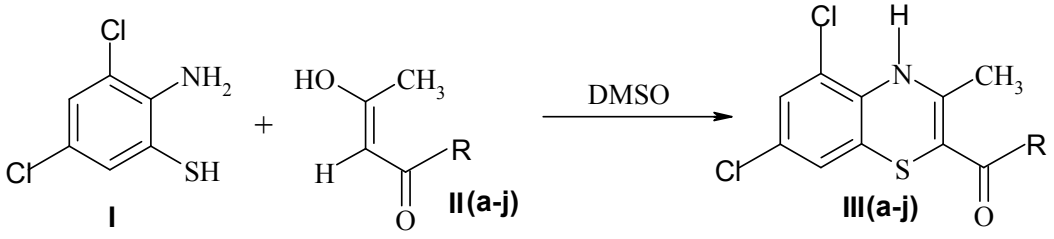
Experimental:

Melting points of the synthesized compounds were determined on an electric melting point apparatus and are uncorrected. IR spectra were recorded in KBr on SHIMADZU 8400S FT IR spectrophotometer. The ^{1}HNMR spectra were recorded on a model Bruker-DRX-300 NMR

spectrometer at 300 MH_Z respectively using $CDCl_3$ as a solvent and TMS as an internal standard. The Mass spectrum of the representative compound was recorded on JEOL-SX-102/DA-6000 mass spectrometer.

(i)Preparation of 3-methyl -5, 7-dichloro-2-substituted-4H-1,4-Benzothiazines (III a-j)

To the stirred suspension of substituted diketones II (10mmoles) in DMSO (5ml) was added 3,5-dichloro-2-amino benzenethiol I (10mmoles) and mixture was refluxed for 30-40mins.The reaction mixture was concentrated and cooled down to room temperature. The solid separated out was filtered, washed with petroleum ether and crystallized from methanol (Scheme- 1).

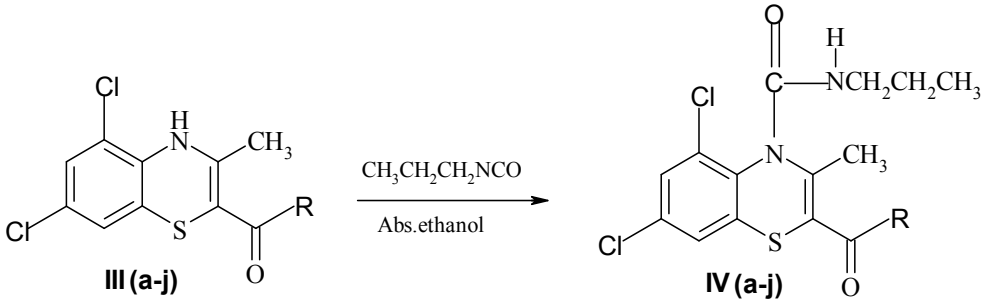


R=CH_3, OCH_3, OC_2H_5, $C_6H_4Cl(p)$, $C_6H_4Br(p)$, $C_6H_4F(p)$,
$C_6H_4CH_3(p)$, $C_6H_4OCH_3(p)$, $C_6H_4OCH_3(m)$, $C_6H_3OCH_3(m,p)$

Scheme-1

(ii) Preparation of 3-methyl-5,7-dichloro-2-substituted–4-(N-propylamido)-1,4-benzothiazines (IVa-j)

A mixture of 3-methyl-5,7-dichloro-2-substituted-4H-1,4-Benzothiazines III (10 mmoles),10 ml of absolute alcohol and propyl isocyanate (10mmoles) was refluxed on hot plate for 2 hrs .Then the solvent was removed under vacuum rotatory evaporator The product 3-methyl-5,7-dichloro-2-substitted–4-(N-propyl amido)-1,4-benzothiazines was crystallised from ethanol (Scheme 2).



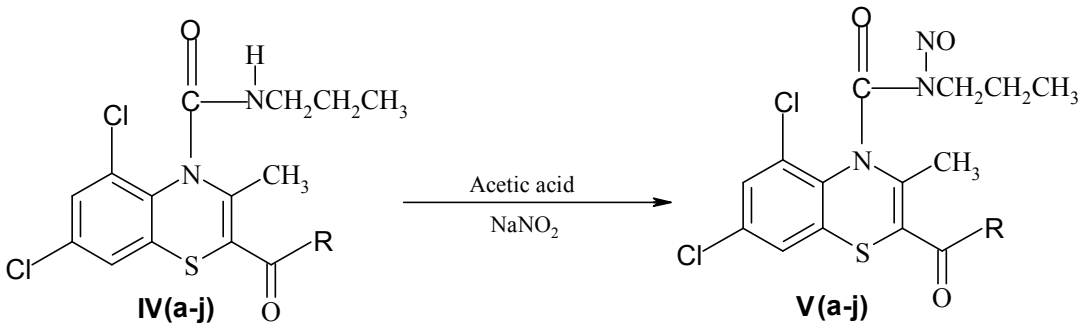
R=CH_3, OCH_3, OC_2H_5, $C_6H_4Cl(p)$, $C_6H_4Br(p)$, $C_6H_4F(p)$,
$C_6H_4CH_3(p)$, $C_6H_4OCH_3(p)$, $C_6H_4OCH_3(m)$, $C_6H_3OCH_3(m,p)$

Scheme-2

(iii) Preparation of 3-methyl-5,7-dichloro-4-(N-propyl-N-nitrosoamido)-2-sbstitted-4H-1,4-Benzothiazines (Va-j)

3-Methyl-5,7-dichloro-2-substituted–4-(N-propylamido)-1,4-benzothiazines IV (3mmoles) was dissolved in 50 ml of acetic acid, sodium nitrite (5mmoles) was added portion wise with stirring. The mixture was stirred for 30mins at room temperature and for one hour at 50^0 C. Acetic acid

was evaporated under reduced pressure in vacuum rotatory evaporator. The residue was treated with water. The resulting precipitate of 3-methyl-5,7-dichloro-4-(N-propyl-N-nitrosoamido)-2-substituted-4H-1,4-Benzothiazines was collected and crystallized from methanol. (Scheme 3)



R=CH_3, OCH_3, OC_2H_5, $C_6H_4Cl(p)$, $C_6H_4Br(p)$, $C_6H_4F(p)$, $C_6H_4CH_3(p)$, $C_6H_4OCH_3(p)$, $C_6H_4OCH_3(m)$, $C_6H_3OCH_3(m,p)$

Scheme-3

Table 1: Physical data of 3-methyl-5, 7-dichloro-4-(N-propyl-N-nitrosoamido)-2-substituted-4H-1, 4-Benzothiazines

Compound	Molecular formula	M.P ^0C	Yield %	% C (Found) (Calc.)	H (Found) (Calc.)	N (Found) (Calc.)
A	$C_{15}H_{15}N_3Cl_2O_3S$	179	51	(46.00) (46.40)	(4.00) (3.89)	(10.75) (10.82)
B	$C_{15}H_{15}N_3Cl_2O_4S$	170	56	(44.45) (46.56)	(3.28) (3.74)	(10.50) (10.39)
C	$C_{16}H_{17}N_3Cl_2O_4S$	165	60	(45.32) (45.94)	(4.12) (4.10)	(9.95) (10.05)
D	$C_{20}H_{16}N_3Cl_3O_3S$	170	50	(49.45) (49.55)	(3.28) (3.33)	(8.50) (8.67)
E	$C_{20}H_{16}N_3Cl_2BrO_3S$	172	58	(45.51) (45.39)	(2.99) (3.05)	(7.95) (7.94)
F	$C_{20}H_{16}N_3Cl_2FO_3S$	163	55	(51.20) (51.29)	(3.41) (3.44)	(8.87) (8.97)
G	$C_{21}H_{19}N_3Cl_2O_3S$	181	61	(54.23) (54.32)	(4.22) (4.12)	(8.85) (9.05)
H	$C_{21}H_{19}N_3Cl_2O_4S$	169	55	(51.99) (52.51)	(4.05) (3.99)	(9.01) (8.75)
I	$C_{21}H_{19}N_3Cl_2O_4S$	173	57	(52.04) (52.51)	(4.00) (3.99)	(8.88) (8.75)
J	$C_{22}H_{21}N_3Cl_2O_5S$	177	58	(51.59) (51.77)	(4.02) (4.15)	(8.15) (8.23)

Table 2: Infra red spectral data of 3-methyl-5,7-dichloro-4-(N-propyl-N-nitrosoamido)-2-substituted -4H-1,4-Benzothiazines

Compound	Molecular formula	C=O (cm^{-1})	C-Cl (cm^{-1})
A	$C_{15}H_{15}N_3Cl_2O_3S$	1585, 1665	780
B	$C_{15}H_{15}N_3Cl_2O_4S$	1605,1665	785
C	$C_{16}H_{17}N_3Cl_2O_4S$	1595, 1675	782
D	$C_{20}H_{16}N_3Cl_3O_3S$	1600,1695	790
E	$C_{20}H_{16}N_3Cl_2BrO_3S$	1600,1700	804
F	$C_{20}H_{16}N_3Cl_2FO_3S$	1610,1695	800
G	$C_{21}H_{19}N_3Cl_2O_3S$	1605,1690	799
H	$C_{21}H_{19}N_3Cl_2O_4S$	1600,1695	790
I	$C_{21}H_{19}N_3Cl_2O_4S$	1585, 1697	790
J	$C_{22}H_{21}N_3Cl_2O_5S$	1815,1700	775

Table 3: NMR Spectral data of 3-methyl-5,7-dichloro-4-(N-propyl-N-nitrosoamido)-2-substituted-4H-1,4-Benzothiazines

S.No	Molecular formula	Solvent	δ(ppm)	Hydrogen	Multiplicity	Assignment
A	$C_{15}H_{15}N_3Cl_2O_3S$	$CDCl_3$	7.04-7.05	2	Doublet	Aromatic protons
			1.71	3	Singlet	CH_3 protons at C_3
			0.94 –0.98	3	Triplet	CH_3 protons at C'_1 of propyl group
			1.57-1.60	2	Multiplet	CH_2 protons at C'_2 of propyl group
			3.14--3.19	2	Triplet	CH_2 protons at C'_3 of propyl group
			2.30	3	Singlet	CH_3 protons at C_2 $COCH_3$ group
B	$C_{15}H_{15}N_3Cl_2O_4S$	$CDCl_3$	7.04-7.05	2	Doublet	Aromatic protons
			1.73	3	Singlet	CH_3 protons at C_3
			0.96 –0.98	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.54-1.63	2	Multiplet	CH_2 protons at C'_2 of propyl group
			3.16--3.19	3	Triplet	CH_3 protons at C'_3 of propyl group
			3.76	3	Singlet	CH_3 protons at C_2 Of $COOCH_3$ group
C	$C_{16}H_{17}N_3Cl_2O_4S$	$CDCl_3$	7.04-7.05	2	Doublet	Aromatic protons
			1.72	3	Singlet	CH_3 protons at C_3
			0.95 –0.98	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.55-1.63	2	Multiplet	CH_2 protons at C'_2 of propyl group
			3.18--3.22	3	Triplet	CH_3 protons at C'_3 of propyl group
			1.32-1.35	3	Triplet	CH_3 protons at C_2 Of $COOC_2H_5$group
			4.15-4.22	2	Quartet	CH_2 protons at C2 Of $COOC_2H_5$group
D	$C_{20}H_{16}N_3Cl_3O_3S$	$CDCl_3$	7.46-7.75	6	Multiplet	Aromatic protons
			0.95 –0.97	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.59-1.63	2	Multiplet	CH_2 protons at C'_2 of propyl group
			3.16--3.20	3	Triplet	CH_3 protons at C'_3 of propyl group
			1.67	3	Singlet	CH_3 protons at C_3

						Of $COCH_3$ group
E	$C_{20}H_{16}N_3Cl_2BrO_3S$	$CDCl_3$	7.62-7.70	6	Multiplet	Aromatic protons
			0.98 –1.00	2	Triplet	CH_2 protons at C′$_1$ of propyl group
			1.69-1.74	2	Multiplet	CH_2 protons at C′$_2$ of propyl group
			3.26--3.30	3	Triplet	CH_3 protons at C′$_3$ of propyl grouP
			1.76	3	Singlet	CH_3 protons at C_3 Of $COCH_3$ group
F	$C_{20}H_{16}N_3Cl_2FO_3S$	$CDCl_3$	7.16-7.79	6	Multiplet	Aromatic protons
			0.9 –1.00	2	Triplet	CH_2 protons at C′$_1$ of propyl group
			1.62-1.77	2	Multiplet	CH_2 protons at C′$_2$ of propyl group
			3.22--3.30	3	Triplet	CH_3 protons at C′$_3$ of propyl group
			1.61	3	Singlet	CH_3 protons at C_3 Of $COCH_3$ group
G	$C_{21}H_{19}N_3Cl_2O_3S$	$CDCl_3$	7.25-7.69	6	Multiplet	Aromatic protons
			082 –0.90	2	Triplet	CH_3 protons at C′1 of propyl group
			1.52-1.62	2	Multiplet	CH_2 protons at C′$_2$ of propyl group
			3.10--3.18	3	Triplet	CH_2 protons at C′3 of propyl group
			1.65	3	Singlet	CH_3 protons of C_3 Of $COCH_3$ group
			2.35	3	Singlet	CH_3 protons at para Position of $C_6H_4CH_3$ group
H	$C_{21}H_{19}N_3Cl_2O_4S$	$CDCl_3$	6.96-7.69	6	Multiplet	Aromatic protons
			088 –0.90	2	Triplet	CH_3 protons at C′1 of propyl group
			1.56-1.60	2	Multiplet	CH_2 protons at C′$_2$ of propyl group
			3.10--3.25	3	Triplet	CH_2 protons at C′3 of propyl group
			1.66	3	Singlet	CH_3 protons at C_3 Of $COCH_3$ group
			3.73	3	Singlet	OCH_3 protons at para Position of $C_6H_4OCH_3$
I	$C_{21}H_{19}N_3Cl_2O_4S$	$CDCl_3$	7.05-7.37	6	Multiplet	Aromatic protons
			082 –0.94	2	Triplet	CH_3 protons at C′1 of propyl group
			1.55-1.61	2	Multiplet	CH_2 protons at C′$_2$ of propyl group
			3.2--3.25	3	Triplet	

			1.76	3	Singlet	CH_2 protons at C′3 of propyl group
			3.93	3	Singlet	CH_3 protons at C_3 Of $COCH_3$ group
						OCH_3 protons at para Position of $C_6H_4OCH_3$ group
J	$C_{22}H_{21}N_3Cl_2O_5S$	$CDCl_3$	6.85-7.26	5	Multiplet	
			072 –0.80	2	Triplet	Aromatic protons
			1.51-1.61	2	Multiplet	CH_3 protons at C′1 of propyl group
			3.12--3.20	3	Triplet	CH_2 protons at C′$_2$ of propyl group
			1.70	3	Singlet	CH_2 protons at C′3 of propyl group
			3.73	6	Singlet	CH_3 protons at C_3 Of $COCH_3$ group
						OCH_3 protons at meta and para positions of $C_6H_3(OCH_3)_2$ group

Results and Discussion:

The synthesis of 3-methyl-5,7-dichloro-4-(N-propyl-N-nitrosoamido)- -substituted-4H-1,4-benzothiazines is based on the synthesis of substituted 3-methyl-5,7-dichloro- 2- substitted -4H-1,4-Benzothiazines reported elsewhere[1]. 4H-1,4-Benzothiazines are analogs of phenothiazines and like phenothiazines they bear a fold along nitrogen and sulphur axis which is considered responsible to impart them biological activities. So it was considered worthwhile to incorporate the activities of benzothiazines and nitrosoureas into one molecule i.e nitrosourea derivatives of 3-methyl -5,7- dichloro- 2- substituted -4H-1,4-Benzothiazines. 4H-1,4-Benzothiazines are key compounds to synthesize the above mentioned compounds. Here the 4H-1,4-benzothiazines were allowed to undergo isocyanation at 4-position, thereby giving 3-methyl-5,7-dichloro- 2-substituted–4-(N-propyl amido)-1,4-benzothiazines. These were then let to undergo nitrosation with sodium nitrite in acetic acid.

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