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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2014, Vol. 30, No. (2):
Pg. 755-759

Synthesis of 5- [(1[1]substitutedphenothiazinoacetyl) semicarbazidothio-semicarbazido]-2- oxo/thiobarbiuric Acid as Anticonvulsant Agents

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http://dx.doi.org/10.13005/ojc/300248

(Received: March 02, 2014; Accepted: March 28, 2014)

ABSTRACT

2-Substitutedphenathiazine was prepared according to the reported method. Ethyl-substitutedphenothiazinoacetates(1a-1b) were prepared by the reaction of ethylchloroacetate in the presence of anhydrous K_2CO_3 2-amino-5-N[10]substitutedphenothiazinoacetyl)–semicarbazdes/ thiosemicarbazides (2a-2d) were synthesized by refluxing compound (1a-1b) with thiosemicarbazide/semicarbazide. Compounds (2a-2d) were then underwent mannich reaction to yield compounds 3a-3d. All the newly synthesized compounds (i.e. 2a-2d and 3a-3d) were evaluated for their anticonvulsant activity. Almost all the compounds have shown promising anticonvulsant activity. Compound 3d was the most potent compound of this series. The most potent compound was evaluated for its anticonvulsant activity and acute toxicity.

Key words: Substitutedphenothiazinoacetylsemicarbazides/thiosemicarbazides, substitutedphenothiazinoacetylsemicarbazido/thiosemicarbazido-2 oxo/thiobarbituric acids, anticonvulsant activity, acute toxicity.

INTRODUCTION

Research in the field of barbituric acid derivatives has yielded a number of clinically useful anticonvulsant drugs. 10H- Phenothiazine nucleus has gained prominance due to its diverse activities like-anticonvulsant,[1-6]antinflammatory[7]and cardiovascular[8]. The introduction of various heterocyclic / aliphatic moieties at 10- position of phenothiazine led to the discovery of promethazine [10-(2-methylaminopropyl) phenothiazine hydrochloride]. Chlorpromazine[2-chloro-10-3-(3-dimethylaminopropyl)phenothiazinehydrochloricle], which posses potent antihistamic and CNS depressant activities respectively. Researchers has revealed that various 5-substituted barbituric acid derivatives possess potent anticonvulsant activity[9-16]. In view of these observations, it was thought worthwhile to synthesize a new series of 5-substituted barbituric acid derivatives bearing phenothiazinyl moiety. All the newly synthesized compounds were evaluated for their anticonvulsant activity and acute toxicity studies.

Ethylsubstitutedphenothiazinoacetates (1a-1b) were prepared by reacting phenothiazine/ substitutedphenothiazine with ethylchloroacetate (in acetone) in the presence of small amount of

anhydrous K_2CO_3. Appearance of a quartet at d 4.25 due to 2-protons of $COOCH_2CH_3$ group and a triplet at d 1.40 due to 3-protons of $COOCH_2CH_3$ group in the ^1H NMR spectrum and a band at 2860 cm^{-1}due to CH_2, 3044 cm^{-1}(aromatic C-H), 2960 cm^{-1} (aliphatic C-H), 1742 cm^{-1}(C=O), 1560 cm^{-1} (C...C of aromatic ring), 1250 cm^{-1}(C-N) and 1140 cm^{-1} (C-S) group which were present in the IR spectrum of compound 1a proves the formation of compound 1 a. Compounds (1a-1b) were refluxed with thiosemicarbazide/semicarbazide to yield compounds (2a-2d). The IR spectrum of compound 2c showed additional peaks of 3340 cm^{-1} (due to NH NH_2), 1160 cm^{-1} (due to C=S) and 1670 cm^{-1} (due to CO of CO NH). Its ^1H NMR spectrum exhibited signals at d 7.72 (m, 4H, NHNH $CSNH_2$), which confirms the structure of compound 2c. Compounds (2a-2d) were then underwent mannich reaction to yield compounds 3a-3d. The formation of compound 3c is supported by the disappearance of a multiplet at d7.75 due to 4 protons of ($NHNHCSNH_2$) and appearance of a multiplied at 8.30 due to 3- protons of (NHNHCSNH), a single singlet at d 9.25 due to 1-proton of (NHCO), a singlet at d 2.95 due to the 1-proton of CH of barbituric acid and a doublet at 4.45 due to 2-protons of ($NHCH_2$) in the ^1H NMR spectrum. Its structure is further confirmed by the presence of bands at 1720, 1710, 1680 due to (C=O of barbituric acid, amidic CO).

Pharmacological activities

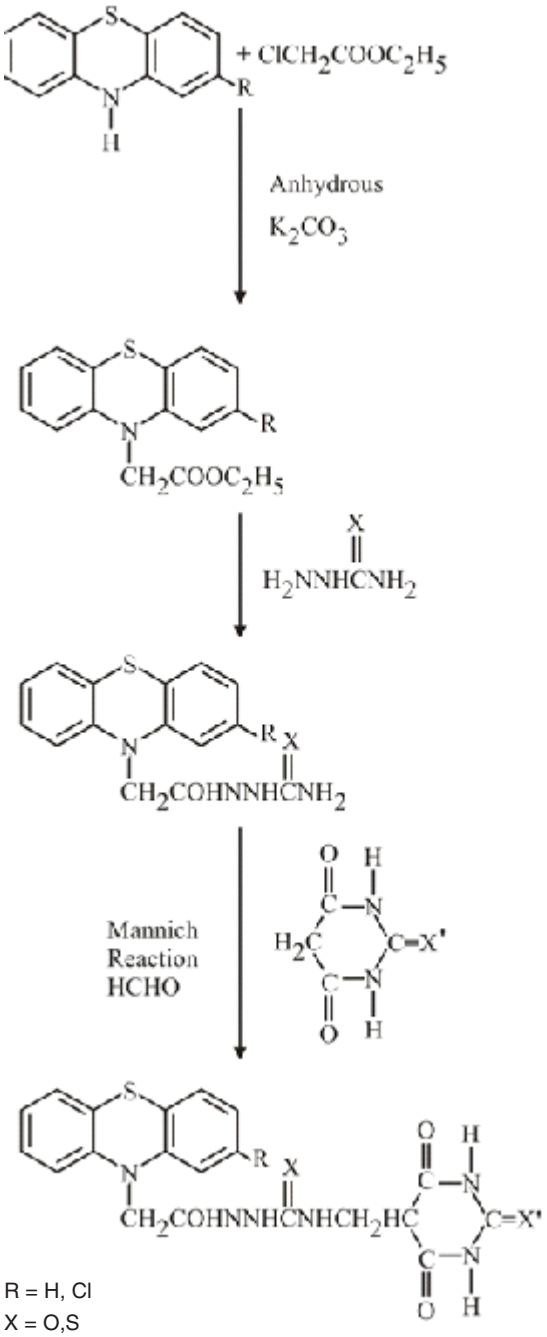
Anticonvulsant activity

Maximum electroshock seizure (MES) test

This test was performed according to the method of Tomanet. al[17] The group of ten rats was treated with test drugs (50 mg/kg i.p.) / phentoin sodium (30 mg/kg i.p.) after 1h they were subjected to the shock of 150 mA by convulsiometer through ear electrodes for 0.2s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

Pentylenetetrazole (PTZ) induced seizures Test

This test was performed by following the method of Fischer[18]. The rats were injected with pentylenetetrazol in dose of 70 mg /kg subcutaneously in scruff of neck. After 2-4 min. of PTZ injection animals developed sequence of excitement, myclonic jerks, clonic seizures, one or more maximum tonic seizures. Animals exhibiting these seizures patterns were selected.Standard drug used in this model was sodium valproate (80 mg/kg i.p.) and was injected 60 min prior to PTZ challenge. All the newly synthesized compounds



R = H, Cl
X = O,S
X' = O. S

Scheme 1

were studied for their anticonvulsant activity at a dose of 50 mg /kg i.p. in maximal electroshock and pentylenetetrazole induced seizures respectively. All the mewly synthesized compounds have shown anticonvulsant activity in both the models (ranging from 30 to 90% and 20 to 90% in MES and PTZ models, respectively). The anticonvulsant activity of all the compounds are reported in Table 2. Compound 3d was found to possess potent anticonvulsant activity it was studied three graded doses (17. 5, 25, and 50 mg/kg i.p.).

Acute toxicity study

ALD_{50}values of some promising compounds were determined by observing 50% mortality after 24 hr[19]. ALD^{50}value of most active compound i. e. 3d was > 2000 mg/kg p.o. (maximum dose tested).

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H, N, were within ±0.04% of the theoretical value. IR spectra (KBr) are recorded on BackmannAcculab - 10- spectrophotometer. ^{1}H NMR spectra were recorded by Bruker WM 400 FT instrument using $CDCl_3$as solvent and tetramethylsilance (TMS) as internal reference standard. All chemical shift (d) are in ppm. The purities of the compounds were checked by thin layer chromatography (TLC) on silicagel – G plates of 0.5 mm thickness. The elemental analysis of the compounds were performed on Heracus Carlo Erba 1108 analyser.

Preparation of ethylsubstitutedphenothiazino acetates (1a-1b)

A mixture of substitutedphenothiazine/ phenothiazine (0.01 mole), ethylchloroacetate(0.01 mole) and anhydrous K_2CO_3(8.0 gm) in acetone (90 ml) were refluxed for 24 hours. After refluxing, the excess of solvent was distilled off. The reaction mixture was cooled, filtered and washed with water and recrystallized from appropriate solvents (Table 1).

Preparation of 2-amino-5- (N^{10} – substituted phenothiazinoacetyl) semicarbazides/ thiosemi carbazides (2a-2d)

Compounds (1a-1b) (0.075 mole) and thiosemicarbazide / semicarbazide (0.075 mole)

Table 1: Physical and analytical data of compounds (1a-1b), (2a-2d), and (3a-3d)

S. No.	R.	X	X^1	M.P. °C	Yield %	Recrystallisation solvent	Molecular formula (Mol. Wt.)	Elemental analysis %					
								C		H		N	
								Calc.	Found	Calc.	Found	Calc.	Found
1a	H	-		203°C	80%	Methanol	$C_{16}H_{15}NO_2S$(285)	67.36	67.33	5.26	5.27	4.91	4.90
1b	Cl	-		210°C	70%	Methanol	$C_{16}H_{14}NO_2SCl$(319.5)	60.09	60.12	4.38	4.35	4.38	4.42
2a	H	O		130°C	75%	Ethanol/water	$C_{15}H_{14}N_4SO_2$(314)	57.32	57.36	4.45	4.42	17.83	17.87
2b	Cl	O		100°C	70%	Methanol/water	$C_{15}H_{13}N_4SO_2Cl$(348.5)	51.64	51.68	3.73	3.70	16.06	16.10
2c	H	S		161-162°C	70%	Ethanol/water	$C_{15}H_{14}N_4S_2O$(330)	54.54	54.58	4.24	4.22	16.96	16.93
2d	Cl	S		150°C	75%	Methanol/water	$C_{15}H_{13}N_4S_2OCl$(364.5)	49.38	49.36	3.56	3.54	15.36	15.33
3a	H	O		180°C	80%	Methanol/water	$C_{20}H_{18}N_6O_5S$(454)	52.86	52.84	3.96	3.92	18.50	18.54
3b	Cl	O		170°C	80%	Methanol/water	$C_{20}H_{17}N_6O_4S_2Cl$(504.5)	47.57	47.54	3.36	3.33	16.65	16.68
3c	H	S		190°C	70%	Methanol/water	$C_{20}H_{18}N_6O_4S_2$(470)	51.06	51.10	3.82	3.80	17.87	17.90
3d	Cl	S		175°C	75%	Methanol/water	$C_{20}H_{17}N_6O_3S_3Cl$(520.5)	46.10	46.08	3.26	3.29	16.13	16.17

Table 2: Pharmacological data of Compounds (2a-2d) and (3a-3d)

Comp.	R	X	Dose (mg/kg i.p.)	Anticonvulsant Activity		ALD_{50} (mg/kg i.p.)
				MES	PTZ	
2a	H	O	50	30	20	>1000
2b	Cl	O	50	40	30	>1000
2c	H	S	50	40	40	>1000
2d	Cl	S	50	50	40	>1000
3a	H	O	50	50	50	>1000
3b	Cl	O	50	60	60	>1000
3c	H	S	50	70	60	>1000
3d	Cl	S	50	90	90	>2000
			25	60	50	
			17.5	30	30	
Phenytoin sodium		30	80			
Sodium valproate		80		80		
Propylene glycol		50	0	0		

in methanol (dry 70 ml) were refluxed on a steam both for about 15 hrs. The excess of the solvent was distilled off and the viscous mass poured into ice – cold water, filtered and recrystallised from appropriate solvents (Table 1).

Preparation of 5- [(1^1 – N^{10}- substituted phenothiazinoacetyl) thiosemicarbazido / semicarbazido] -2- oxo/thiobarbituric acids (3a-3d)

Compounds (2a-2d) underwent mannich reaction to yield compounds (3a-3d). To a solution of oxo/thibarbituric acid (0.01 mole) in methanol (50-70 ml), formaldehyde (0.02 mole) and compounds (2a-2d) (0.02 mole) were added dropwise and the reaction mixture was refluxed for 4 hours. The excess of the solvent was distilled off and the solid thus obtained were washed with petrolem ether (40-60^{0}C) and recrystallised from appropriate solvents (Table 1).

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