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SYNTHESIS, CHARACTERIZATION OF 10H-PHENOTHIAZINE-1-CARBOXYLLIC ACID HYDRAZIDE DERIVATIVES

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ABSTRACT

Ten novel compounds have been synthesized containing Phenothiazine ring, Phenothiazine(I) was synthesized by reacting diphenylamine,sulfur,and iodine which subsequently reacted with Oxalyl Chloride and dichloromethane was heated under reflux for 6 hours on a Steam bath produces Oxo-Phenothiazine-10yl acetyl chloride(II). acetyl chloride(II) was further treated with Aluminium Chloride and it was heated under reflux for 24 hours on steam bath. Then produces Pyrido [3,2,1] Phenothiazine-1,3-dione[III]. Pyrido[3,2,1] Phenothiazine-1,3-dione[III] is treated with an aqueous solution of sodium hydroxide at room temperature for one hour and produces 10H-Phenothiazine-1-Carboxyllic acid methyl ester.then it is further treated with hydrazine hydrate form the 10H-Phenothiazine-1-Carboxyllic acid hydrazide[IV] treated with ethanol and dil HCl and different aldehyde(0.02) mole are refluxed under steam bath for 4-8 hours.A series of compound like 10H-Phenothiazine-1-Carboxyllic acid hydrazide derivatives were synthesized. The yield of novel compound was recorded 67-92%. All compounds were characterized on the basis of melting point, I.R spectra, N.M.R spectra and mass spectra to establish their molecular weight, formula.

INTRODUCTION

Phenothiazine also called dibenzothiazine or thiodiphenylamine is a yellow or green crystalline compound, which is soluble in hot acetic acid, benzene, and ether. It is obtained by fusing diphenylamine with sulfur. It is a benzo derivative of thiazine although thiazine itself is not used as a starting point in the manufacturing of this molecule. It is a three-ring structure compound in which two benzene rings are joined by a sulfur and nitrogen atom at nonadjacent positions.

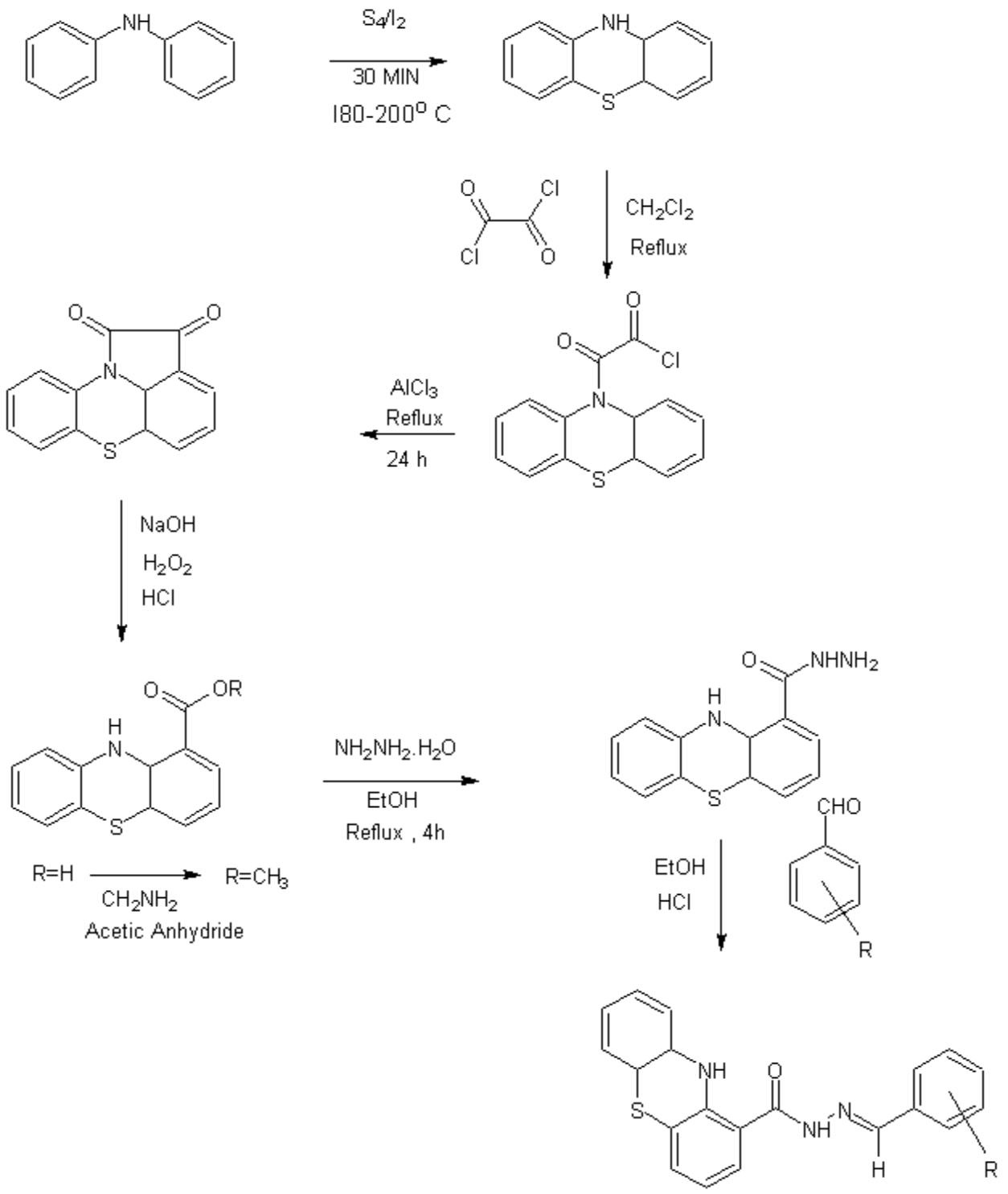
The term "phenothiazines" is used to describe the largest of the five main classes of neuroleptic antipsychotic drugs. These drugs have antipsychotic and, often, antiemetic properties, although they may also cause severe side effects such as akathisia, tardive dyskinesia, extrapyramidal symptoms, and the rare but potentially fatal neuroleptic malignant syndrome as well as substantial weight gain. The phenothiazine class of neuroleptic antipsychotic psychotropics are closely related to the thioxanthenes which are very similar pharmacologically.

There are three groups of phenothiazine antipsychotics, differing by their chemical structure and their pharmacological effects. They are the aliphatic compounds, the piperidines and piperazines. An aliphatic compound, piperidine or piperazine branch is added to the phenothiazine molecule for the purpose of enhancing absorption and bioavailability of the phenothiazine chemical[1].

Phenothiazines will intercalate between the bases of nucleotides of the major groove of DNA, and interfere with replication of DNA and RNA polymerase activity. Although it is doubtful that this mechanism plays any role in the in vitro bacteriostatic activity, substantially higher concentrations of the phenothiazines may be reached within lysosomes of macrophages that have phagocytosed the organism perhaps affording conditions that provide access to the DNA, and hence, result in the killing of the bacterium[2].

Scheme for Synthesis

SCHEME



Table

Physicochemical Data of 10H-Phenothiazine-1-Carboxyllic acid hydrazide Derivatives

Sr.No	Compound	R	M.P (°C)	Yield (%)	Molecular weight	Molecular formula
1.	VIa	H	202-204	87.2	347.43	$C_{20}H_{17}N_3OS$
2.	VIb	o-Cl	235-237	88.3	381.88	$C_{20}H_{16}ClN_3OS$
3.	VIc	p-Cl	248-250	90.2	381.88	$C_{20}H_{16}ClN_3OS$
4.	VId	o-OH	218-220	75.3	363.43	$C_{20}H_{17}N_3O_2S$
5.	VIe	p-OH	228-230	77.2	363.43	$C_{20}H_{17}N_3O_2S$
6.	VIf	o-NO_2	215-217	67.4	390.42	$C_{20}H_{16}N_4O_3S$
7.	VIg	o-OCH_3	252-254	68.4	377.46	$C_{21}H_{19}N_3O_2S$
8.	VIh	p-OCH_3	238-240	92.2	377.46	$C_{21}H_{19}N_3O_2S$
9.	VIi	o-OH	225-227	87.2	363.43	$C_{20}H_{17}N_3O_2S$
10.	VIj	o-OCH_3 p-OH	204-206	81.3	393.46	$C_{21}H_{19}N_3O_3S$

MATERIALS AND METHODS

Materials

2-chloro benzaldehyde (National chemical), 4-chloro benzaldehyde (Loba chemie) , 2-hydroxy benzaldehyde (Loba chemie), 4- hydroxy benzaldehyde (Merck) , 3- hydroxy benzaldehyde (Merck), 2-nitro benzaldehyde (Loba chemie), 2-methoxy benzaldehyde (National chemicals), 4-methoxy benzaldehyde (Merck), Diphenylamine (Merck,Iodine – Loba chemie), Benzaldehyde (Loba chemie), Pyridine (Loba chemie), o-phenylenediamine (Loba chemie) sulfur powder purified (Merck).

Synthesis of 10H-Phenothiazine-1-Carboxyllic acid hydrazide Derivatives.

All the melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked on silica gel plates by using appropriate solvents. The IR spectra (KBr) were recorded on a Shimadzu IR spectrophotometer.

^{1}H- NMR spectra were recorded on Bruker NMR spectrophotometer.

(AMX 400 MHz) using $CDCl_3$, DMSO as internal standard. The chemical shift values are expressed in δ ppm (parts per million). The MASS spectrum was recorded on Autospec Mass spectrometer.

General procedure ; A mixture 10H-Phenothiazine-1-Carboxyllic acid hydrazide with ethanol(50ml) and Dil Hydrochloric acid(10ml) and Different Aromatic aldehyde(0.02mole) are refluxed under Steam bath for 4-8 hours then cool the reaction mixture, dried in vaccum dessicator and recrystallised by different solvents. Then final derivative is obtained[3-10].

RESULT AND DISCUSSION

10H-Phenothiazine-1-Carboxylic acid N^{1-} benzalhydrazide (VIa)

The characteristic peaks in IR and NMR are as follows:

IR(KBr)- 611, 3115, 1649, 1111, 1325, 3321, 1371, 1649 cm^{-1}

^{1}HNMR($CDCl_3$)- 6.97(d, , 2H Phenothiazine), 6.70 (t, , 2H Phenothiazine), 6.60 (t, 2H Phenothiazine), 6.67 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.66 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.90 (d, 2H Methylene group),. 7.06-7.14(m,10HAromatic Benzene)

Mass – m\z 347.4

10H-Phenothiazine-1-Carboxylic acid N^{1-} (2-Chloro-benzyl)hydrazide (VI b)

The characteristic peaks in IR are as follows:

IR (KBr) - 671, 2954, 1762, 1178, 1298, 3354, 1413,1762,1035 cm^{-1}

^{1}HNMR($CDCl_3$)- 6.89(d, , 2H Phenothiazine), 6.74 (t, , 2H Phenothiazine), 6.64 (t, 2H Phenothiazine), 6.66 (d, 2H Phenothiazine), 6.89 (d, , 2H Phenothiazine), 7.68 (t, , 2H Phenothiazine), 8.11 (d, , 2H Proton of Sec.amine), 3.94 (d, 2H Methylene group),. 7.06-7.14(m,10HAromatic Benzene)

. **Mass** – m\z 381.8

10H-Phenothiazine-1-Carboxylic acid N^{1-} (4-Chloro-benzyl)hydrazide (VIc)

The characteristic peaks in IR are as follows:

IR (KBr)- 671, 2964, 1762, 1176, 1298, 3354, 1415,1762,1029 cm^{-1}

^{1}HNMR(DMSO)- 6.95(d, , 2H Phenothiazine), 6.75 (t, , 2H Phenothiazine), 6.68(t, 2H Phenothiazine), 6.66 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.65 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.95(d, 2H Methylene group),. 7.06-7.14(m,10HAromatic Benzene)

Mass – m\z 381.8

10H-Phenothiazine-1-Carboxylic acid N^{1-} (2-Hydroxy-benzyl)hydrazide (VId)

The characterstic peaks in IR are as follows:

IR(KBr)- 689, 3063, 1626, 1160, 1301, 3300, 1347, 1846,3500 cm^{-1}

^{1}HNMR(DMSO)- 6.99(d, , 2H Phenothiazine), 6.73(t, , 2H Phenothiazine), 6.65(t, 2H Phenothiazine), 6.69 (d, 2H Phenothiazine), 6.89 (d, , 2H Phenothiazine), 7.62 (t, , 2H Phenothiazine), 8.11 (d, , 2H Proton of Sec.amine), 3.96(d, 2H Methylene group),. 7.00-7.15(m,10HAromatic Benzene)

Mass – m\z 363.4

10H-Phenothiazine-1-Carboxylic acid N^{1-} (4- Hydroxy -benzyl)hydrazide (VIe)

The characteristic peaks in IR are as follows:

IR (KBr) - 690, 2989, 1746, 1181, 1301, 3300, 1346, 1746, 3500 cm^{-1}

^{1}HNMR(DMSO)-6.94(d,,2H Phenothiazine), 6.71 (t,,2H Phenothiazine),6.91 (t, 2H Phenothiazine),6.68 (d, 2H Phenothiazine), 6.91 (d,,2H Phenothiazine),7.66 (t, , 2H Phenothiazine),8.00(d,,2HProtonofSec.amine), 3.90 (d, 2H Methylene group),.5.00(s,,1H Proton of hydroxyl group) 6.61-6.90 (m,10HAromatic Benzene) **Mass** – m\z 363.4

10H-Phenothiazine-1-Carboxylic acid N^{1-} (2- Nitro-benzyl)hydrazide (VIf)

The characteristic peaks in IR are as follows:

IR (KBr)- 618, 3028, 1768, 1055, 1292, 3313, 1346, 1919,1583,1346 cm^{-1}

^{1}HNMR (DMSO)- 6.97(d, , 2H Phenothiazine), 6.70 (t, , 2H Phenothiazine), 6.60 (t, 2H Phenothiazine), 6.67 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.66 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.91 (d, 2H Methylene group),. 5.00(s, , 1H Proton of hydroxyl group) 6.61-6.89 (m,10HAromatic Benzene)

Mass – m\z 384.4

10H-Phenothiazine-1-Carboxylic acid N^{1-} (2- Methoxy -benzyl)hydrazide (VIg)

The characteristic peaks in IR are as follows:

IR (KBr)- 626, 3010, 1700, 1024, 1271, 3377, 1340, 1840,2900,1311,1109 cm^{-1}

^{1}HNMR(DMSO) - 6.99(d, , 2H Phenothiazine), 6.70 (t, , 2H Phenothiazine), 6.60 (t, 2H Phenothiazine), 6.67 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.66 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.90 (d, 2H Methylene group),. 7.32-8.07(m,10HAromatic Benzene)

Mass – m\z 368.4

10H-Phenothiazine-1-Carboxylic acid N^{1-} (4- Methoxy -benzyl)hydrazide (VIh)

Characteristic peaks in IR are as follows:

IR (KBr) - 700, 3000, 1625, 1033, 1271, 3300, 1388, 31900,2900,1313,1033 $cm^{-1\backslash}$

^{1}HNMR(DMSO)- 6.95(d, , 2H Phenothiazine), 6.73 (t, , 2H Phenothiazine), 6.65 (t, 2H Phenothiazine), 6.68 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.66 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.91 (d, 2H Methylene group),. 6.65-6.96 (m,10HAromatic Benzene) .

Mass – m\z 377.4

10H-Phenothiazine-1-Carboxylic acid N^{1-} (3-Hydroxy -benzyl)hyd (VIi)

The characteristic peaks in IR are as follows:

IR (KBr) - 700, 3026, 1695, 1016, 1237, 3300, 1346, 1695,3550 cm^{-1}

^{1}HNMR(DMSO)- 6.97(d, , 2H Phenothiazine), 6.70 (t, , 2H Phenothiazine), 6.60 (t, 2H Phenothiazine), 6.67 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.66 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.91 (d, 2H Methylene group), 5.00(s, , 1H Proton of hydroxyl group) 6.65-6.95 (m,10HAromatic Benzene)

Mass – m\z 363.4

10H-Phenothiazine-1-Carboxylic acid N[1-](4-Hydroxy -2- Methoxy benzyl)hydrazide (VIj)

The characteristic peaks in IR are as follows:

IR(KBr)- 600, 2976, 1741, 1371, 3489, 1371, 1982, 3554,2873,1236,1006 cm^{-1},

^{1}HNMR(DMSO)- 6.99(d, , 2H Phenothiazine), 6.75 (t, , 2H Phenothiazine), 6.68(t, 2H Phenothiazine), 6.67 (d, 2H Phenothiazine), 6.91 (d, , 2H Phenothiazine), 7.66 (t, , 2H Phenothiazine), 8.00 (d, , 2H Proton of Sec.amine), 3.90 (d, 2H Methylene group), 5.00(s, 1H Proton of hydroxyl group) 6.12-6.78(m,10HAromatic Benzene) .

Mass – m\z 363.4

CONCLUSION

Researchers from different parts of the world have reported such an activity in antihistamines, antipsychotic, anti-inflammatory agents, cardiovascular Drugs, antispasmodic drugs and even local anesthetics. Such compounds having antimicrobial properties in addition to their predesignated pharmacological actions have been christened 'non-antibiotics' some of these compounds have also been recognized for their anti tubercular activity. From all these studies, it is apparent that the phenothiazine and structurally related compounds possessing three benzene rings are often endowed with potent antimicrobial action. Compounds VIc, VIf, VIg shows good activity against *E.Coli* (gram negative) *B.subtilis*, *S.aureus*. compound VId, VIe shows moderate avtivity against *E.Coli*, *B.subtilis*, *S.aureus* . The structures of the synthesized compounds were characterized with the help of TLC, IR and NMR, Mass.

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