Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(5):262-266

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Preparation and biological evaluation of phenothiazine derivatives

B. Satyanarayana*, P. Muralikrishna, D. Ravi Kumar and D. Ramachandran

Department of Chemistry, Acharya Nagrjuna University, Guntur, (A.P), India

---

ABSTRACT

Preparation and biological evaluation of 7/8/9-Substituted - 10 – N-[(carboxymethyl)-sulfanylacetyl]-phenothiazine - 1 - carboxylic acids. 7/8/9-Substituted 10-N-[bis (2-chloroethyl/diethyl)-amino]-methylphenothiazine- 1-carboxylic acidshave been prepared by the reactionof different substituted phenothizines, dichloroethylamine, diethylamine, and formaldehyde in acidic medium.

Keywords: 7/8/9-Substituted-10-N-[(carboxymethyl)-sulfanylacetyl]-phenothiazine, acidic medium, biological evaluation, Synthesis.

INTRODUCTION

Phenothiazine was first prepared by Bernthsenin 1883in the course ofproof of structure studies on Lauth's violet and methylene blue. Since then it has played an important role in dye chemistry as the parent compound of the thiazine dyes [1]**.** In the last twenty years phenothiazine and its derivatives have found numerous applications in other fields, and this has stimulated further research on these compounds.Phenothiazine was discovered to have insecticidal properties in 1934; further work demonstrated its usefulness as a urinary antisepticand an anti-helmintic [2]. Its derivatives have been particularly valuable in human medicine as antihistamines [3-5], in the treatment of Parkinson's disease [6], and as antiemetics [7], to mention a few of their many applications.

They have also been successfully employed as antioxidants [8]. Meyer and Jacobsen have given an excellent summary of the chemistry of phenothiazine up to 1920 with particular emphasis on its relation to methylene blue [9]. Gilman's students [10-12] have reviewed the literature on phenothiazine in their doctoral dissertations. Metcalf has discussed the chemistry of phenothiazine in his monograph on insecticides. Two excellent reviews on phenothiazine as an antihelmintic have appeared: a monograph by Beeler and a chapter in a book by Findlay. Since no recent survey on phenothiazine chemistry has appeared, it seemed desirable to present a review on this subject, with special emphasis on the period from 1920 to 1953. This review deals only very briefly with the oxidized (quinonoid) forms of phenothiazineor the benzophenothiazines.

When two benzene nucleus are fused with 2, 3 and 5, 6 positions of thiazine is called as phenothiazine. Phenothiazine is also known as thiodiphenyl amine. The structure and numbering of phenothiazine is given bellow. A. Bentsen has synthesized phenothiazine by the reaction of diphenylamine and sulfur in the presence of catalytic amount of iodine particlesin 1883. The most important application of phenothiazine are as an anthelmintic [2, 3]and insecticidal agents.

EXPERIMENTAL SECTION

Preparation of 1-Carboxy-4'-methyl diphenylamine (1)
A mixture of 2-chloro benzoic acid (1.56gm, 0.01M) and p-toluidine (1.07gm, 0.01M) in dimethylformamide (20ml) was refluxed in presence ofanhydrous potassium hydroxide (1gm) fortwo hours using an oil bath. The mixture was

filtered and residue was washedwith 10.0 ml hot dimethylformamide. The filtrate so obtained was poured intoice cold water and followed by acidification with 10.0 ml dil. Hydrochloric acid. The precipitated acid was then dried in air and recrystallized from ethanol. Yield: 69%, M.P.: 158°C,
Found: C: 73.87%; H, 5.67%; N, 6.13%)

Preparation of 1-Carboxy-7-methyl phenothiazine (2)
A mixture of 1-carboxy-4'-methyl diphenyl amine (2.27gm, 0.01M), sulfur powder (0.64gm, 0.02M) and iodine (0.3gm) in 1,2-dichloro benzene (20ml) was refluxed for five hours in oil bath. The reaction mixture was distilled to remove excess solvent. The product so obtained was recrystallized from toluene. Yield: 58%, M.P.: 96°C
Found: C: 65.24%; H, 4.21%; N, 5.36%)

Preparation of 10-N-[bis-(2-chloroethyl)amino]-methyl-7-methyl- phenothiazine-1 carboxylic acids
A mixture of 1-carboxy-7-methyl phenothiazine (2.57gm, 0.01M), 2- chloro-N-(2-chloroethyl) ethanamine hydrochloride (1.78 gm,0.01M) and formaldehyde (2-3 ml) in 20.0 ml of dioxane was refluxed for 8 to10 hours. The reaction mixture was cooled and poured in to cold water. The product soobtained was filtered, dried and crystallized from dioxane.
Yield: 49%, M.P.: 119°C
Found: C: 55.37%; H, 4.77%; N, 6.74%)

Preparation of 1-Carboxy-4'-methyl diphenylamine (3_{a-j})
1-Carboxy-4'-methyl diphenylamine has been prepared accordingto procedure. Similarly, other compounds (3a-j) were synthesized in Table 1.

Preparation of 1-Carboxy-7-methyl phenothiazine (3_{k-t})
1-Carboxy-7-methyl phenothiazine has been prepared according to procedure. Similarly, other compounds (3_{k-t}) were synthesized in Table 2.

Table 1: Physical Constants Of Substituted 1-Carboxy diphenylamines (3_{a-j})

Comp. No	R	Mol. F	M. Wt	Yield	M.P	R_f value		% of Nitrogen	
						R_{f1}	R_{f2}	Calc	Found
3_a	H	$C_{13}H_{11}NO_2$	213	70	97	0.52/0.57		6.57/6.52	
3_b	4-CH_3	$C_{14}H_{13}NO_2$	227	69	158	0.59/0.65		6.17/6.13	
3_c	3-CH_3	$C_{14}H_{13}NO_2$	227	71	164	0.64/0.60		6.17/6.11	
3_d	2-CH_3	$C_{14}H_{13}NO_2$	227	68	143	0.60/0.58		6.17/6.12	
3_e	4-OCH_3	$C_{14}H_{13}NO_3$	243	76	188	0.46/0.50		5.76/6.72	
3_f	3-OCH_3	$C_{14}H_{13}NO_3$	243	75	108	0.50/0.54		5.76/5.70	
3_g	2-OCH_3	$C_{14}H_{13}NO_3$	243	67	126	0.58/0.61		5.76/5.71	
3_h	4-NO_2	$C_{13}H_{10}N_2O_4$	258	62	192	0.54/0.59		5.86/4.88	
3_i	3-NO_2	$C_{13}H_{10}N_2O_4$	258	71	185	0.61/0.57		5.82/4.82	
3_j	2-NO_2	$C_{13}H_{10}N_2O_4$	258	60	121	0.53/0.62		5.88/4.92	

Table 2: Physical Constants of 7/8/9-Substituted-1-Carboxy Phenothiazines (3_{k-t})

Comp. No	R	Mol. F	M. Wt	Yield	M.P	R_f value		% of Nitrogen	
						R_{f1}	R_{f2}	Calc	Found
3_k	H	$C_{13}H_9NO_2S$	243.0	63	123	0.48/0.55		5.76/5.70	
3_l	4-CH_3	$C_{14}H_{11}NO_2S$	257.0	58	96	0.53/0.62		5.44/5.36	
3_m	3-CH_3	$C_{14}H_{11}NO_2S$	257.0	66	113	0.58/0.53		5.45/5.39	
3_n	2-CH_3	$C_{14}H_{11}NO_2S$	257.0	49	186	0.60/0.64		5.45/5.39	
3_o	4-OCH_3	$C_{14}H_{11}NO_3S$	273.0	60	172	0.42/0.48		5.13/5.07	
3_p	3-OCH_3	$C_{14}H_{11}NO_3S$	273.0	54	101	0.56/0.50		5.13/5.07	
3_q	2-OCH_3	$C_{14}H_{11}NO_3S$	273.0	68	146	0.50/0.46		5.13/5.08	
3_r	4-NO_2	$C_{13}H_8N_2O_4S$	288.0	52	175	0.48/0.52		5.06/5.01	
3_s	3-NO_2	$C_{13}H_8N_2O_4S$	288.0	64	168	0.52/0.58		5.06/5.00	
3_t	2-NO_2	$C_{13}H_8N_2O_4S$	288.0	50	186	0.54/0.56		5.08/5.01	

Preparation of 10 - [(carboxymethyl) – sulfanyl]-acetyl-7-methylphenothiazine -1-carboxylic acid (4)
A mixture of 1-carboxy-7-methyl phenothiazine (2.70gm, 0.01M), chloroacetyl chloride (1.2 ml 0.012 M) in 10.0 ml of toluene and diisopropyl amine (5 mL) was stirred at 30^0C for 10 to 12 hours and monitored the reaction by TLC. After completion of the reaction, a solution of thioglycolic acid (0.8 ml 0.012 M) in 5.0 ml of toluene is added and refluxed the mixture for 5 hours. The reaction was monitored by TLC. After completion of reaction the excess toluene was distilled out and remaining slurry was treated with hexane. The solid product so obtained was filtered, dried and crystallized from toluene. Yield: 38%, M.P. 118°C, (Required: C, 55.46 %; H, 3.85 %; N, 3.59 % for

$C_{18}H_{15}NO_5S_2$, Found: C, 55.50%; H, 3.88%; N, 3.56%). TLC solvent system: Ethyl Acetate: Hexane = 1.0: 9.0= 0.46 TLC solvent system: Acetone: Benzene = 8.0: 1.5= 0.61

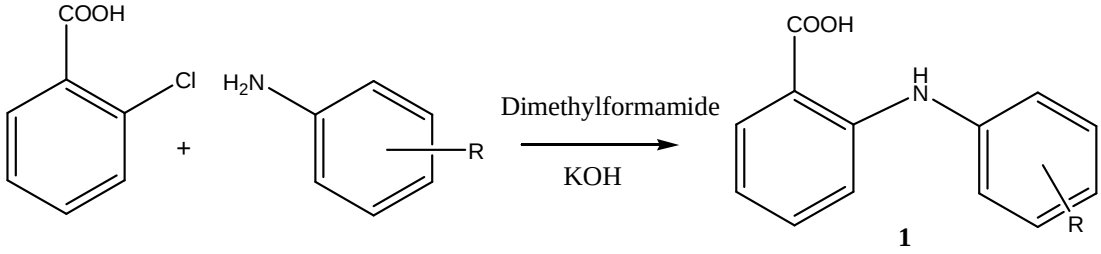
Similarly, other compounds (4_{a-t}) were synthesized. The physical data are recorded in Table 3.

Table 3: Physical constants of 7/8/9-Substituted-10-N (Carboxy Methyl) -Sulfanyl] -Acetyl - Phenothiazine-1-Carboxylic Acids

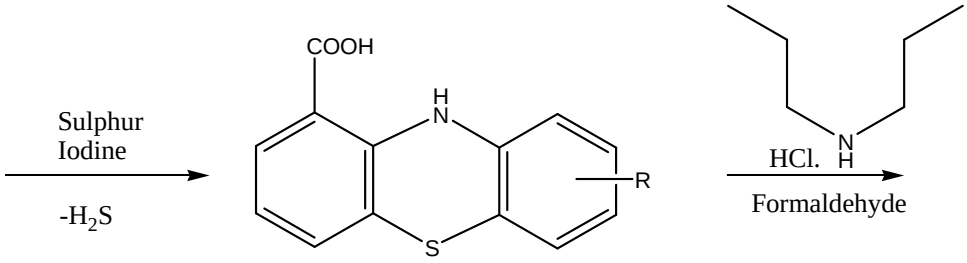
Comp. No	R	Mol. F	M. Wt	Yield	M.P	R_f value		% of Nitrogen	
						R_{f1}	R_{f2}	Calc	Found
4_a	H	$C_{17}H_{13}NO_5S_2$	375	46	99	0.50 / 0.55		3.73 / 3.73	
4_b	4-CH_3	$C_{18}H_{15}NO_5S_2$	389	38	118	0.46 / 0.61		3.59 / 3.56	
4_c	3-CH_3	$C_{18}H_{15}NO_5S_2$	389	39	124	0.49 / 0.62		3.17 / 3.56	
4_d	2-CH_3	$C_{18}H_{15}NO_5S_2$	389	32	123	0.61 / 0.59		3.17 / 3.56	
4_e	4-OCH_3	$C_{18}H_{15}NO_6S_2$	405	45	128	0.48 / 0.55		3.45 / 3.41	
4_f	3-OCH_3	$C_{18}H_{15}NO_6S_2$	405	46	118	0.53 / 0.50		3.45 / 3.41	
4_g	2-OCH_3	$C_{18}H_{15}NO_6S_2$	405	43	116	0.52 / 0.59		3.45 / 3.41	
4_h	4-NO_2	$C_{17}H_{12}N_2O_7S_2$	420	49	112	0.52 / 0.61		3.33 / 3.31	
4_i	3-NO_2	$C_{17}H_{12}N_2O_7S_2$	420	39	125	0.60 / 0.52		3.33 / 3.31	
4_j	2-NO_2	$C_{17}H_{12}N_2O_7S_2$	420	32	111	0.55/ 0.45		3.33 / 3.31	

Mol.F: *Molecular formula,* ***M.Wt:*** *Molecular weight,* ***M.P:*** *melting point,* ***Calc:*** *Calculated,*

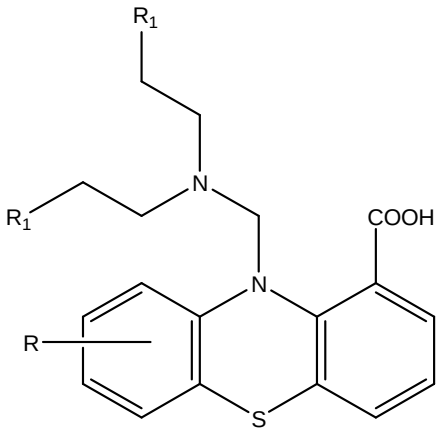
Scheme -1



1



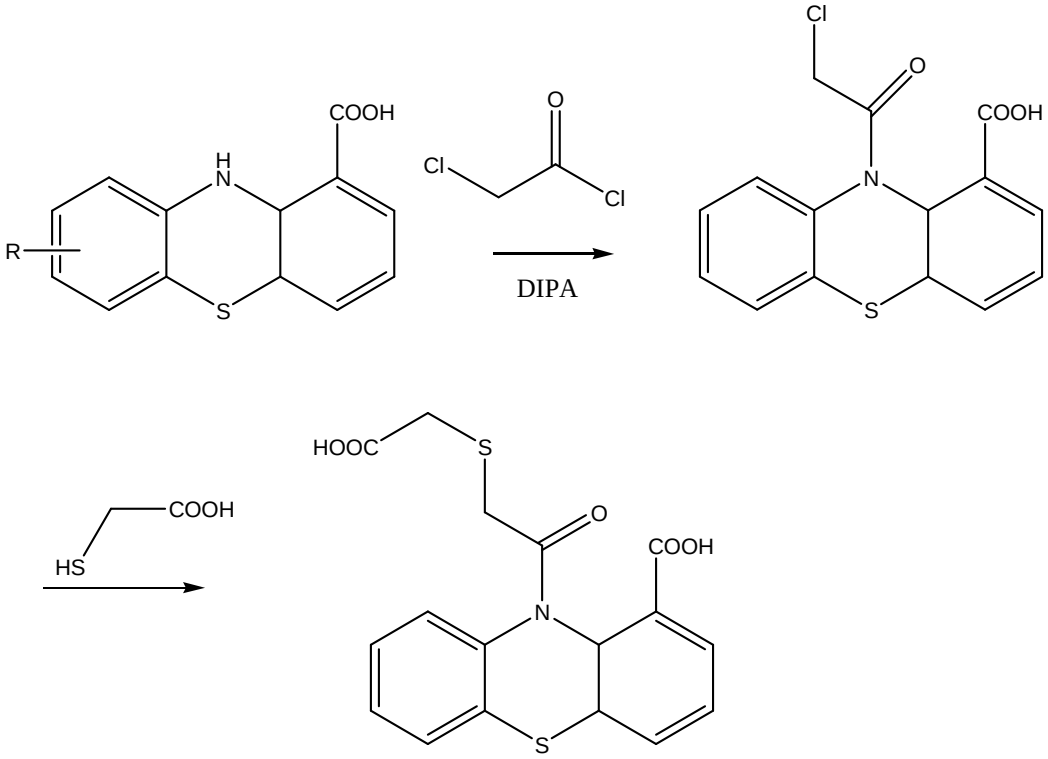
2



3a-t

R = o/m/p -CH_3, -OCH_3, -NO_2
R_1= Cl / H

Scheme-2



4a-t
R=H, o/m/p, -CH_3, OCH_3, NO_2

RESULTS AND DISCUSSION

Recent litrature survey on substituted phenothiazines for their other applications [13--20] 97-109 and various pharmacological profile [21-27] 110-170 suggest to structually redesign and synthesize some newer bioactive phenothiazines. The synthesis of 7/8/9/-substituted10-N-[bis-(2-chloroethyl/ethyl)-amino]methyl-phenothiazines **(Scheme-1)**have been under taken by the reaction of 7/8/9-substituted 1-Carboxy phenothiazines, formaldehyde and 2-chloro-N-(2-chloroethyl) ethanamine / diethyl amine in acidic media, which is known as Mannich reaction.

The constitution of the products 3_{a-t}have been delineated by elemental analyses, IR, PMR and Mass spectral data The products 3_{a-t} and 4_{a-t}were assayed for their in vitro biological assaynlike antibacterial activity towards S. pyogens MTCC-443, S. aureus MTCC- 96 and P. aeruginosa MTCC-441 (Gram positive) and E. coli MTCC-442 (Gram negative) bacterial strains and antifungal activity towards Aspergillusniger MTCC-282 and A. clavatus MTCC-1323 at different concentrationsi.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration)values. The biological activities of the synthesized compounds were compared with standard drugs, viz., Amplicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin(antibacterial), Greseofluvin, Nystatin(antifungal).

The substituted phenothiazines for their other applications and various pharmacological profiles suggest to structually redesign and synthesize some newer bioactive phenothiazines. The synthesis of 7/8/9-Substituted-10-N-[(carboxymethyl)-sulfanyl]-acetylphenothiazine-1-carboxylic acids **(Scheme-2)**have been under taken by the reaction of 7/8/9-Substituted-1-Carboxy phenothiazines, chloroacetyl chloride followed by the action of thioglycollic acid in basic media

CONCLUSION

Phenothiazines possess a wide spectrum of pharmacological activites such as antituberculer, antitumor, anticonvulsant, tranquilizers, antiemetic etc. N-substituted phenothiazine nucleus causes a marked difference in activities and therefore phenothiazines with varied substituents has been synthesized and further their condensation reaction with secondary amine in presence of formaldehyde has been carried out and tested for activities in search of bettermedicinally interested agents.

REFERENCES

[1] Venkataraman, k.:The chemistruofsynthetic dyes, Vol. II, p. 791. Academic Press, inc., Newyork (**1952**).
[2] Findlagy,G. M.: Recent advances in Chemotherapy, 3rd edition, vol. I, p. 124. TheblakistonCompany, Philadelphia (**1950**).
[3] Halpern, B. N.: *Compt. Rend. Soc. Biol*. 140, 363 (**1946**)
[4] Halpern, B. K., and Ducrot, R.: *Compt. Rend. Soc. Biol*. 140, 361 (**1946**).
[5] Vanderbrook, M. J., Olson, k. J., Richmon&di, R., and Iuizenema, H.: *J. Pharmacol. Exptl. Therap*. 94, 19i (**1948**).
[6] Burger, A.: Medicinal chemistry, vol. I, p. 456. Interscience Publishers, inc., New York (**1951**).
[7] Friend, D. G., and Cummins, j. f.: *J. Am. Med. Assoc*. 163, 481 (**1953**).
[8] Murphy, C. M.,Rainer, H., and Smith, N. L.: *Anal. Chem*. 42,2479 (**1950**).
[9] Meyer,V., and Jacobsen, P.: Lehrbuchder organischen Chemie, vol. 2, part 3, p. 1490. Veit and Co., leipzig (**1920**).
[10] Nelson, R. D.: Doctoral dissertation, Iowa state college, **1951**.
[11] Shirley, D. A.:doctoral dissertation, Iowa state college, **1943**.
[12] Van Ess, P. R.: Doctoral dissertation, Iowa state college, **1936**.