SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 10-N-ARYLAMINOMETHYL - 1,3,7,9 - TETRACHLORO / H-PHENOTHIAZINES

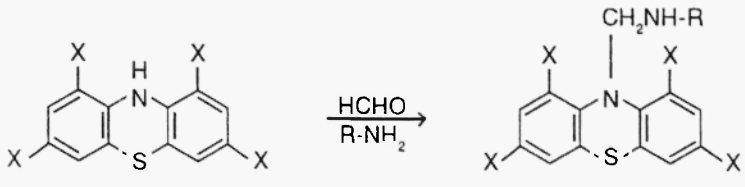
D.M. PUROHIT, D.S. MEHTA AND V.H. SHAH*
DEPARTMENT OF CHEMISTRY, SAURASHTRA UNIVERSITY,
RAJKOT - 360 005. (INDIA)

ABSTRACT : The titled compounds have been synthesised by the reaction of formaldehyde and arylamine with 1,3,7,9-tetracholoro/H-phenothiazines in the presence of hydrochloricacid (Mannich reaction). The constitution of the products have been delineated by spectral data. The products have been evaluated for their antimicrobial activity. Some of the compounds have found to be having comparable activity with standard drugs viz. Ampicillin, Chloramphanicol, Norfloxacin and Griseofulvin.

INTRODUCTION :

Phenothiazine derivatives(1-5) are important heterocycles owing to their widespread use in biological and pharmaceutical fields. Mannich base derivatives(6) have been reported to possess various biological activities including antinflammatory. In view of getting potent therapeutic agent, present paper reports the synthesis of titled compounds by combining phenothiazine moiety with mannichbases (2a-z, 2a'-z')

The titled compounds have been synthesised by the reaction of formaldehyde, arylamine on 1,3,7,9-tetrachloro/H-phenothiazine(7) in the presence of hydrochloricacid (Mannich reaction) (Scheme-I). The constitution of the products have been delineated by spectral data. The products have evaluated for their antimicrobial activity.



1 2

Scheme - I
R = Aryl
X = H/Cl

EXPERIMENTAL :

Melting points were taken in open capillaries and are uncorrected. IR absorption spectra (ν in cm-1) were recorded on a shimadzu IR-435 spectrophotometer using KBr pellet and 1HNMR spectra on Hitachi R-1200 (60 MHz) spectrometer using TMS as internal standard (Chemical shifts in δ ppm.). The purity of the compounds were routinely checked by TLC using silica gel G.

10-N-(p)-Methoxyphenylamino methylphenothiazines 2q :

A mixture of phenothiazine (0.01 M), formaldhyde solution (2.0 ml), p-anisidine (0.01 M), HCl (5 ml) and dioxane (25 ml) was refluxed for 4 hours on oilbath. The cold reaction mixture was filtered and poured on cold water. The isolated product was crystallised from dioxane. Yield 82.3%, M.P. 145° C. (Found : C, 71.82;H, 5.34, N,8.33 $C_{20}H_{18}ON_2S$ requires C,71.85; H,5.38 % N, 8.39%); IR(KBr) : 3340-3250 (N-H-str), 2960 (C-H-str),1160 (C-H vib), 680 cm-1 (C-S-C. str). PMR (TFA) : δ:4.01 (s,3H, $-OCH_3$), 5.01 (s,2H, $-CH_2$), 8.1-8.94 (m,11H, Ar-H)

Similarly, other compounds (2a-z) were prepared and their physical constants are recorded in Table-1.

10-N-(p)-methoxyphenylaminomethyl-1,3,7,9-tetrachlorophenothiazine 2q' :

A mixture of 1,3,7,9 - tetrachlorophenothiazine (0.01 M), formaldehyde solution (2.0 ml.) p-anisidine (0.01 M), HCl (5 ml) and dioxane (25ml) was refluxed for 4 hours on oil-bath. The cold reaction mixture was filtered and poured on ice water. The isolated products was crystallised from dioxane, yield 79 %, M.P. 139° c (found : C, 50.81; H 2.95; N, 5.88 $C_{20}H_{14}ON_2SCl_4$ requires C, 50.85; H.2.97; N. 5.93 %) IR (KBr): ν : 3300-3240 (N-Hstr), 2950 (C-Hstr), 1165 (C-N vib), 755 (C-Cl str), 678 cm^{-1} (C-S-C str), PMR (TFA): δ : 4.00 (s,3H, $-OCH_3$), 4.95 (s,2H, $-CH_2$), 7.95 - 8.85 (m, 7H, Ar-H).

Similary other compounds (2a'-z') were prepared and their physical constants are recorded in Table-1.

ANTIMICROIAL ACTIVITY :

Mannich bases were evaluted in vitro for Antibacterial activity against B.mega, B. subtilis, E. coli and A. arogens and for antifungal activity against A. awamori using DMF as solvent at 50 μg concentration by cup-plate method (9). After 24 hrs. of incubation at 37°c, the Zone

of inhibition were measured in m.m. The activity was compared with the known antibiotics viz. Chloramphanicol, Ampicillin. Norfloxacin.

In the case of antibacterial activity and antifungal activity compounds of type 2a-z and 2a'-z' exhibited moderate activity against B.mega and A. awamori but not comparable with any standard drugs viz. Griseofulvin at the same concentration. In case of antibacterial activity compounds of type 2a-z, 2a'-z' showed moderate to comparable activity with standard drugs at same concentration against B. subtilies, E. coli, A.arogens. Compounds 2e, 2s, ad', 2z', 2j', 2k', 2m', showed comparable activity with standard drug viz. Ampicillin, Chloramphanicol and Norfloxacin against B.subtilis. Compounnds 2a, 2d, 2e, 2f, 2g, 2i, 2m, 2o, 2p, 2a', 2e', 2d', 2h', 2i', 2j', 2m', 2q', 2t', 2w', 2x'. exhibited comparable activity with known choosen standard, viz. Ampicillin, Chloramphanicol, Norfloxacin against E. coli at same concentration, Compounds such as, 2c, 2g, 2j, 2l, 2m, 2n, 2r, 2s, 2x, 2c', 2d', 2e', 2f', 2g', 2m', 2n', 2o', 2s', 2v', 2z' showed comparable activity with known choosen standard drugs viz. Ampicillin. Chloramphanicol, Norfloxacin against A. arogens at same concentration.

ACKNOWLEDGEMENT :

The authors are thankful to Dr. A.R.Parikh, Professor and Head of the Chemistry Department, Saurashtra University, Rajkot for providing research facilities.

REFERENCES :

(1.) K.H.M. Hassan, S.R.F. Lazbaurya and A.A. Abdul wahab
J. Indian Chem. Soc. 59 (1979) 290.

(2.) G.W. Anderson, H.E. Faith, H.W. Marson, P.S. Winnek and R.O. Robin,
J. Am. Chem. Soc, 64 (1942) 290[6].

(3.) Schmax and D.Max ; Swiss pat, (1970) 497121.

(4.) M. Hinrich, D. Christan and S.C.H.Harld, Ger. Pat ; (1973) 2164851.

(5.) M. Verma, V.R. Gujrathi, A.K. Saxena and K.Shanker,
J. Indian. Chem. Soc. 58 (1981) 1119.

(6.) E.M. Fry, E.L. May, J. Org. Chem. 24, (1959) 116, ; Chem Abstr. 54, (1960) 6714 f.

(7.) Bernthsen ; Ber ; 16, (1983) 2896.

(8.) M. Fujimoto, Bull. Chem. Soc. Jpn. 32 (1959) 294.

(9.) A.L.Barry, "The antimicrobic susceptibility Test", Principle and practices, (1976) 180-193.

TABLE NO. 1 : PHYSICAL CONSTANTS AND ANTIMICROBIAL ACTIVITY OF 10-N-ARYLAMINOMETHYL -1,3,7,9,-TETRACHLORO/H-PHENOTHIAZINES

NO.	R	X	Molecular Formula	M P. °C	%of Nitrogen Calcd / Found.		Antibacterial Activity Zone of inhibition in mm			Antibacterial Activity	
							B.mega	B.subtilis	E.coli	A.arogens	A.awamori
1	2	3	4	5	6	7	8	9	10	11	12
2a	Phenyl	H	$C_{19}H_{16}N_2S$	115	9.21 /	9.19	14	12	22	20	15
2b	2-Chloropheny	H	$C_{19}H_{15}N_2SCl$	125	8.27 /	8.24	13	13	16	19	17
2c	4-Chloropheny	H	$C_{19}H_{15}N_2SCl$	164	8.27 /	8.23	16	16	20	22	12
2d	2,6-Dichlorophenyl	H	$C_{19}H_{14}N_2SCl_2$	143	7.50 /	7.47	12	11	25	22	14
2e	2,6-Dichoioro--4-nitrophenly	H	$C_{19}H_{13}O_2N_3SCl_2$	217	10.05 /	10.03	20	18	24	23	14
2f	3-Chloro-6-methylphenyl	H	$C_{20}H_{17}N_2SCl$	123	7.94 /	7.90	12	14	23	22	15
2g	2-Methyl phenyl	H	$C_{20}H_{18}N_2S$	245(d)	8.81 /	8.76	13	13	24	23	18
2h	3-Methyl phenyl	H	$C_{20}H_{18}N_2S$	109	8.81 /	8.77	11	12	20	22	17
2i	4-Methyl phenyl	H	$C_{20}H_{18}N_2S$	210	8.81 /	8.75	10	11	22	23	12
2j	4-Methyl-3-nitro-phenyl	H	$C_{20}H_{17}O_2N_3S$	159	11.57 /	11.53	14	13	19	22	15
2k	2-Methyl-3-nitro-phenyl	H	$C_{20}H_{17}O_2N_3S$	198	11.57 /	11.54	14	12	17	20	17
2l	2.5-Dimethyl-phenyl	H	$C_{21}H_{20}N_2S$	133	8.43 /	8.39	11	12	20	23	17
2m	2-Nitro phenyl	H	$C_{19}H_{15}O_2N_3S$	110	12.03 /	12.00	15	12	22	26	12
2n	3-Nitro phenyl	H	$C_{19}H_{15}O_2N_3S$	139	12.03 /	11.99	10	11	19	25	15
2o	4-Nitro phenyl	H	$C_{19}H_{15}O_2N_3S$	169	12.03 /	11.98	14	12	24	20	13
2p	2-Methoxy phenyl	H	$C_{20}H_{18}ON_2S$	80	8.39 /	8.34	11	14	28	22	14
2q	4-Methoxy phenyl	H	$C_{20}H_{18}ON_2S$	145	8.39 /	8.33	14	14	20	17	11
2r	2.5-Dimethoxy-phenyl	H	$C_{21}H_{20}O_2N_2S$	147	7.69 /	7.65	13	12	19	24	13

1	2	3	4	5	6 7	8	9	10	11	12
2s	3-Hydroxy phenyl	H	$C_{19}H_{16}ON_2S$	267	8.75 / 8.71	14	19	16	26	12
2t	2-Hydroxy phenyl	H	$C_{19}H_{16}ON_2S$	97	8.75 / 8.80	12	17	18	22	15
2u	2-pyridyl	H	$C_{18}H_{15}N_3S$	106	13.77 / 13.74	12	14	20	13	17
2v	4-Antipyryl	H	$C_{24}H_{22}ON_4S$	148	13.52 / 13.50	18	15	16	20	18
2w	2-Thiazolyl	H	$C_{16}H_{13}N_3S_2$	165	13.50 / 13.45	15	19	19	19	19
2x	4-Arseno Phenyl	H	$C_{19}H_{16}O_3N_2SAs$	219	6.55 / 6.60	14	13	17	23	17
2y	2-Carboxy-phenyl	H	$C_{20}H_{16}O_2N_2S$	121	8.04 / 8.01	17	14	16	22	14
2z	4-Carboxy-phenyl	H	$C_{20}H_{16}O_2N_2S$	201	8.04 / 8.00	16	13	16	21	15
2a'	phenyl	Cl	$C_{19}H_{12}N_2SCl_4$	205	6.33 / 6.30	11	13	21	22	12
2b'	2-Chlorophenyl	Cl	$C_{19}H_{11}N_2SCl_5$	98	5.87 / 5.81	12	17	19	20	14
2c'	4-Chlorophenyl	Cl	$C_{19}H_{11}N_2SCl_5$	173	5.87 / 5.82	11	15	23	23	18
2d'	2.5-Dichloro-phenyl	Cl	$C_{19}H_{10}N_2SCl_6$	142	5.48 / 5.44	12	27	24	24	17
2e'	2,6-Dichloro-4-nitrophenyl	Cl	$C_{19}H_9O_2N_3SCl_6$	180	7.55 / 7.51	12	17	23	25	15
2f	3-Chloro-6-methylphenyl	Cl	$C_{20}H_{13}N_2SCl_5$	134	5.71 / 5.67	15	12	22	23	17
2g'	2-Methyl phenyl	Cl	$C_{20}H_{14}N_2SCl_4$	152	6.14 / 6.11	14	13	19	23	17
2h'	3-Methyl phenyl	Cl	$C_{20}H_{14}N_2SCl_4$	80	6.14 / 6.10	12	15	22	13	20
2i'	4-Methyl phenyl	Cl	$C_{20}H_{14}N_2SCl_4$	178	6.14 / 6.09	13	24	22	20	11
2j'	4-Methyl-3-nitro phenyl	Cl	$C_{20}H_{13}O_2N_3SCl_4$	163	8.38 / 8.33	15	26	20	22	14
2k'	2-Methyl-5-nitro phenyl	Cl	$C_{20}H_{13}O_2N_3SCl_4$	155	8.38 / 8.34	17	18	18	19	13
2l'	2.5-Dimethyl phenyl	Cl	$C_{21}H_{16}N_2SCl_4$	109	5.95 / 5.91	13	12	24	20	12
2m'	2-Nitro phenyl	Cl	$C_{19}H_{11}O_2N_3SCl_4$	155	8.62 / 8.58	12	20	25	25	15

Received August 5, 1996

1	2	3	4	5	6 7	8	9	10	11	12
2n'	3-Nitro phenyl	Cl	$C_{19}H_{11}O_2N_3SCl_4$	266	8.62 / 8.57	14	17	20	24	18
2o'	4-Nitro phenyl	Cl	$C_{19}H_{11}O_2N_3SCl_4$	171	8.62 / 8.60	16	16	19	23	14
2p'	2-Methoxy phenyl	Cl	$C_{20}H_{14}ON_2SCl_4$	136	5.93 / 5.89	18	15	20	20	13
2q'	4-Methoxy phenyl	Cl	$C_{20}H_{14}ON_2SCl_4$	139	5.93 / 5.88	17	14	22	20	13
2r	2,5-Dimethoxy-Phenyl	Cl	$C_{21}H_{16}O_2N_2SCl_4$	202	5.58 / 5.53	14	12	20	22	15
2s'	3-Hydroxy Phenyl	Cl	$C_{19}H_{12}ON_2SCl_4$	165	6.11 / 6.08	15	15	21	23	17
2t'	2-Hydroxy Phenyl	Cl	$C_{19}H_{12}ON_2SCl_4$	267(d)	6.11 / 6.07	12	10	15	22	18
2u'	2-pyridyl	Cl	$C_{18}H_{11}N_3SCl_4$	273	9.48 / 9.45	11	13	18	13	18
2v'	4-Antipyryl	Cl	$C_{24}H_{18}ON_4SCl_4$	206	10.14 / 10.12	13	15	20	25	17
2w'	2-Thiazolyl	Cl	$C_{16}H_9N_3S_2Cl_4$	147	9.35 / 9.32	16	14	21	22	19
2x'	4-Arseno Phenyl	Cl	$C_{19}H_{12}O_3N_2SAsCl_4$	135	4.96 / 4.94	15	11	24	18	18
2y'	2-Carboxy-Phenyl	Cl	$C_{20}H_{12}O_2N_2SCl_4$	208	5.76 / 5.73	20	17	18	20	12
2z'	4-Carboxy-Phenyl	Cl	$C_{20}H_{12}O_2N_2SCl_4$	135	5.76 / 5.74	18	12	17	23	20

Antimicrobial activiy :

ZONES OF INHIBITION FOR STANDARD DURGS :

1	2	B.mega 3	B.subtilis 4	E.coli 5	A.arogens 6	A.awamori 7
1.	Ampicillin	23	18	17	27	-
2.	Chloramphanicol	24	19	25	26	-
3.	Norfloxacin	24	19	25	26	-
4.	Griseofulvin	-	-	-	-	23