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NOTE

Synthesis of Some New N′-[5′-(N^{10}-Phenothiazinomethyl)-1′,3′,4′-Thiadiazol-2′-yl] N-Aryl Guanidine Hydrochlorides with Possible Antithyroid Activity

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Several new N′-[5′-(N^{10}-phenothiazinomethyl)-1′,3′,4′-thiadia-zol-2′-yl] N-aryl guanidine hydrochlorides (I) have been synthesized by the reaction of 2-amino-5-(N^{10}-phenothiazinomethyl)-1,3,4-thiadiazole with different aryl cyanamides. All these synthesized aryl guanidines have been screened for their antithyroid activity. The compounds were characterised by elemental analysis, IR and NMR spectra.

Key Words: Synthesis, N-Aryl guanidines, Antithyroid activity.

Guanidines which are related to thiourea in having the bivalent imino group (=NH) in place of sulphur atom also exhibit marked pharmacological properties. *p*-Amino benzene sulphonyl guanidine has attained importance for the treatment of certain pathogenic intestinal infections[1-3]. A series of nitro and amino derivatives of triphenyl guanidines have been reported in the chemotherapy of tuberculosis[4]. Some guanidine derivatives were found to possess antimalarial, analgesic[5] and antihistaminic[6] activities. A review of literature on antithyroids[7,8] revealed that the essential requirements for antithyroid are the thioureylene linkage and aminobenzene or amino heterocycles with free amino group.

Keeping this in view it was thought worth while to synthesize some new N-aryl guanidine hydrochlorides possessing antithyroid activity with lesser toxicity.

Preparation of N′-[5′-(N^{10}-Phenothiazinomethyl)-1′,3′,4′-thiadiazol-2′-yl] N-phenyl guanidine hydrochloride (I)

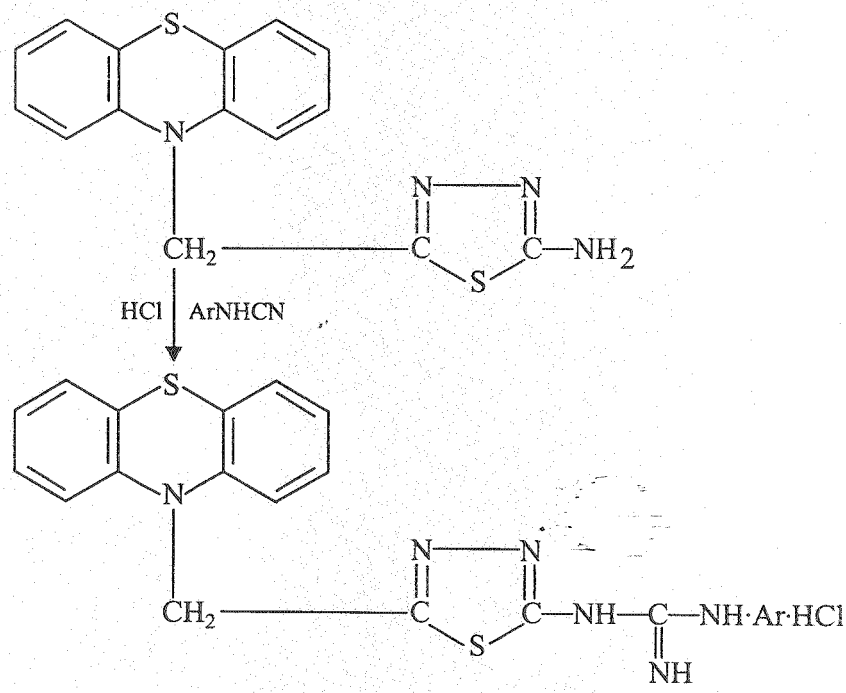
In an ice-cooled etherial solution of phenyl cyanamide (3.5 g) dry hydrogen chloride was passed for about 5 min. The phenyl amidine chloride which separated as a sticky mass was dissolved in acetone. To this solution was added a solution of 2-amino-5-(N^{10}-phenothiazinomethyl)-1,3,4,-thiadiazole (4 g) in acetone. N′-[5′-(N^{10}-Phenothiazinomethyl)-1′,3′,4′-thiadiazol-2′-yl] N-phenyl guanidine hydrochloride which separated was filtered and washed with warm acetone and recrystallised from HCl.

Similarly other guanidine hydrochlorides were synthesized accordingly and their analytical data are incorporated in Table-1. The synthesized compounds have been characterized by IR, PMR spectral studies and elemental analysis. The purity of the compounds have been checked by TLC. The m.p.s were determined in open capillaries and are uncorrected.

The antithyroid activities of synthesized compounds and standard drug were checked in intact rats. The process is based upon the uptake of radioactive iodine

TABLE-1
DATA SHOWING CHARACTERISTICS OF NEWLY SYNTHESIZED N′-[5′-(N^{10}-PHENOTHIAZINOMETHYL)-1′,3′,′4′-THIADIAZOL-2′-YL] N-ARYL GUANIDINE HYDROCHLORIDES AND THEIR ANTITHYROID ACTIVITY

Compd. No.	Nature of Ar (m.f.)	Yield (%)	m.p. (°C)	Elemental analysis (%) Found (Calcd.)		Antithyroid activity	
				N	S	No of animals in each group	%age of incorporation of I^{125}/mg of thyroid tissue in comparison with control
I	Phenyl- ($C_{22}H_{19}N_6S_2Cl$)	68	232–234	17.82 (18.00)	13.53 (13.71)	3	9.12
II	*p*-chlorophenyl- ($C_{22}H_{18}N_6S_2Cl_2$)	59	208–210	16.52 (16.76)	12.54 (12.77)	3	36.56
III	*p*-bromophenyl ($C_{22}H_{18}N_6S_2BrCl$)	56	216–217	15.14 (15.39)	11.52 (11.73)	3	78.76
IV	*o*-nitrophenyl- ($C_{22}H_{18}O_2N_7S_2Cl$)	62	222–224	18.92 (19.15)	12.30 (12.51)	3	26.42
V	*p*-nitrophenyl- ($C_{22}H_{18}O_2N_7S_2Cl$)	65	228–230	18.96 (19.15)	12.36 (12.51)	3	112.12
VI	*o*-tolyl- ($C_{23}H_{21}N_6S_2Cl$)	61	222–224	17.28 (17.48)	13.12 (13.31)	3	66.22
VII	*p*-tolyl- ($C_{23}H_{21}N_6S_2Cl$)	62	216–217	17.00 (17.48)	13.26 (13.31)	3	104.56
VIII	*o*-anisyl- ($C_{23}H_{21}O_1N_6S_2Cl$)	56	204–206	16.78 (16.91)	12.72 (12.89)	3	28.54
IX	*p*-anisyl- ($C_{23}H_{21}O_1N_6S_2Cl$)	58	214–216	16.74 (16.91)	12.72 (12.89)	3	26.32
X	*p*-phentyl- ($C_{24}H_{23}O_1N_6S_2Cl$)	60	210–212	16.22 (16.45)	12.32 (12.53)	3	178.66



(I^{125}) by thyroid gland. The result is presented as % incorporation in comparison with control for the standards are incorporated in Table-1.

Characteristics of compound **I** and results of antithyroid activity are given in Table-1. The main absorption bands observed in IR spectra are described as follows: 3340 ν(=NH), 3215–3175 ν(—NH), 695 ν(C—S—C), 1610 ν(C=N), 1260 ν(C—N).

The position of signals in NMR spectra can be assigned to different types of protons as follows: δ 7.20–7.65 (m, 13H, Ar-H), 4.1–4.3 (s, 2H, 2-NH), 3.62 (s, 2H, —N—CH_2).

If a compound is not potent even at 1/4th level of the standard drug (thiouracil), then it is of little biological significance. Compounds having activity twice as much as that of thiouracil are good enough since a potency higher than this is likely to be toxic. Biologically, compounds **II, IV, VIII** and **IX** were found to be antithyroid but their activity was very low and was not even equivalent to 25% of the activity of thiouracil while the compound **I** was found to be more active than thiouracil. The activity was more than twice of the activity of thiouracil standard antithyroid drug.

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