SYNTHESIS AND ANTITHYROID ACTIVITY OF SOME BENZIMIDAZOLYL AND BENZENESULPHONYL THIOCARBAMIDES

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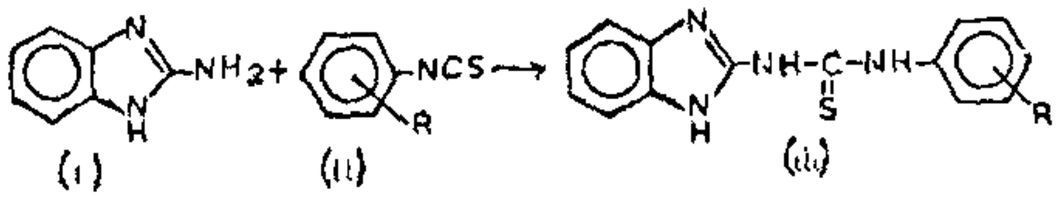
ABSTRACT

A series of N-aryl-N′-2-(benzimidazolyl) thiocarbamides and N-aryl-N′-benzenesulphonyl thiocarbamides have been synthesised and tested for antithyroidal activity.

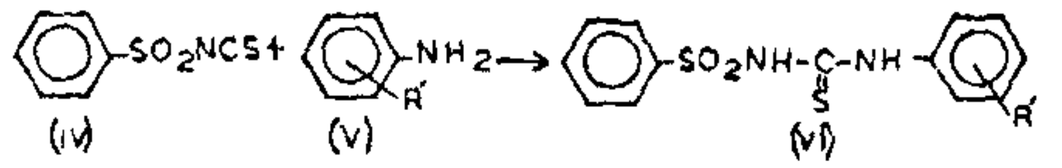
INTRODUCTION

THE antithyroid agents are of great therapeutic interest as they offer a method for correcting a hyperfunctioning gland without resort to surgery. The highly active antithyroid substances contain thiourylene moiety [>N—C(S)—N<], capable of being easily oxidized; hence suggestion has been made that the interference with thyroxine synthesis is by a direct reaction between I2 and —SH (formed by enolization) to form a disulfide[1–8].

The present communication deals with the synthesis and pharmacological studies of some N-aryl-N′-2-(benzinuidazolyl) thiocarbamides and N-aryl-N′-benzenesulphonyl thiocarbamides. In view of the pronounced antithyroidal activity of neomercazole, it was of interest to prepare some benzimidazolyl thiocarbamides consisting of a benzimidazole nucleus along with an extra thiourylene grouping by the action of aryl isothiocyanates (ii) with 2-aminobenzimidazole (i). Also the interest in the synthesis and pharmacological studies of benzenesulphonyl thiocarbamides as antithyroid drug is due to the fact that these compounds contain an extra sulphonamido grouping along with the thiourylene linkages. The synthesis has been effected by the condensation of benzenesulphonyl isothiocyanate (iv) with appropriate amines (v).



(i) (ii) (iii)



(iv) (v) (vi)

where R and R′ respectively are H, 2-CH_3, 3-CH_3, 4-CH_3, 2-CH_3O, 4-CH_3O, 2-Cl, 3-Cl, 4-Cl and 4-OC_2H_5.

The structure of these compounds have been confirmed on the basis of their analytical results, chemical behaviour and Ir. spectra. Ir. spectra (nujol phase) of these compounds show characteristic peaks at 1525–1500 cm^{-1}, 1355–1330 cm^{-1} and 780–750 cm^{-1} corresponding to thioureido linkage, sulphonamido group and substituted phenyl ring respectively.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. Arylisothiocyanates were prepared according to the method reported in the literature[9]. Benzenesulphonylisothiocyanate was prepared by the method of McFarland and Heuser[10].

N-Phenyl-N′-2-(benzimidazolyl)-thiocarbamide

A mixture of phenylisothiocyanate (2·7 g) and 2-aminobenzimidazole (2·66 g) in dry benzene (25 ml) was refluxed for 2 hours. After the reaction the excess of benzene was distilled off and the residue was washed with petroleum ether (b.p. 40–60°) and finally with ether to remove any unreacted constituents. The product was recrystallized from ethanol and could be desulphided with alkaline plumbite solution, yield 4·2 g, 80%, m.p. 110°.

Anal : Calc. for $C_{14}H_{12}N_4S$: C, 62·68; H, 4·47; N, 20·89; S, 11·94%.

Found : C, 62·62; H, 4·38; N, 20·82; S, 11·90%.

Ir. ~ 1525 cm^{-1} (>N = C = N<), ~ 780 cm^{-1} (substituted benzene ring).

Similarly other N-aryl-N′-2-(benzimidazolyl) thiocarbamides were prepared and are listed in Table I.

N-phenyl-N′-benzenesulphonylthiocarbamide

A solution of aniline (1·86 g) in benzene (20 ml) was gradually added to a solution of benzene sulphonylisothiocyanate (3·98 g) in benzene (20 ml). After few minutes a white precipitate of N-phenyl-N′-benzenesulphonylthiocarbamide was formed, which was collected and washed freely with ether to remove any unreacted constituents. This was recrystallized from ethanol and could be desulfided with alkaline plumbite solution, yield 5·25 g, 90%, m.p. 120°.

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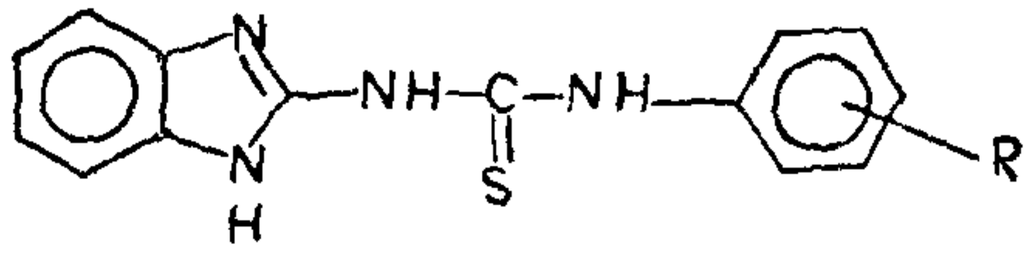
TABLE I

N-aryl-N'-2 (benzimidazolyl) thiocarbamides[a]

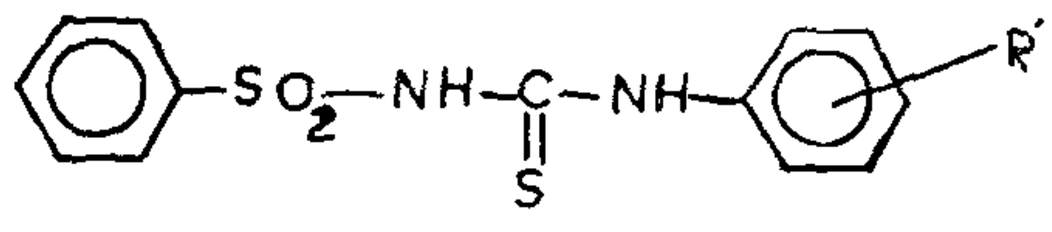


No.	R	Yield %	M.P. °C
1.	H	80	110
2.	2-CH_3	72	150
3.	3-CH_3	70	78
4.	4-CH_3	74	65
5.	2-OCH_3	75	70
6.	4-OCH_3	78	80
7.	2-Cl	74	60
8.	3-Cl	72	80
9.	4-Cl	75	155
10.	4-OC_2H_5	78	130

[a] Elemental analytidal results for C, H, N and S are within ±0·04% of the theoretical values.

TABLE II

N-aryl-N'-benzenesulphonylthiocarbamides[b]



No.	R'	Yield %	M.P. °C
11.	H	90	120
12.	2-CH_3	85	130
13.	3-CH_3	80	140
14.	4-CH_3	82	124
15.	2-OCH_3	78	122
16.	4-OCH_3	76	132
17.	2-Cl	68	130
18.	3-Cl	70	136
19.	4-Cl	74	125
20.	4-OC_2H_5	72	102

[b] Elemental analytical results for C, H, N and S are within ±0·04% of the theoretical values.

TABLE III

Pharmacological screening results of N-aryl-N'-(substituted) thiocarbamides

Compound* No.	Thyroid radioactivity, (dpm) ± std. error			Approximate estimated activity in rats (thiouracil = 1·0)
	^{131}I uptake	PB ^{131}I	Inorganic ^{131}I	
Blank	8478±50	7196±42	1238±28	
Thiouracil	4463±62	3822±30	620±18	1·0
1	3662±12	2842±15	738±32	>1·0
2	3546±42	2985±25	510±14	>1·0
3	3682±40	2781±15	886±28	>1·0
4	3487±50	3033±22	430±14	>1·0
5	4234±38	3679±13	530±16	⩾1·0
6	4386±24	3812±18	526±11	⩽1·0
7	3165±22	2517±12	619±15	>1·0
8	3286±30	2452±14	802±24	>1·0
9	3132±18	2367±24	714±17	>1·0
10	3614±15	2937±26	655±16	>1·0
11	5522±19	4897±23	587±12	<1·0
12	5731±15	5126±10	578±14	<1·0
13	5653±18	5120±17	506±19	<1·0
14	5613±12	4976±20	612±14	<1·0
15	4602±25	4123±12	465±18	<1·0
16	4598±16	3976±14	592±13	<1·0
17	4427±12	3792±18	603±11	⩾1·0
18	4398±20	3688±16	678±24	>1·0
19	4265±14	3661±13	569±21	>1·0
20	5836±24	5189±11	620±15	>1·0

* Correspond to those in Tables I and II.

Anal. : Calc. for $C_{13}H_{12}N_2O_2S_2$: C, 53·42; H, 4·14; N, 9·58; S, 21·91%.

Found : C, 53·30; H, 4·02; N, 9·52; S, 21·88%.

Ir. ~ 1500 cm^{-1} (> N=C=N <), ~ 750 cm^{-1} (substituted benzene ring), 1330 cm^{-1} (sulphonamido group).

Similarly other N-aryl-N'-benzenesulphonylthiocarbamides were prepared and are recorded in Table II.

Pharmacological screening[11]

Male Holtzman rats (100–125 g) were maintained on a low iodide diet for 3 days then divided into groups consisting of four rats in each group. The animals in each group received an intraperitoneal injection of 1 ml of either a blank (0·9% NaCl), thiouracil, or one of the test compounds. One hour later 1 μ ci of Na ^{131}I (carrier free) was injected intraperitoneally. Three hours after the injection of ^{131}I, the animals were sacrificed and the thyroids were removed. The whole lobes were placed in ground glass homogenizing tubes and counted in Nuclear-Chicago Well Scintillation Counter to determine total thyroid uptake. The whole lobes were then homogenized in 1 ml of 0·05 M barbital buffer (pH 8·6) containing $1·0 \times 10^{-5}$ thiouracil. One ml of cold 20% trichloroacetic acid (TCA) was added and the homogenate was centrifuged. The precipitate was washed twice with 1·0 ml of cold 10% TCA. The original supernatant and the two washes were combined and the radioactivity was determined. The ^{131}I in this fraction indicated the concentration of inorganic ^{131}I or TCA-soluble ^{131}I. The washed precipitate was counted in the homogenizing tube. The radioactivity in this fraction indicated the PB ^{131}I (protein-bound iodine) or the TCA-precipitable ^{131}I. The counts were all corrected for counting efficiency and are expressed as disintegration per minute.

All compounds were dissolved in saline for injection. Thiouracil was dissolved with heating to 50°. All compounds were assayed at concentration equimolar to 0·5 mg of thiouracil (3·9 μ mole) and the biological effect was noted. Table III summerizes the observations made with compounds 1 to 20.

It is evident from the results of pharmacological studies (showed in Table III) that the introduction of methyl, chloro, methoxy, and ethoxy groups in benzene ring enhances the antithyroidal activity, when compared with unsubstituted compounds. Compounds 2–5, 7–10, 17–19 appear to be slightly more potent than thiouracil.

ACKNOWLEDGEMENT

The authors are thankful to Prof. B. M. Shukla, Head, Department of Chemistry, Banaras Hindu University, Varanasi, for providing necessary laboratory facilities. Financial assistance from C.S.I.R. is also gratefully acknowledged.

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