[Agr. Biol. Chem., Vol. 32, No. 11, p. 1392~1394, 1968]

Synthesis of Benzothiazolylguanidines as Antituberculars and Antibacterials

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Received April 10, 1968

The synthesis of twenty three new N-*p*-tolyl-N'-2-(substituted)benzothiazolyl-N''-alkyl-guanidines has been reported. Several of these including some N-*p*-tolyl-N'-2-(substitued)-benzothiazolylguanidines* have been evaluated for their antitubercular activity against *M. tuberculosis* (H 37 Rv) and also for their antibacterial activity. Among these N-*p*-tolyl-N'-2-(6-methoxy)benzothiazolylguanidine and N-*p*-tolyl-N'-2-(6-methyl)benzothiazolyl-N''-methyl-guanidine are the most active as antituberculars but all the tested compounds are inactive as antibacterials.

The discovery of definite *in vitro* antitubercular activity¹⁾ of sulphanilamidothiurea and 2-mercaptobenzothiazole, and the outstanding tuberculostatic properties of N,N'-di-(*p*-n-butoxyphenyl)thiurea^{2,3)} has considerably received interests in thioureas^{4,5)} and the compounds derived from them. Eisman and his coworkers⁶⁾ obtained thiazolines and thiazolidinones on cyclization of tuberculostatic thiocarbanilides and observed that two of them having *p*-isoamyloxy groups were especially active in extending the survival rate of infected mice and showed greater activity than their thiocarbanilide precursors. Besides these, many thiazole compounds including 4-

thiazolidones⁷⁾ and 2-alkoxysubstituted aryl-benzothiazoles⁸⁾ have been found to possess high degree of antitubercular activity.

Encouraging antitubercular properties in *in vitro* tests have been reported in several biguanido derivatives.^{9,10)} Among a series of bisdiganides, prepared by Rose and Swain,¹¹⁾ one compound, chlorohexidine B. P. C. (Hibitane), has found practical use as an antibacterial agent in medical and veterinary practice. Recently, Bhargava and coworkers^{12,13)} have reported that the hydrochlorides of some benzothiazolylguanidines are more active against gram-positive bacteria as compared to the gram-negative ones. The above findings have led the authors to synthesize

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and study the antitubercular and antibacterial activity of some new *N-p*-tolyl-*N'*-2-(substituted)benzothiazolyl-*N''*-alkylguanidines (I) having typical substituents at 4-, 5- and 6-position of the benzothiazolyl nucleus.

(I) where $R=CH_3$ or C_2H_5

The compounds of the above type have been synthesized by condensing 2-aminobenzothiazoles with *p*-tolyl isothiocyanate and subsequently desulphurizing the resulting benzothiazolyl thiocarbamide with lead oxide in alcoholic alkylamine.

EXPERIMENTAL

2-Aminobenzothiazole, the starting compound, was obtained by the action of liquid bromine on asymmetrical phenyl thiourea in an inert solvent like chloroform. Similarly, various 2-amino-(substituted)-benzothiazoles¹⁴ have been prepared from the corresponding as-aryl thiourers.

N-p-Tolyl-*N'*-2-(substituted)benzothiazolyl thiocarbamides¹⁵ were prepared by the interaction of 2-aminobenzothiazoles with *p*-tolyl isothiocyanate in benzene.

***N-p*-Tolyl-*N'*-2-benzothiazolyl-*N''*-methyl guanidine.** A mixture of *N-p*-tolyl-*N'*-2-benzothiazolyl thiocarbamide (3.0 g), yellow lead oxide (5 g), 35% aqueous methylamine solution (3.0 ml) and ethanol (30 ml) was heated in a glass autoclave on a water bath for about 3 hr. After cooling, the autoclave was opened carefully and the reaction mixture was filtered. The black residue was extracted further with two 20 ml portions of ethanol. The combined filtrate was concentrated to get the desired guanidine. It was recrystallized from ethanol, yield 45%, mp 188°C. (Found: N, 18.90; S, 10.89. $C_{16}H_{16}N_4S$ requires N, 18.92; S, 10.81%).

The yields, melting points and analytical data of other *N-p*-tolyl-*N'*-2-(substituted)benzothiazolyl guanidines are given in Table I.

***N-p*-Tolyl-*N'*-2-benzothiazolyl-*N''*-ethyl guanidine.** It was prepared as described above, except that in place of methylamine, 2.5 ml of 50% aqueous ethylamine solution was used. The required guanidine was obtained in 60% yield, mp 102°C. (Found: N, 18.00; S, 10.45. $C_{17}H_{18}N_4S$ requires N, 18.06; S, 10.32%).

Similarly other guanidines in this series were prepared as recorded in Table II.

Pharmacological screening results. The compounds were tested for their antitubercular and antibacterial activity at the Central Drug Research Institute, Lucknow, India. The pharmacological screening *in vitro* against *Mycobacterium tuberculosis* var. *hominis* (Strain H 37 Rv) has shown that out of

TABLE I. *N-p*-TOLYL-*N'*-2-(SUBSTITUTED) BENZOTHIAZOLYL-*N''*-METHYLGUANIDINES

S. No.	Substituent X	Yield, %	mp °C	mol. formula	% Nitrogen		% Sulphur	
					Found	Calcd.	Found	Calcd.
1	4-Methyl	48	125	$C_{17}H_{18}N_4S$	18.02	18.06	10.23	10.32
2	5-Methyl	70	113	$C_{17}H_{18}N_4S$	17.96	18.06	10.19	10.32
3	6-Methyl	74	153	$C_{17}H_{18}N_4S$	18.17	18.06	10.46	10.32
4	4-Chloro	50	148	$C_{16}H_{15}ClN_4S$	17.00	16.94	9.50	9.68
5	5-Chloro	42	149	$C_{16}H_{15}ClN_4S$	16.81	16.94	9.69	9.68
6	6-Chloro	95	136	$C_{16}H_{15}ClN_4S$	16.94	16.94	9.57	9.68
7	6-Bromo	60	151	$C_{16}H_{15}BrN_4S$	14.98	14.94	8.55	8.53
8	4-Methoxy	50	176	$C_{17}H_{18}N_4OS$	17.09	17.18	9.99	9.82
9	6-Methoxy	25	127	$C_{17}H_{18}N_4OS$	17.20	17.18	9.74	9.82
10	4-Ethoxy	92	135	$C_{18}H_{20}N_4OS$	16.43	16.47	9.22	9.41
11	6-Ethoxy	66	130	$C_{18}H_{20}N_4OS$	16.65	16.47	9.58	9.41

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TABLE II. N-*p*-TOLYL-N'-2-(SUBSTITUTED) BENZOTHAZOLYL-N''-ETHYLGUANIDINES

S. No.	Substituent X	Yield, %	mp °C	mol. formula	% Nitrogen		% Sulphur	
					Found	Calcd.	Found	Calcd.
1	4-Methyl	95	109	C ₁₈ H ₂₀ N ₄ S	17.20	17.29	9.91	9.88
2	5-Methyl	80	82	C ₁₈ H ₂₀ N ₄ S	17.15	17.29	9.75	9.88
3	6-Methyl	86	117	C ₁₈ H ₂₀ N ₄ S	17.26	17.29	9.98	9.88
4	4-Chloro	80	140	C ₁₇ H ₁₇ ClN ₄ S	16.22	16.26	9.00	9.29
5	5-Chloro	30	194	C ₁₇ H ₁₇ ClN ₄ S	16.37	16.26	9.37	9.29
6	6-Chloro	50	144	C ₁₇ H ₁₇ ClN ₄ S	16.29	16.26	9.34	9.29
7	4-Methoxy	65	166	C ₁₈ H ₂₀ N ₄ OS	16.38	16.47	9.51	9.41
8	6-Methoxy	30	123	C ₁₈ H ₂₀ N ₄ OS	16.43	16.47	9.40	9.41
9	4-Ethoxy	68	120	C ₁₉ H ₂₂ N ₄ OS	15.94	15.82	9.06	9.04
10	6-Ethoxy	63	143	C ₁₉ H ₂₂ N ₄ OS	15.80	15.82	9.13	9.04

TABLE III. ANTITUBERCULAR SCREENING RESULT OF N-*p*-TOLYL-N'-2-(SUBSTITUTED)BENZOTHAZOLYL-N''-ALKYL (OR H)GUANIDINES

S. No.	Substituent X	Alkyl group or H	<i>Mycobacterium tuberculosis</i> (H37Rv)	
			Dose, μg/ml	Activi- ty
1	4-Chloro	H	100	++
2	5-Chloro	H	100	++
3	6-Chloro	H	100	++
4	6-Bromo	H	200	+
5	6-Methoxy	H	40	+++
6	5-Methyl	CH ₃	200	—
7	6-Methyl	CH ₃	40	+++
8	4-Chloro	CH ₃	200	—
9	6-Chloro	CH ₃	100	++
10	4-Methoxy	CH ₃	200	+
11	4-Ethoxy	CH ₃	200	+
12	6-Ethoxy	CH ₃	200	+
13	H	C ₂ H ₅	200	—
14	4-Methyl	C ₂ H ₅	200	—
15	6-Methyl	C ₂ H ₅	200	—
16	6-Chloro	C ₂ H ₅	200	—
17	4-Methoxy	C ₂ H ₅	200	—
18	4-Ethoxy	C ₂ H ₅	200	—

(—) inactive, (+) slight, (++) marked, (+++) very high.

all the tested compounds (see Table III), N-*p*-tolyl-N'-2-(6-methoxy)benzothiazolyl guanidine and N-*p*-tolyl-N'-2-(6-methyl)benzothiazolyl-N''-methyl guanidine are the most active. It is also evident from Table III that the replacement N-methyl by N-ethyl results in the total loss of activity.

The antibacterial activity of all the compounds, as reported in Table III, has been screened against *Salmonella typhi*, *Staphylococcus aureus* and *-Comma*. It was observed that these were inactive at concentration of 200 μg/ml.

Acknowledgements. Thanks of the authors are due to Prof. G. B. Singh, Head of the Department of Chemistry, for providing the necessary facilities; Dr. Nityanand, Secretary, C.D.R.I., Lucknow, India, for pharmacological screening and to the Council of Scientific and Industrial Research, New Delhi, India for the award of a Junior Research Fellowship to one of us (R.L.).