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Studies on 1, 3, 5-S-Triazine : Synthesis of Some Possible Antituberculous Compounds

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In the present investigation some N′-[N-2-(4-arylamino)-1,3,5-S-Triazino glycyl]-N^2-(arylidene) hydrazines, 1-[N-2′-(4′-arylamino)-1,3,5-Triazino glycyl)-4-Aryl semicarbazide and 1-[N-2′(4′-arylamino)-1,3,5-triazino glycyl]-4-aryl thiosemicarbazides have been synthesised with a view to studying their tuberculostatic activity.

Derivatives of 1,3,5-triazine have attained considerable importance in recent years. Derivatives of this nucleus have been used successfully for a variety of purposes viz., as fungicides, bactericides and diuretic[1]. They have also been used as anti-hypertensive agents having vasodilatory activity and can also be used as antisecretory agents and as central nervous system depressants[2].

The present communication describes the preparation of some aryl substituted hydrazines, semicarbazides and thiosemicarbazides derived from 2-amino-4-aryl substituted-1,3, 5-triazines with a view to evaluating the antitubercular activity, if any. It is earlier known that substituted hydrazines, semicarbazides and thiosemicarbazides possess antitubercular properties[3],[4].

Compounds of this type with different heterocyclic units have successfully been prepared[5].

2-Amino 4-aryl substituted-1,3,5-s-triazines were prepared by the standard method[6].

The present scheme follows the initial preparation of the intermediate hydrazides by the condensation of 2-amino-4-aryl substituted-1,3,5-triazines with ethyl chloro acetate in the presence of sodium acetate to give the ethyl ester of N-2-(4-arylamino)-1,3,5-triazino glycine[7].

$$RNH_2 + ClCH_2COOC_2H_5 \xrightarrow{CH_3COONa} RNHCH_2COOC_2H_5$$

The glycine esters on subsequent reaction with hydrazine hydrate gave the acid hydrazides.

$$RNHCH_2COOC_2H_5 + H_2NNH_2, H_2O \longrightarrow RNHCH_2COHNNH_2$$

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5. V. S. Misra and R. S. Verma, *J. Indian Chem. Soc.*, 1963, **40**, 799.
6. *Chem. Abst.*, 1966, **64**, 3573, and 1959, **53**, 420.
7. Hansdorfer, *Ber.*, 1889, **22**, 1799.

The acid hydrazides thus obtained were made to condense with :

(i) aromatic aldehydes to give hydrazine derivatives[8]

$$RNHCH_2COHNNH_2+R_1CHO \longrightarrow RNHCH_2COHNN=HC-R_1$$

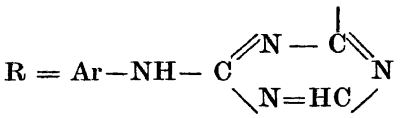
(ii) Aryl isocyanates to give semicarbazides[9]

$$RNHCH_2COHNNH_2+R_2-N=C=O \rightarrow RNHCH_2COHNNH-\underset{\underset{O}{\|}}{C}-NH-R_2$$

and

(iii) aryl isothiocyanate to give thiosemicarbazides[10]

$$RNHCH_2COHNNH_2+R_3-N=C=S \rightarrow RNHCH_2COHNNH-\underset{\underset{S}{\|}}{C}-NH-R_3$$



EXPERIMENTAL

N-2(4-*anilino*)-1,3,5-*triazino glycine ethyl ester* : A mixture of 7·5 g. of 2-amino-4-anilino 1,3,5-triazine, 6·56 g. of sodium acetate and 4·8 g. of ethyl chloro acetate was suspended in 35 ml. of water. It was heated in a steam bath for 2 hrs. cooled and diluted. The solid obtained was washed with water, filtered and crystallised from benezene. M.P. 147°, yield—70%; (Found : N, 25·10; $C_{13}H_{15}N_5O_2$ requires N, 25·64%). N-2(4-*o*-chloro anilino)-1,3,5-triazino glycine ethyl ester was prepared in an analogous manner. M.P. 198°, yield—65% (Found : N, 22·25; $C_{13}H_{14}ClN_5O_2$ requires 22·77%).

N-2-(4-*anilino*)-1,3,5-*triazino glycyl hydrazide* : A solution of 10·9 g. of N-2(4-anilino)-1,3,5-triazino glycine ethyl ester in ethanol was taken in a conical flask and 2·5 g. of 95% hydrazine hydrate was added to it. The mixture was refluxed for 6 hrs. in a water bath. The solvent was removed. The solid obtained was crystallised repeatedly from absolute ethanol. M.P. 162°, yield—65% (Found : N, 37·31; $C_{11}H_{13}N_7O$ requires 37·84%). N-2 (4-*o*-chloro anilino)-1,3,5-triazino glycyl hydrazide was prepared in an analogous manner. M.P. 196°, yield, 60% (Found : N, 32·98; $C_{11}H_{12}ClN_7O$ requires N, 33·39%).

N'-[*N*-2(4-*anilino*)-1,3,5-*triazino glycyl*] *N"*-(*benzylidene*) *hydrazine* : 10·4 g. of N-2 (4-anilino)-1,3,5-triazino glycyl hydrazide was added to hot ethanolic solution of 4·3 g. of benzaldehyde containing a few drops of sulphuric acid. The mixture was refluxed in a waterbath for 2 hrs. The solid separated out on cooling in ice. It was filtered and crystallised from alcohol-acetic acid (1 : 1) mixture.

8, 9. V. S. Misra and R. S. Verma, *J. Indian Chem. Soc.*, 1963, **40**, 799.

10. Buu-Hoi, D. Xuong and H. Nam, *J. Chem. Soc.*, 1956, 2160.

The analytical data are given in Table I.

TABLE I

[*Corresponding to reaction* (*i*)]

Sl. no.	Nature of Ar	Nature of R_1	M.P. °C	Yield %	Formula	% N Found	% N Calc.
1.	Phenyl	Phenyl	171	69	$C_{18}H_{17}N_7O$	28.32	28.24
2.	,,	*p*-anisyl	166	71	$C_{19}H_{19}N_7O_2$	25.66	25.99
3.	,,	*o*-Hydroxy phenyl	208	69	$C_{18}H_{17}N_7O_2$	26.83	27.00
4.	,,	Cinnamyl	146	36	$C_{20}H_{19}N_7O$	26.03	26.27
5.	*o*-Chloro phenyl	Phenyl	238	60	$C_{18}H_{16}N_7OCl$	25.53	25.68
6.	,,	*p*-Anisyl	127	58	$C_{19}H_{18}N_7O_2Cl$	23.77	23.82
7.	,,	*o*-hydroxy phenyl	205*	49	$C_{18}H_{16}N_7O_2Cl$	24.58	24.65
8.	,,	Cinnamyl	193	43	$C_{20}H_{18}N_7OCl$	24.13	24.05

* denotes decomposition.

1-[*N*-2′-(4′-*anilino*)-1′,3′,5′-*triazino glycyl*] 4-*phenyl semicarbazide* : 4·7 g. of phenyl isocyanate was taken in 35 ml. benzene and 10·4 g. of the N-2(4-anilino)-1,3,5-triazino glycyl hydrazide was added to it. The mixture was refluxed for 2 hrs. in a water bath. The product obtained on cooling was recrystallised from ethanol.

The compounds prepared are given in Table II.

TABLE II

[*Corresponding to reaction* (*ii*)]

Sl. no.	Nature of Ar	Nature of R_2	M.P. °C	Yield %	Formula	% N Found	% N Calc.
1.	Phenyl	Phenyl	118	45	$C_{18}H_{18}N_8O_2$	29.46	29.63
2.	,,	alpha-Naphthyl	182	25	$C_{22}H_{20}N_8O_2$	26.25	26.17
3.	*o*-Chlorophenyl	Phenyl	191	36	$C_{18}H_{17}N_8O_2Cl$	26.98	27.15
4.	,,	alpha-Naphthyl	240	47	$C_{22}H_{19}N_8O_2Cl$	24.34	24.22

1-[*N*-2′-(4′-*anilino*) 1′,3′,5′-*triazino glycyl*]-4-*phenyl thiosemicarbazide* : A mixture of 5·4 g. of phenyl isothiocyanate and 10·4 g. of N-2-(4-anilino)1,3,5-triazino glycyl hydrazide was taken in benzene (35 ml), and the mixture was refluxed for about 2 hrs. in a water bath. On cooling the unreacted substance precipitated out. It was filtered. The filtrate on concentration yielded the desired product which was collected and crystallised, from absolute alcohol. M.P. 183°, yield—67% (Found : N, 27·97; $C_{18}H_{18}N_8OS$ requires N, 28·43%).

1-[*N*-2′-(4′-o-*chloro anilino*)-1′,3′,5′-*triazino glycyl*) 4-*phenyl thiosemicarbazide* was prepared in an analogous manner. M.P. 142°. Yield—70% (Found : N, 25·88%, $C_{18}H_{17}ClN_8OS$ requires N, 26·14%).

The pharmacological screening of these compounds will be published elsewhere.

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