Potential Anti-viral Compounds. II

Synthesis of some Aromatic aldehyde thiosemicarbazones and derivatives of 5-carboxymethyl thiazolidine-2:4-dione

By V. S. Misra and N. S. Agarwal

Summary

Ten new thiosemicarbazones by condensing two different aldehydes with 4-aryl thiosemicarbazides and their ten condensation products, with maleic anhydride, i. e. derivatives of 5-carboxymethyl thiazolidine-2,4-dione, have been synthesised with a view to study their anti-viral activity.

Hamre et al.[1]) were one of the earliest to report the anti-viral activity of benzaldehyde thiosemicarbazones. Since then thiosemicarbazones of a number of aromatic and heterocyclic aldehydes have been synthesised and shown to possess significant anti-viral activity[2–4]). Thompson et al.[5]) have suggested that their activity is possibly due to the presence of a cyclic component and a $=N \cdot NH \cdot \underset{\underset{S}{\|}}{C} \cdot NH_2$ grouping. Recently Krbavcic et al.[6]) have, by the condensation of thiosemicarbazones with maleic anhydride, obtained derivatives of 5-carboxymethyl thiazolidine-2, 4-dione. This condensation has led to considerable anti-viral activity.

The present authors have extended this work by preparing 4-aryl thiosemicarbazones of 2-Methoxy and 2-Ethoxy Naphthaldehydes and then condensing these with maleic anhydride so as to obtain the derivatives of 5-carboxymethyl thiazolidine-2, 4-dione.

[1]) D. Hamre, Bernstein jr. and R. Donovick, Proc. Soc. Exper. Biol. and Med. **73**, 275 (1950).

[2]) K. A. Brownlee and D. Hamre, J. Bact. **61**, 127 (1951).

[3]) D. Hamre, K. A. Brownlee and R. Donovick, J. Immunol. **67**, 305 (1951).

[4]) R. L. Thompson, M. L. Price and S. A. Minton jr., Proc. Soc. Exper. Biol. and Med. **78**, 11 (1951).

[5]) R. L. Thompson, S. A. Minton jr., J. E. Officer and G. H. Hitchings, J. Immunol. **70**, 229 (1953).

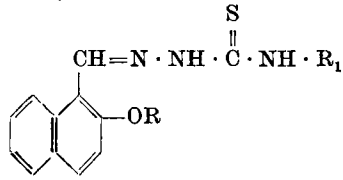
[6]) A. Krbavcic, M. Plut, A. Pollak, M. Tisler, M. Likar and P. S. Schauer, J. Med. Chem. **9**, 430 (1966).

Experimental

(1) 2-Methoxy and 2-Ethoxy Naphthaldehydes were prepared by the method of BUU HOI et al.[7]). In the case of 2-Methoxy Naphthaldehyde, however, the mixture was heated on water bath for 90 mts. only when 0.1 mole of Nerolin was taken, as prolonged heating led to the formation of a tarry mass.

2. 4-Aryl thiosemicarbazides were prepared according to the method of KAZAKOV et al.[8]).

Table 1
4-Aryl-1-(1-Naphthaldehyde-2-alkoxy)-3-thio-semicarbazones



No.	R =	R_1 =	M. P. °C	Formula	% Nitrogen Calculated	% Nitrogen Found
1	CH_3	o-$CH_3 \cdot C_6H_4$—	182	$C_{20}H_{19}N_3OS$	12.03	11.76
2	CH_3	m-$CH_3 \cdot C_6H_4$—	167	$C_{20}H_{19}N_3OS$	12.03	11.54
3	CH_3	p-$CH_3 \cdot C_6H_4$—	181	$C_{20}H_{19}N_3OS$	12.03	11.96
4	CH_3	o-$C_2H_5O \cdot C_6H_4$—	160	$C_{21}H_{21}N_3O_2S$	11.08	11.20
5	CH_3	p-$C_2H_5O \cdot C_6H_4$—	190	$C_{21}H_{21}N_3O_2S$	11.08	10.94
6	CH_3	p-Cl · C_6H_4—	187	$C_{19}H_{16}ClN_3OS$	11.36	10.82
7	C_2H_5	C_6H_5—	183	$C_{20}H_{19}N_3OS$	12.03	12.02
8	C_2H_5	m-$CH_3 \cdot C_6H_4$—	183	$C_{21}H_{21}N_3OS$	11.57	11.09
9	C_2H_5	p-$CH_3 \cdot C_6H_4$—	196	$C_{21}H_{21}N_3OS$	11.57	11.36
10	C_2H_5	o-$C_2H_5O \cdot C_6H_4$—	168	$C_{22}H_{23}N_3O_2S$	10.68	10.36

3. 4-Aryl 1-(2-alkoxy naphthaldehyde)-3-thiosemicarbazones (Table 1). Equimolar amounts of the corresponding aldehyde and 4-Aryl thiosemicarbazide in 95% ethanol were refluxed for one hour on a steam bath. The excess solvent was distilled off, the residue filtered after cooling and then recrystallised from acetone or acetone—water mixture in 75—90% yield.

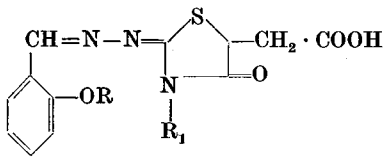
4. Derivatives of 5-Carboxymethyl thiazolidine-2,4-dione (Table 2). Equimolar amounts of the corresponding thiosemicarbazone and maleic anhydride were suspended in either benzene or toluene and the mixture was refluxed for 2—3 hours. The excess solvent was distilled off, the residue cooled, filtered and recrystallised from a suitable solvent.

The anti-viral activity of these compounds will be reported later on.

---

[7]) NG. PH. BUU HOI and DENISE LAVIT, J. chem. Soc. London **1955**, 2776—2779.
[8]) V. YA. KAZAKOV and I. YA. POSTOVSKII, C. A. **55**, 23415e (1961).

Table 2
Derivatives of 5-carboxymethyl thiazolidine-2,4-dione



No.	R =	R_1 =	M. P. °C	% yield (of theory)	Solvent used for crystallisation	Formula	% Nitrogen Calc.	% Nitrogen Found
1	CH_3	o-CH_3 · C_6H_4—	118—119	62	Benzene	$C_{24}H_{21}N_3O_4S$	9.39	9.91
2	CH_3	m-CH_3 · C_6H_4—	200	76	Acetone—water	$C_{24}H_{21}N_3O_4S$	9.39	9.02
3	CH_3	p-CH_3 · C_6H_4—	229—231	59	Acetone—water	$C_{24}H_{21}N_3O_4S$	9.39	8.89
4	CH_3	o-C_2H_5O · C_6H_4—	173—174	54	Alcohol	$C_{25}H_{23}N_3O_5S$	8.80	9.31
5	CH_3	p-C_2H_5O · C_6H_4—	227—228	73	Acetone—water	$C_{25}H_{23}N_3O_5S$	8.80	8.34
6	CH_3	p-Cl · C_6H_4—	245d	46	Acetone	$C_{23}H_{18}ClN_3O_4S$	8.98	8.99
7	C_2H_5	C_6H_5—	222	64	Acetone—water	$C_{24}H_{21}N_3O_4S$	9.39	9.36
8	C_2H_5	m-CH_3 · C_6H_4—	226—228	48	Acetone—water	$C_{25}H_{23}N_3O_4S$	9.07	9.05
9	C_2H_5	p-CH_3 · C_6H_4—	214	65	Acetone—water	$C_{25}H_{23}N_3O_4S$	9.07	9.10
10	C_2H_5	o-C_2H_5O · C_6H_4—	188	57	Acetone—water	$C_{26}H_{25}N_3O_5S$	8.53	8.55

d = decomposition.

The authors are thankful to Dr. A. B. SEN, Professor and Head, Department of Chemistry, Lucknow University, for his kind interest in the work. One of us (N.S.A.) is indebted to the C.S.I.R. New Delhi, for the award of a J.R.F.

Lucknow (India), Chemistry Department, Lucknow University.

Bei der Redaktion eingegangen am 24. Juni 1967.