SYNTHESIS OF 1-BENZYL-6-AZAURACIL DERIVATIVES, CHLORINATED IN THE NUCLEUS*

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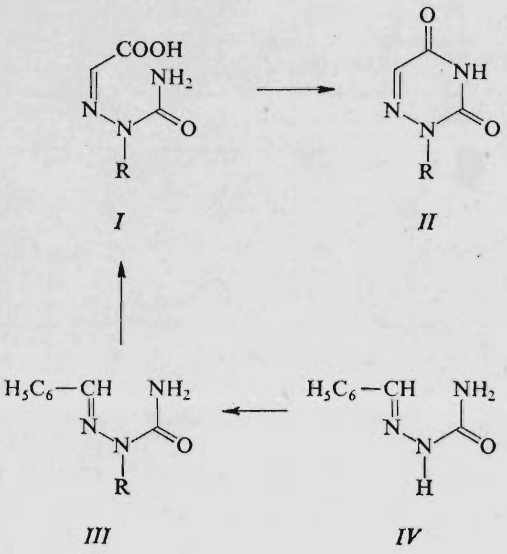
Received November 4th, 1980

Glyoxylic acid 2-benzylsemicarbazone derivatives, chlorinated in the aromatic nucleus (*Ia—Id*) were prepared either by reaction of glyoxylic acid semicarbazone with the corresponding benzyl chlorides or by treatment of benzylidene semicarbazide with substituted benzyl chlorides and reaction of the formed semicarbazides *IIIa—IIId* with glyoxylic acid. The semicarbazones *Ia—Id* were cyclized by heating with sodium hydroxide in ethylene glycol to give the corresponding 1-benzyl-6-azauracils *IIa—IId*.

It has been found recently that derivatives of 1-benzyl-6-azauracil (2-benzyl-3,5--dioxo-2,3,4,5-tetrahydro-1,2,4-triazine, *II*), in which electronegative groups such as halogen, cyano or nitro group are attached to the benzene ring, exhibit significant coccidiostatic activity[1]. These compounds can be prepared by procedures, already described for 1-benzyl-6-azauracil, however, neither the direct benzylation of 6-azauracil[2] nor its modified version[1] afford high yields of products which, moreover, are contaminated with 3-benzyl- and 1,3-dibenzyl-6-azauracil. The formation of isomers can be suppressed by use of protecting groups; this, necessarily, represents two additional reaction steps. The synthesis from 3,5-bis(trimethylsilyloxy)-1,2,4--triazine[3] is also not very suitable because it affords low yields of products[1]. A substantially better method consists in benzylation of 3-benzoyl-6-azauracil[4], using the well removable benzoyl protecting group[5]. The method of choice, however, seems to be benzylation of glyoxylic acid semicarbazone[2] (*I*, $R = H$) which, as the result of greater difference in nucleophilicity of the nitrogen atoms leads exclusively to the 2-benzylsemicarbazone *I* ($R = CH_2C_6H_5$). Similarly, benzylidenesemicarbazide (*IV*) is benzylated to give solely 1-benzylidene-2-benzylsemicarbazide (*III*, $R = CH_2C_6H_5$) which on reaction with glyoxylic acid can be converted into the semicarbazone *I* (ref.[2]).

* Part X in the series Chemistry of 1,2,4-Triazine; Part IX; This Journal *41*, 465 (1976).

We modified the mentioned reaction sequence[2] in order to prepare the 1-benzyl--6-azauracils *IIa–IId* which arise from the semicarbazones *I* by cyclization in alkaline medium (Scheme 1).



I *II* *III* *IV*

In formulae *I*, *II*, *III*:

a, R = 3-$ClCH_2C_6H_4$
b, R = 4-$ClCH_2C_6H_4$
c, R = 2,4-$Cl_2CH_2C_6H_3$
d, R = 3,4-$Cl_2CH_2C_6H_3$

In coccidiostatic activity assays, compound *IIa–IId* exhibited an activity greater than 80%. The results agree with the literature data[1]: compounds with benzyl group in the position 1 of the 6-azauracil moiety are active, the activity being enhanced by introduction of a negative substituent into the benzene ring.

EXPERIMENTAL

The melting points were determined on a Kofler block. Analytical samples were dried at 60°C and 130 Pa for 5 h.

Glyoxylic Acid 2-(4-Chlorobenzyl)semicarbazone (*Ib*)

A) Glyoxylic acid semicarbazone (5·2 g; 0·04 mol) was dissolved at 50–60°C in a solution of sodium hydroxide (3·36 g; 0·084 mol) in water (60 ml). 4-Chlorobenzyl chloride (7·08 g; 0·044 mol) was added at this temperature and the mixture was stirred in a steam bath for 6·5 h, pH being maintained at 8. While hot (50°C), the aqueous layer was decanted from the oily residue and filtered (charcoal). The filtrate was acidified (pH 2) with dilute (1 : 1) hydrochloric acid

(7·5 ml), the separated product was collected on filter, washed with water (till the washings had pH 4·5—5) and dried. The analytical sample was crystallized from ethanol. Derivatives *Ia*, *Ic* and *Id* were prepared analogously (Table I).

B) 2-(4-Chlorobenzyl)-1-benzylidenesemicarbazide (14·35 g; 0·05 mol) was added to a mixture of glyoxylic acid solution (3·7 g, 0·05 mol, in 600 ml of water) and concentrated sulfuric acid (2·5 ml). The mixture was taken to the boil and the formed benzaldehyde was distilled off. The solution was concentrated to one third of the original volume, cooled down to 10°C and the

TABLE I

Properties of the synthesized compounds

Starting compound	Product (yield, %)	M.p., °C (ethanol)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
III	*Ia* (70)	190—194[a]	$C_{10}H_{10}ClN_3O_3$ (255·7)	46·97 46·84	3·94 3·90	16·43 16·29
III	*Ib* (67·6)	196—198	$C_{10}H_{10}ClN_3O_3$ (266·7)	46·97 46·81	3·94 3·91	16·43 16·31
III	*Ic* (73·6)	211—214[a]	$C_{10}H_9Cl_2N_3O_3$ (290·1)	41·40 41·27	3·13 3·10	14·48 14·39
III	*Id* (68)	193—197[a]	$C_{10}H_9Cl_2N_3O_3$ (290·1)	41·40 41·31	3·13 3·09	14·48 14·32
IV	*IIIa* (85·7)	188—190	$C_{15}H_{14}ClN_3O$ (287·7)	62·61 62·59	4·90 4·86	14·60 14·56
IV	*IIIb* (84·3)	181—183	$C_{15}H_{14}ClN_3O$ (187·7)	62·61 62·60	4·90 4·85	14·60 14·58
IV	*IIIc* (94·7)	210—212	$C_{15}H_{13}Cl_2N_3O$ (322·2)	55·91 55·83	4·07 4·09	13·04 13·20
IV	*IIId* (73)	134—135	$C_{15}H_{13}Cl_2N_3O$ (322·2)	55·91 55·86	4·07 4·00	13·04 13·10
I	*IIa* (71)	179—181	$C_{10}H_8ClN_3O_2$ (237·6)	50·54 50·50	3·39 3·31	17·68 17·61
I	*IIb* (72)	234—236	$C_{10}H_8ClN_3O_2$ (237·6)	50·54 50·51	3·39 3·34	17·68 17·60
I	*IIc* (82—84)	212—214	$C_{10}H_7Cl_2N_3O_2$ (272·1)	44·14 44·26	2·59 2·65	15·44 15·54
I	*IId* (83)	178—180	$C_{10}H_7Cl_2N_3O_2$ (272·1)	44·14 44·28	2·59 2·61	15·44 15·56

[a] Crystallized from acetic acid.

separated solid was collected on filter, washed with water and dried, affording 8·8 g (69%) of the crude *Ib*, sufficiently pure for the cyclization. The analytical sample was crystallized from 90% acetic acid, m.p. 196—198°C; no depression on admixture with the compound obtained by procedure *A*. The identity of both samples was proved also by chromatography.

2-(4-Chlorobenzyl)-1-benzylidenesemicarbazide (*IIIb*)

A solution of sodium hydroxide (4·0 g; 0·1 mol) in water (33·5 ml) was added dropwise at 50°C to a stirred mixture of 1-benzylidenesemicarbazide (8·14 g; 0·05 mol), ethanol (200 ml), water (20 ml) and 4-chlorobenzyl chloride (12·88 g; 0·08 mol), until the resulting mixture had pH 8. After refluxing for 1·5 h, the remaining portion of the sodium hydroxide solution was added. The mixture was refluxed for 9 h, neutralized (pH 7) with acetic acid and concentrated to about one half of its original volume. The separated 2-(4-chlorobenzyl)-1-benzylidenesemicarbazide was collected on filter and washed with water and dilute ethanol. The analytical sample was crystallized from ethanol. Compounds *IIIa*, *IIIc* and *IIId* were prepared analogously (Table I).

2-(4-Chlorobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (*IIb*)

Sodium hydroxide (2·4 g; 0·06 mol) was dissolved under stirring in ethylene glycol (20 ml) at 120—125°C and the solution mixed with glyoxylic acid 2-(4-chlorobenzyl)semicarbazone (5·1 g; 0·02 mol). The mixture was kept at the mentioned temperature for 2 h, diluted with water (100 ml) and acidified with dilute (1 : 1) hydrochloric acid (pH 2). The separated solid was filtered, washed with water and dried, yielding 3·41 g (72%) of the crude *IIb* which was crystallized from ethanol. Analogously were prepared also the compounds *IIa*, *IIc* and *IId* (Table I).

Determination of Anticoccidial Activity

Each compound was tested on 10 chickens (sexed cockerels), infected experimentally with *Eimeria lenella* coccidia. Aministration of the feed, containing the tested compound at a level of 125 ppm, started two days before the infection. The activity was evaluated by calculation of the anticoccidial index which was related to the controls. The active compounds were tested further: chickens were infected with a mixed culture of oocysts of *E. tenella*, *E. maxima*, *E. necatrix* and *E. acervolina* species. The tested compounds were applied at the levels 250, 125 and 60 ppm. The activity against the given coccidia species was evaluated according to Johnson and Reid[6]. Suitable compounds were then tested by box test on litter.

REFERENCES

1. Mylari L., Miller M. W., Howes H. L., jr, Figdor S. K., Lynch J. E., Koch R. C.: J. Med. Chem. *20*, 475 (1977).
2. Nováček A., Hesoun D.: This Journal *30*, 3890 (1965).
3. Durr G. J., Keiser J. F., Ierardi P. A.: J. Heterocycl. Chem. *4*, 291 (1967).
4. Nováček A., Šauliová J., Hromas J., Gut J.: Czech. 193.883 (1979).
5. Nováček A., Hesoun D., Gut J.: This Journal *30*, 1890 (1965).
6. Johnson J., Reid W. H.: Exp. Parasitology *28*, 30 (1970).

Translated by M. Tichý.