

REACTION OF 1-SUBSTITUTED SEMICARBAZIDE DERIVATIVES WITH BENZALDEHYDEA. NOVÁČEK^a and J. GUT^b^b*Chemopharma, 400 00 Ústí nad Labem and*^b*Institute of Organic Chemistry and Biochemistry,
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Semicarbazidoacetic acid (*Va*) or its cyclohexylammonium salt *Vb* and 1-benzylsemicarbazide (*Vc*) when boiled with benzaldehyde in aqueous ethanol or in acetic acid gives 2-benzylidene-1-carbamoylhydrazinoacetic acid (*Via*) or its cyclohexylammonium salt *VI* and 1-benzylidene-2-benzylsemicarbazide (*Vic*), respectively. Under analogous conditions 1-phenylsemicarbazide (*Vd*) and 1-benzylsemicarbazide (*Ve*) split off the carbamoyl group giving rise to N-phenyl-N'-benzylidenehydrazine (*VIIIa*) and N-benzoyl-N'-benzylidenehydrazine (*VIIIb*) resp. 1-(*p*-Toluenesulfonyl)-semicarbazide and 1-(*p*-acetamidobenzenesulfonyl)semicarbazide cyclize under the effect of benzaldehyde to 3-phenyl-4,5-dihydro-1,2,4-triazol-5-one (*IX*).

Recently we described¹ the reaction of three types of cyclic hydrazides with six-membered rings (type *A*), *i.e.* hexahydropyridazin-3-one (*II*), cyclic succinic acid hydrazide (*III*), and hexahydro-1,2,4-triazine-3,5-dione (*IV*) with benzaldehyde, leading to N-benzylidene derivatives of isomeric substances with a five-membered ring (type *B*). Formally the reaction consists in a rearrangement of cyclic 1,2-disubstituted derivatives of hydrazine to cyclic 1,1-disubstituted derivatives. The same reaction has already been described earlier² with 1,2,3,4-tetrahydrophtalazinedione (*I*). The reaction products were in all instances of the same type, so that it could be expected that the mechanism of their formation would also be the same. However, as in no case we were able to obtain the intermediary product of this reaction its course can be estimated only indirectly.

Two mechanisms may be considered. The first is the isomerization of substance *A* to *B*, and the reactions of *B* with benzaldehyde to stable benzylidene derivative. In the second case it may be supposed that the primary reaction of substance *A* with benzaldehyde affords the unstable product *A'* which is then converted to the stable benzylidene derivative of substance *B*. Of course, it is not excluded that in the case of some of the substances investigated both mechanisms may be operative parallelly.

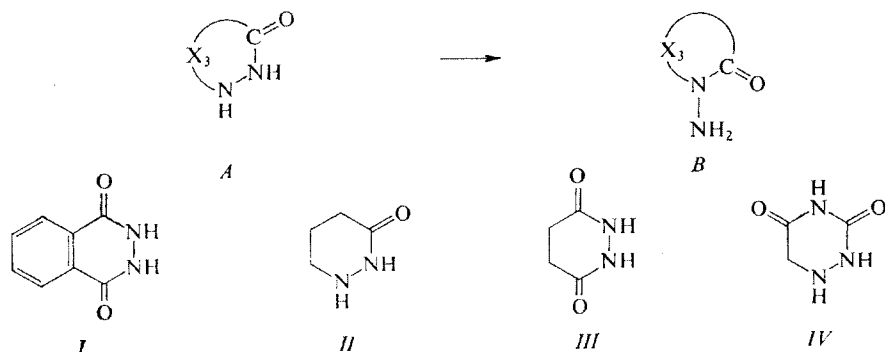
With phthalazinedione *I* the isomerization *A* → *B* has not been observed either by us or by other authors². We were also unable to prove it in the case of triazinedione *IV*. In both these cases the formation of a non-isolated unstable intermediate *A'* may

be expected which was also already considered by Drew and Hatt² in the case of substance *I*. In contrast to this we found that at elevated temperatures the substances *II* and *III* do indeed undergo a partial isomerization to five-membered isomers *B* even in the absence of benzaldehyde (*i.e.* to 1-amino-2-pyrrolidone or N-aminosuccinimide). Hence in these cases the first of the mentioned mechanisms, or at least its participation, cannot be excluded.

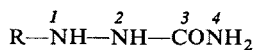
In order to verify whether the mentioned reaction is limited to cyclic compounds with a possible contraction $A \rightarrow B$ only, or whether it is also possible in some other substances with the hydrazide group, we had to apply it in this study to acyclic analogues of substance *IV*; 1-substituted semicarbazides may be considered such substances.

Among 1-substituted semicarbazides semicarbazidoacetic acid (*Va*) as well as its cyclohexylammonium salt *Vb* are most similar to substance *IV*. Substances *Va* and *Vb* are also formed on hydrolysis³ of substance *IV*. Refluxing of substances *Va* and *Vb* with benzaldehyde in aqueous ethanol gave 2-benzylidene-1-carbamoylhydrazineacetic acid (*VIa*) or its cyclohexylammonium salt *VIb*, from which the acid *VIa* can be set free with acetic acid. The structure of substances *VI* is confirmed by their cyclisation to the known 1-benzylideneaminohydantoin⁴ (*VIII*) which is also formed by direct reaction of substance *IV* with benzaldehyde¹. A further confirmation of its structure is the hydrolysis of hydantoin *VIII* in the presence of cyclohexylamine, affording the salt *VIb*.

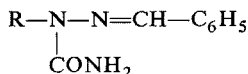
As another type 1-benzylsemicarbazide (*Vc*) was used, which was prepared from semicarbazide and benzyl chloride in aqueous solution of sodium hydroxide. On refluxing of substance *Vc* with benzaldehyde in acetic acid 1-benzylidene-2-benzylsemicarbazide (*VIc*) is formed the structure of which was proved by comparison with an authentic sample⁵. The reaction course in the case of semicarbazides substituted in the position 1 with an alkyl group or a substituted alkyl group (substances *Va, b, c*) is therefore analogous to the reaction of the cyclic substance *IV*. The reaction could also serve for a preparative preparation of 2-alkylsubstituted semicarbazides.



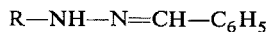
However, the reactions of 1-phenylsemicarbazide (*Vd*) and 1-benzoylsemicarbazide (*Ve*) have a different course. From substance *Vd* N-phenyl-N'-benzylidenehydrazine (*VIIId*) is formed on boiling with toluene, and substance *Ve* gives on boiling in acetic acid N-benzoyl-N'-benzylidenehydrazine (*VIIe*). Hence in both two last cases the splitting off of the carbamoyl group takes place, which could not be prevented even when lower-boiling solvents were used.



V

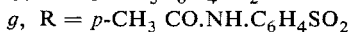
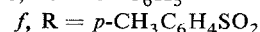
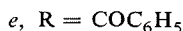
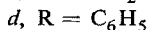
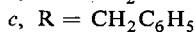
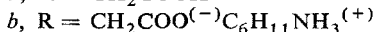


VI



VII

In formulae V–VII

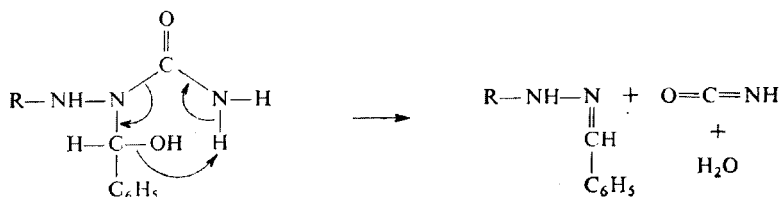


The reaction of further types of 1-substituted semicarbazides, *i.e.* 1-(*p*-toluenesulfonyl)semicarbazide (*Vf*) and 1-(*p*-acetamidobenzenesulfonyl)semicarbazide (*Vg*) with benzaldehyde takes place with considerably greater difficulty. Only after prolonged boiling in acetic acid 3-phenyl-4,5-dihydro-1,2,4-triazol-5-one (*IX*) was obtained. Its structure was proved by comparison with a sample prepared by a known⁶, but slightly modified, procedure, *i.e.* by oxidative cyclisation of benzylidenehydrazide in the presence of ferric chloride in ethylene glycol at 130°C. The comparison of both methods of preparation of substance *IX* also enables the proposition of a probable reaction mechanism for the reaction of substances *Vf* and *Vg* with benzaldehyde. The possibility that benzylidenesemicarbazide is first formed in the reaction with benzaldehyde under splitting off of arylsulphonic groups can be excluded, because its cyclization to substance *IX* takes place in the presence of oxidative agents only⁶. Therefore a primary formation of the intermediate *X* must be assumed, which is then dehydrogenated to triazol *IX* by the splitting off of arylsulfinic acids.

From the mentioned results the following conclusions can be drawn: 1) The reaction of hexahydrotriazinedione *IV* and its acyclic analogues *Va*–*Vc* with benzaldehyde takes place in the same manner. Therefore the ring contraction in substance *IV* may be excluded as the first step. On the contrary, it must be supposed that an unstable product is formed on reaction with benzaldehyde, which is then stabilized by further reaction. 2) The reaction was carried out in various solvents, depending on the reaction temperature required and the solubility of the reacting substances. Therefore the effect of the solvent on the reaction course is evidently unsubstantial. 3) As evident from examples of substances *Va*–*Vg* the reaction course with benzaldehyde is distinctly affected by the substituent in the position 1. If the quite different course

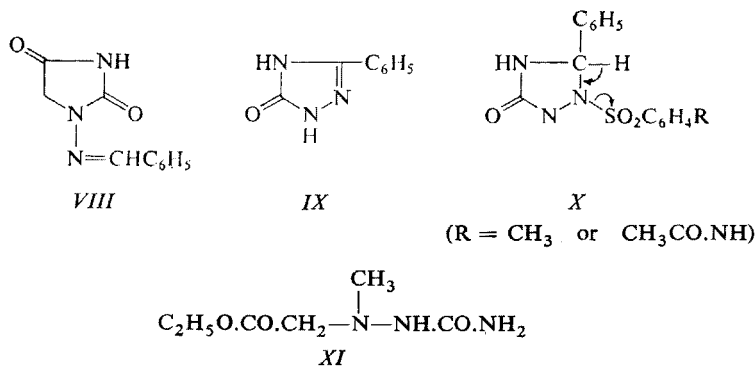
in the case of substances *Vf* and *Vg* is excluded, then the splitting off of the carbamoyl group in the reactions of substances *Vd* and *Ve* is of special interest for our further considerations concerning the reaction mechanism.

The splitting off of the carbamoyl group under the effect of benzaldehyde, and the subsequent formation of cyanic acid and the corresponding benzylidenehydrazine *VII* may be illustrated by Scheme 1. In the reaction of substances *Vd* and *Ve* 2-benzylidene-1-phenylhydrazine (*VIIId*) and 1-benzoyl-2-benzylidenehydrazine (*VIIe*) are the end products, because the readdition of cyanic acid (which could lead to substances *VI*) is impossible. In the case of benzylidenehydrazine *VIIId* this was also demonstrated experimentally^{7,8}. The addition of cyanic acid takes place both with phenylhydrazine and benzoylhydrazine^{9,10} on the nitrogen atom in the position 2, so that it cannot take place in benzylidene derivatives *VIIId* and *VIIe*.



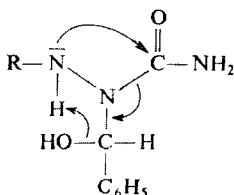
SCHEME 1

In contrast to aryl- and acylhydrazines alkyhydrazines or their alkylsubstituted derivatives do react with cyanic acid on the nitrogen atom in the position 1. Hence, if the reaction of substances *Va* – *Vc* with benzaldehyde took place in its first step also according to Scheme 1, it would be possible to explain the formation of the end products *VIa* – *VIc* by readdition of the cyanic acid to the primarily formed benzylidene derivatives *VIIa* – *VIIc*. In the case of 2-benzylidenehydrazine-1-acetic acid¹¹, some



other hydrazinoacids⁷, and 1-benzyl-2-benzylidenehydrazine⁸, such an addition of cyanic acid was also made use for preparative purposes. In all these cases the reaction proceeds, of course, at a temperature lower than in the examples described here. In order to check whether the reaction under investigation takes place in the case of substances *Va*–*Vc* in two steps, *i.e.* by splitting off and readdition of cyanic acid, we made use of a model substance in which the reverse addition is prevented by substitution – ethyl 1-methylsemicarbazido-1-acetate¹² (*XI*). On refluxing substance *XI* with benzaldehyde in ethanol and in acetic acid no corresponding benzylidene derivative was formed, but only the unchanged starting substance was recovered.

Hence, it is very probable that the reaction of substances *Va*–*Vc* with benzaldehyde takes place in one step by a cyclic mechanism according to Scheme 2. The assumption that benzaldehyde takes part already in the first phase of the reaction and that it does not form benzylidene derivative secondarily with the rearranged product may also be confirmed by thermal isomerization (by heating above the melting point) of 2-benzylsemicarbazide to 1-benzylsemicarbazide⁸. Its course is just the reverse of that which should be expected in the case studied by us.



SCHEME 2

The reaction of substances *Vd* and *Ve* in which, indeed, the splitting off of the carbamoyl group takes place under the effect of benzaldehyde is, then, of a different character, caused evidently by the nature of the substituent in the position 1.

EXPERIMENTAL

The melting points were determined on a Kofler block. Samples for analysis were dried at 60°C and 20 Torr.

1-Benzylsemicarbazide (*Vc*)

Benzyl chloride (12.7 g, 0.1 mol) was added to a solution of semicarbazide hydrochloride (14.5 g, 0.13 mol) in water (100 ml) and the mixture was heated on a boiling water bath under heating and gradual addition of a NaOH solution (total amount 12 g, 0.3 mol) in 80 ml of water, so that the pH value would be about 8.5. After 4 hours of heating the solution was allowed to stand at room temperature overnight and the separated product was crystallized twice from ethanol. Yield 13.3 g (62%) of product of m.p. 155–156°C. Literature¹³ gives m.p.⁶ 155°C.

2-Benzylidene-1-carbamoylhydrazinoacetic Acid (*Via*)

A mixture of substance^{3,3} *Va* (2.66 g, 0.02 mol), benzaldehyde (8 ml), water (10 ml) and ethanol (10 ml) was refluxed for one hour, evaporated *in vacuo* to dryness and the residue co-distilled twice with 50% ethanol (20 ml) and once with ethanol (20 ml). After crystallization from 50% ethanol 3.2 g (72%) of substance *Via* were obtained, m.p. 235–237°C (decomp.). Literature⁸ gives m.p. 239–241°C. For $C_{10}H_{11}N_3O_3$ (221.2) calculated: 54.29% C, 5.01% H, 19.00% N; found: 54.19% C, 5.09% H, 19.21% N. Applying a known procedure¹¹ substance *Via* was converted to 1-(benzylideneamino)hydantoin (*VIII*) of m.p. 254–255°C, undepressed on admixture of an authentic sample.

Cyclohexylammonium Salt of 2-Benzylidene-1-carbamoylhydrazinoacetic Acid (*Vib*)

A. Using a procedure analogous to that for the preparation of substance *Via* substance *Vib* (4.5 h; 71%), m.p. 208–210°C, was prepared from 4.64 g (0.02 mol) of substance³ *Vb*. For $C_{16}H_{24}N_4O_3$ (320.4) calculated: 59.98% C, 7.54% H, 17.49% N; found: 60.04% C, 7.61% H, 17.54% N. On dissolution of substance *Vib* in hot 50% ethanol and acidification with acetic acid and cooling substance *Via* was obtained.

B. A solution of benzylideneaminohydantoin (*VIII*, 4.06 g, 0.02 mol), cyclohexylamine (4 ml), water (5 ml) and ethanol (50 ml) was refluxed for 8 hours, evaporated in a vacuum to 30 ml volume, and the separated substance was filtered off under suction and crystallized from ethanol. Yield 4.6 g (72%) of a substance melting at 210–212°C, undepressed on admixture with a sample obtained as under *A*.

2-Benzyl-1-benzylidenesemicarbazide (*Vic*)

A mixture of substance *Vc* (2.3 g, 0.02 mol), benzaldehyde (5 ml) and acetic acid (15 ml) was refluxed for 3 hours, the solution was evaporated *in vacuo* to dryness and the residue was co-distilled twice with 50% ethanol (30 ml) and once with pure ethanol (30 ml). On crystallization of the residue from ethanol 3.9 g (79%) of product was obtained, m.p. 153–154°C, undepressed on admixture with a sample prepared by a different procedure⁵. For $C_{15}H_{15}N_3O$ (253.3) calculated: 71.12% C, 5.97% H, 16.59% N; found: 71.54% C, 5.90% H, 16.48% N.

2-Benzylidene-1-phenylhydrazine (*Viid*)

A solution of 1-phenylsemicarbazide (3.02 g, 0.02 mol), benzaldehyde (30 ml) and toluene (100 ml) was refluxed for 16 hours under carbon dioxide. The mixture was evaporated and the residue crystallized from 50% ethanol to afford 3.05 g (78%) of a product melting at 153–156°C. Literature¹⁴ gives m.p. 154.5–155.5°C. For $C_{13}H_{12}N_2$ (196.2) calculated: 79.56% C, 6.16% H, 14.28% N; found: 79.42% C, 6.05% H, 14.16% N. On boiling the mentioned mixture in the presence of air 1,5-diphenyl-2,3-dihydro-1,2,4-triazol-3-one of m.p. 300–302°C was obtained as the main product in addition to substance *Viid*. It melted undepressed on admixture of a product prepared in a different manner¹⁵.

1-Benzoyl-2-benzylidenenhydrazine (*VIIe*)

A mixture of substance⁹ *Ve* (1.79 g, 0.01 mol), benzaldehyde (10 ml), and acetic acid (50 ml) was refluxed for 2 hours, the solution was evaporated in a vacuum and the residue worked up as in the case of substance *Vic*. Crystallization of the residue from ethanol gave 1.54 (69%) of a product, m.p. 204–206°C, undepressed on admixture of a known sample¹⁶.

3-Phenyl-4,5-dihydro-1,2,4-triazol-5-one (*IX*)

A. A mixture of substance *Vf* (2.29 g, 0.01 mol) or substance *Vg* (2.72 g, 0.01 mol), benzaldehyde (4 ml) and acetic acid (50 ml) was refluxed for 20 hours and then allowed to stand at room temperature overnight. The separated product was crystallized twice from ethanol. Yield 1.1 g (68%), m.p. 324–326°C, undepressed on admixture with a sample prepared by a modification of the described procedure⁶ (procedure *B*). Literature⁶ gives m.p. 321–322°C.

B. A mixture of 1-benzylidenesemicarbazide (1.63 g, 0.02 mol), ferric chloride (3.24 g, 0.02 mol) and ethylene glycol (10 ml) was heated at 130°C for 3 hours, then diluted with water (30 ml) and the separated product was crystallized twice from ethanol. Yield 1.16 g (72%).

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