

CHEMISTRY OF 1,2,4-TRIAZINE. III.*

THE REACTION OF HEXAHYDRO-1,2,4-TRIAZINE-3,5-DIONE WITH PRIMARY AMINES

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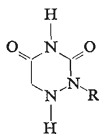
Received March 3rd, 1972

When refluxed in an aqueous solution of cyclohexylamine, hexahydro-1,2,4-triazine-3,5-dione (*Ia*) affords the cyclohexylammonium salt of semicarbazidoacetic acid (*II*). An analogous reflux of compound *Ia* with butylamine or benzylamine leads to 4-butylsemicarbazido-N-butylacetamide (*IIIa*) and 4-benzylsemicarbazido-N-benzylacetamide (*IIIb*), respectively. A similar reaction of compound *Ia* with aniline or of 2-benzylhexahydro-1,2,4-triazine-3,5-dione (*Ib*) with benzylamine affords N,N'-diphenylurea and N,N'-dibenzylurea, respectively.

In connection with our earlier investigations¹ on reactions of hexahydro-1,2,4-triazine-3,5-dione (*Ia*), the hydrolytical and aminolytical cleavage of this substance appeared of interest. With respect to the isolation and characterisation of hydrolytical products, the base-catalysed hydrolysis in the presence of primary amines was the most suitable procedure. Since the hexahydrotriazine *Ia* may be envisaged as a cyclic semicarbazide derivative, the present paper also represents a continuation of the earlier communications^{2,3} on reactions of semicarbazide derivatives with primary amines.

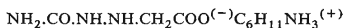
The hydrolysis or aminolysis of compound *Ia* may be expected to comprise a nucleophilic attack on the carbon atom of the carbonyl group at position 3 and the subsequent fission of the lactam bond 2-3 or 3-4, or, an analogous attack on the carbonyl group at position 5 followed by fission of the bond 4-5. By analogy⁴ with the hydrolysis of 2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (6-azauracil) derivatives as well as on the basis of the assumed interaction between the unshared pairs of electrons of nitrogen atoms and the carbonyl group, the latter route of cleavage seems more probable. The assumption was confirmed by reaction of compound *Ia* with an aqueous solution of cyclohexylamine at 100°C to give the cyclohexylammonium salt of semicarbazidoacetic acid (*II*). The structure of compound *II* was established by liberation of the free acid, or, by preparing the salt *II* from the authentic semicarbazidoacetic acid.⁵

* Part II: This Journal 37, 2221 (1972).



Ia, R = H

Ib, R = CH₂C₆H₅



II



IIIa, R = CH₂CH₂CH₂CH₃

IIIb, R = CH₂C₆H₅

An analogous ring cleavage may be observed in the reaction of the hexahydrotriazine *Ia* with anhydrous primary amines. In this cleavage, the substituted amides of semicarbazidoacetic acid occur as primary products. Analogously to reactions of benzylidenesemicarbazide with primary amines^{2,3}, the terminal amino group is immediately replaced by the N-alkylamino group. Thus, a brief reflux (5 min) of the hexahydrotriazine *Ia* with butylamine or benzylamine leads to the formation of 4-butylsemicarbazido-N-butylacetamide (*IIIa*) and 4-benzylsemicarbazido-N-benzylacetamide (*IIIb*), respectively. In contrast to the analogous products obtained from benzylidenesemicarbazide, compounds *IIIa* and *IIIb* are stable in the reaction medium and prolongation of the reaction time (3 hours) is not accompanied by any additional cleavage to give the corresponding N,N'-disubstituted ureas. On the other hand, the reaction of the hexahydrotriazine *Ia* with aniline affords after 5 min N,N'-diphenylurea; the assumed intermediate, namely, 4-phenylsemicarbazido-N-phenylacetamide, cannot be isolated even when shorter reaction times are used. A similar formation of N,N'-dibenzylurea is observed when 2-benzylhexahydro-1,2,4-triazine-3,5-dione⁶ (*Ib*) is refluxed with benzylamine for 15 min. The subsequent formation of substituted ureas obviously depends on the stabilising effect of unshared electron pairs on nitrogen atoms in the neighbourhood of the carbonyl group. This effect is less pronounced with benzylidene derivatives or derivatives substituted at position 2 (compound *Ib*). The inductive effects of the hydrocarbon substituent of the amine group must be however also taken into account as shown by reaction of the hexahydrotriazine *Ia* with aniline.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 60°C/10 Torr for 5 h.

Cyclohexylammonium Salt of Semicarbazidoacetic Acid (*II*)

A solution of hexahydro-1,2,4-triazine-3,5-dione (*Ia*; 5.75 g; 0.05 mol) and cyclohexylamine (25 ml) in water (60 ml) was heated on a steam bath for 30 min, evaporated to dryness under diminished pressure, and the residue crystallised from ethanol (100 ml) to afford 9.1 g (78%) of compound *II*, m.p. 170–172°C. For C₉H₂₀N₄O₃ (232.3) calculated: 46.53% C, 8.68% H, 24.12% N; found: 46.41% C, 8.60% H, 24.02% N. The salt *II* was also obtained by mixing equivalent amounts of authentic semicarbazidoacetic acid⁵ and cyclohexylamine in ethanol.

Reaction of Compound *Ia* and *Ib* with Amines

Compound *I* (0.05 mol) was refluxed in an excess of the corresponding amine (15 ml) and the reaction mixture cooled to 10°C to deposit the product which was collected with suction and purified by crystallisation. 4-Butylsemicarbazido-N-butylacetamide (IIIa). Obtained from *Ia* by heating the reactants for 3 h. Yield, 65%. M.p. 202–205°C (ethanol). For $C_{17}H_{24}N_4O_2$ (244.3) calculated: 54.07% C, 9.90% H, 22.93% N; found: 53.92% C, 9.82% H, 22.78% N. 4-Benzylsemicarbazido-N-benzylacetamide (IIIb). Obtained from *Ia* by heating the reactants for 3 h. Yield, 68%. M.p. 219–222°C (ethanol). For $C_{17}H_{20}N_4O_2$ (312.4) calculated: 65.36% C, 6.45% H, 17.94% N; found: 65.16% C, 6.39% H, 17.81% N.

N,N'-Diphenylurea (obtained from *Ia*) (m.p. 244–246°C, undepressed on admixture with an authentic specimen⁷; yield, 70%) and N,N'-dibenzylurea (obtained from *Ib*) (m.p. 171–173°C, undepressed on admixture with an authentic specimen; yield 68%) were obtained by heating the reactants for 15 min.

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Translated by J. Pliml.