

STUDIES IN THE FORMATION OF HETEROCYCLIC RINGS CONTAINING NITROGEN

Part XIV. Mode of Formation of Hexahydro-*s*-triazines from the Components

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ABSTRACT

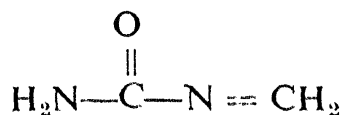
The mode of formation of keto-hexahydro-*s*-triazines has been studied by conducting the reaction in two stages. The experiments revealed that the condensation with aromatic aldehydes is more complex, and the mechanism is not clear, although in the case of aliphatic aldehydes the step-wise formation of hexahydro-*s*-triazines has been reported.

INTRODUCTION

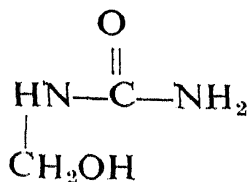
IN an earlier communication,¹ the condensation of urea with aromatic aldehydes and ammonium acetate was described and the products characterised as 2-keto-4,6-diaryl hexahydro-*s*-triazines and 1:3-*bis*-arylidene ureas. With a view to get an insight into the formation of these products, the reaction was split into two stages: (a) Condensation of urea with aromatic aldehydes and cyclization of the resulting products with ammonium acetate in a subsequent step. (b) Condensation of aromatic aldehydes with ammonium acetate in the first instance and allowing the products to react with urea later.

According to earlier work which deals mostly with the reaction between formaldehyde and urea under acidic conditions methylene urea (I)²⁻¹⁰ was reported to be formed whereas under alkaline conditions monomethylol urea and dimethylol urea II (and III) could be isolated.¹¹ By increasing the proportion of formaldehyde even tetramethylol compounds could be obtained.¹² Depending on the pH, the quantity of formaldehyde used and the reaction temperature, other products with more complicated structures were also formed in the reaction.^{13,14} Vanillin was reported to give divanillylidene urea, and furfuraldehyde a mono-

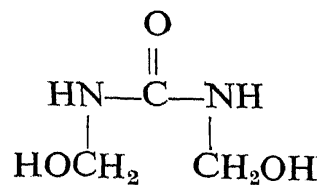
furfurylidene urea under acidic conditions.¹⁵ According to Schiff,¹⁶ benzylidene dicarbamide (IV) is produced by the action of benzaldehyde on urea.



(I)



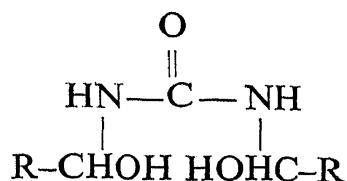
(II)



(III)



(IV)



(V)

In the past, various workers studied the reaction under different conditions and reported the formation of various types of products. The authors have made a study of the condensation of urea with aromatic aldehydes under different conditions in the molar ratio of 1:2 in order to synthesize 1:3-*bis*-(α -hydroxy aryl) ureas (V). These compounds which were postulated as intermediates in the formation of 2-keto-4,6-diaryl-hexahydro-*s*-triazines have been sought after for a study of their subsequent cyclization with ammonium acetate to test the possibility or otherwise of the step-wise formation of these compounds discussed in earlier work.

The results obtained in a detailed study of the reaction between urea (one mole) and benzaldehyde (two moles) under different conditions are summarised in Table I.

Benzaldehyde (two moles) reacted with urea (one mole) in the presence of ethanol alone or with small amounts of concentrated hydrochloric acid or using acetic acid as solvent producing trimeric 1:3-*bis*-(benzylidene) urea in varying yields. But in the presence of 5% sodium hydroxide, the product was a high melting polymeric compound reported earlier¹ during these investigations. The use of methyl alcohol along with 50% sodium hydroxide solution however, resulted in the formation of a mixture from which the trimeric benzylidene urea (6%), benzoic acid (22.1%) and 1:3-*bis*-(α -hydroxybenzyl) urea (0.8) could be isolated. Anisaldehyde gave in the condensation only anisic acid, whereas salicylaldehyde yielded a yellow solid which could not be purified because it turned black immediately. The reaction product from *o*-chloro-benzaldehyde, however, could be

fractionated into 1:3-*bis*-(α -hydroxy-*o*-chlorobenzyl) urea and 1:3-*bis*-(*o*-chlorobenzylidene) urea.

TABLE I

Reaction solvent	Conditions time hours	Nature of the product (s) formed	Percentage yield
1. Ethyl alcohol	2	Trimeric I : 3- <i>bis</i> -(benzylidene) urea, m.p. 239° C	23.7
2. Glacial acetic acid	1	do.	43.2
3. Ethyl alcohol <i>plus</i> one ml. concentrated hydrochloric acid	36	do.	54.2
4. Ethyl alcohol <i>plus</i> 5% sodium hydroxide	40	Polymeric benzylidene urea, m.p. above 300° C	35.6
5. Methyl alcohol <i>plus</i> 50% sodium hydroxide	12	(a) Benzoic acid, m.p. 121° C	22.1
		(b) I: 3- <i>bis</i> -benzylidene-urea, m.p. 239° C	6.0
		(c) I : 3- <i>bis</i> -(α -hydroxy-benzyl) urea, m.p. 184° C	0.8

The cyclization of 1:3-*bis*-(α -hydroxy-*o*-chlorobenzyl) urea with ammonium acetate did not yield *s*-triazine but resulted in the formation of 1:3-*bis*-(*o*-chlorobenzylidene) urea by dehydration. This compound on further condensation with ammonium acetate, however decomposed to *o*-chlorobenzaldehyde.

Benzaldehyde with ammonium acetate,¹⁷ produced N benzoyl N¹ benzylidene-meso-1:2-diphenyl-ethylene diamine. This was subjected to condensation with urea in the molar ratio of 1:1 in ethanol but the reactants were recovered back.

From earlier studies, it may be concluded that in the case of aliphatic aldehydes, a step-wise mechanism for the formation of *s*-triazines seems to be possible. Burke¹⁸ has prepared 2-keto-5-substituted hexahydro-*s*-triazines by condensing methylol urea with primary amines and the work

of Paquin¹⁹ who obtained similar compounds by condensing urea with aldehyde-ammonias through the intermediate 1:3-*bis*-(amino-alkyl) ureas support this conclusion. But in the case of aromatic aldehydes studied by us, the mode of formation seems to be more complex. The formation of by-products such as benzylidene urea or 1:3-*bis*-(α -hydroxybenzyl) urea seems to take place by the condensation of aldehyde with urea, with or without dehydration. These products appear to be quite stable and do not react easily with ammonium acetate. The mechanism of formation of *s*-triazines, however, is not clear.

EXPERIMENTAL

All m.p.'s are uncorrected.

I. Condensation of Aromatic Aldehydes with Urea and Subsequent Cyclization with Ammonium Acetate

Condensation of Urea with Benzaldehyde under Different Conditions

(i) *Ethyl alcohol as solvent*.—Urea (1.5 g) was taken with 95% ethanol (10 ml.) into a conical flask, warmed to dissolve urea and then benzaldehyde (5.2 g) was added. The contents of the flask were shaken thoroughly, stoppered well and kept at room temperature. After one hour some white solid started separating and the reaction mixture solidified after two hours. The solid was filtered, washed with hot water and dried (1.4 g). It was insoluble in common organic solvents but could be purified from boiling nitrobenzene, giving a white amorphous solid, m.p. 239° C. It was found to be identical with trimeric 1:3-*bis*-(benzylidene) urea obtained previously.¹

(ii) *Glacial acetic acid as solvent*.—Urea (1.5 g), benzaldehyde (5.2 g) and glacial acetic acid (5 ml) were mixed thoroughly in a conical flask and kept at room temperature. After 15–20 minutes a white solid separated which on filtration and drying (2.5 g) was found to be identical with trimeric 1:3-*bis*-(benzylidene) urea in all its properties. Recrystallisation from hot boiling nitrobenzene gave a white amorphous solid, m.p. 239–240° C.¹

(iii) *Ethyl alcohol as solvent with 5% NaOH*.—Urea (3 g), benzaldehyde (10.4 g), ethyl alcohol (10 ml) and 5% NaOH (5 ml) were refluxed for six hours, cooled to room temperature but no solid separated even after the solvent was removed under reduced pressure. Urea decomposed because of the alkaline conditions used in the experiment.

At room temperature, under similar conditions, a white amorphous solid (2.1 g), m.p. above 300° C, identical with polymeric 1:3-*bis*-benzylidene urea was obtained.¹

(iv) *Ethyl alcohol as solvent with concentrated hydrochloric acid.*—Urea (3 g), benzaldehyde (10.4 g), ethyl alcohol (20 ml) and concentrated hydrochloric acid (1 ml) were heated gently to dissolve the solids and left at room temperature. After 36 hours the reactants solidified to a white solid which on working up yielded trimeric benzylidene urea (3.3 g).

(v) *Methyl alcohol as solvent with 50% NaOH.*—Urea (6 g) was dissolved in methanol (30 ml), 10 ml of 5% NaOH were added to the solution and then benzaldehyde (20.8 g) was added with constant stirring. Immediately some turbidity appeared but dissolved on shaking. After twelve hours at room temperature some colourless solid separated out. This was fractionated into hot water insoluble (A) and hot water soluble fraction (B). (B) was found to be identical with benzoic acid. The hot water insoluble part (A) being sticky was kept in a vacuum desiccator for one week for drying (2.7 g). On treatment with ethyl acetate it gave a soluble product which on further recrystallisation from the same solvent gave long silky needles, m.p. 184° C (Found: C, 65.9; H, 5.9; N, 9.8%); $C_{15}H_{16}N_2O_3$ requires C, 66.1; H, 5.8; N, 10.2%. The ethyl acetate insoluble part on recrystallisation from nitrobenzene gave a white amorphous solid (0.7 g), m.p. 239–240° C, identical with the trimeric 1:3-*bis*-(benzylidene) urea.

II. Condensation of Other Aromatic Aldehydes with Urea

Condensation of *o*-Chlorobenzaldehyde with Urea

Urea (6 g) was dissolved in methyl alcohol (10 ml) and *o*-chlorobenzaldehyde (28.1 g) was added slowly. Instantaneous reaction was observed and the whole material solidified in a few minutes. This was washed with boiling water, filtered and dried (28.5 g).

(a) 1:3-*bis*-(*o*-hydroxy-*o*-chlorobenzyl) urea.—The solid from the above condensation was extracted with hot boiling *n*-butyl alcohol. On cooling the butanol solution, long rectangular plates (2.4 g) were obtained. On further recrystallisation from the same solvent, white long rectangular plates, m.p. 155° C, were obtained (Found: C, 52.6; H, 4.3; N, 7.9%); $C_{15}H_{14}N_2O_3Cl_2$ requires C, 52.7; H, 4.3; N, 8.2%.

(b) 1:3-*bis*-(*o*-chlorobenzylidene) urea.—The portion sparingly soluble in *n*-butyl alcohol was recrystallised twice from acetone yielding white

needles, m.p. 214° C. Mixed melting point with 1:3-bis(*o*-chlorobenzylidene) urea, obtained earlier,¹ remained undepressed.

III. Attempted Synthesis of Keto-hexahydro-s-triazine from (α -Hydroxy Benzyl) Ureas and 1:3-bis-benzylidene ureas

*(i) Cyclization of 1:3-bis-(α hydroxy-*o*-chlorobenzyl) Urea with Ammonium Acetate*

1:3-Bis-(α -hydroxy-*o*-chlorobenzyl) urea (200 mg) ammonium acetate (500 mg) and ethyl alcohol (10 ml) were refluxed on a steam bath for six hours. The reaction mixture was neutralised with ammonia, keeping the mixture cooled. A small amount of an yellowish solid that separated was filtered and recrystallised from acetone, m.p. 214 ° C. It was found to be identical with 1:3-bis(*o*-chlorobenzylidene) urea.

*(ii) Condensation of 1:3-bis-(*o*-chlorobenzylidene) Urea with Ammonium Acetate*

1:3-bis-(*o*-chlorobenzylidene) urea (800 mg), ammonium acetate (1.5g) and ethyl alcohol (10 ml) were refluxed for five hours on a steam bath. The solid dissolved slowly. On cooling the reaction mixture, only an oily liquid with an irritating odour separated. It was characterised as *o*-chlorobenzaldehyde by reaction with 2:4-dinitro-phenyl hydrazine.

IV. Condensation of Aromatic Aldehyde with Ammonium Acetate and Attempted Cyclization of the Product with Urea

(i) Condensation of Benzaldehyde with Ammonium Acetate¹⁷

Benzaldehyde (15 g) and ammonium acetate (30 g) were refluxed for three hours. The mixture was cooled and the product was filtered and washed repeatedly with ethyl alcohol. Recrystallisation from *n* butyl alcohol gave *N*-benzoyl-*N'*-benzylidene-meso-1:2-diphenyl-ethylene diamine as white crystalline solid (5.5 g), m.p. 258–259° C.

(ii) Reaction between N-Benzoyl-N'-benzylidene-meso-1:2-diphenyl Ethylene Diamine and Urea

The diamine (1.6 g) and urea (0.6 g) were refluxed with ethanol (10 ml) for six hours. After the reaction the solvent was removed by evaporation. The amine and urea were recovered unchanged.

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