STUDIES IN THE FORMATION OF HETEROCYCLIC RINGS CONTAINING NITROGEN

Part VIII. Condensation of Urea with Aromatic Aldehydes and Ammonium Acetate

BY KHALIL AHMED AND N. V. SUBBA RAO, F.A.SC.

(Department of Chemistry, Osmania University)

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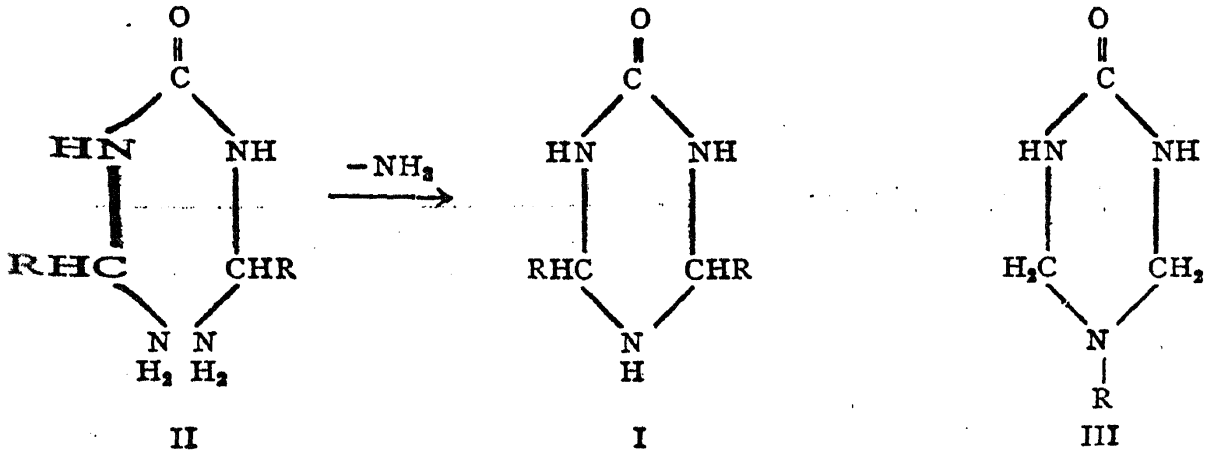
THE reaction between one mole of urea, two moles of aliphatic aldehydes and one mole of ammonia resulting in 2-keto-4, 6-disubstituted hexahydro-*s*-triazines (I) was described by Paquin and Steindorff.[1] According to Paquin[2] the keto-hexahydro-*s*-triazines were produced through the intermediate sym-di-(amino-alkyl) ureas (II). Using acetaldehyde-ammonia and urea, the intermediate sym-di-(amino-ethyl) urea was isolated by him and converted to keto-*s*-triazine with the liberation of ammonia.



II I III

Other aliphatic aldehydes behaved similarly except formaldehyde which produced only hexamethylene-tetramine; if primary amines were substituted for ammonia, formaldehyde reacted normally.

Burke[3] reported essentially the same type of reaction wherein dimethyol urea was condensed with a number of primary and substituted primary amines producing 2-keto-5-substituted-hexahydro-*s*-triazines (III) which he termed as tetrahydro-5-substituted-2 (1)-*s*-triazones.

The present work has been undertaken with a view to studying the reactivity of aromatic aldehydes in the reaction and the mode of formation of hexahydro-*s*-triazines. Aromatic aldehydes do not form aldehyde-ammonias and instead form hydrobenzamide[4] type of compounds with ammonia under

basic conditions. Further they do not yield dimethylol urea type of compounds. Schiff[5] reported the formation of benzylidene dicarbamide by heating urea with benzaldehyde. In order to avoid the formation of hydrobenzamides which are formed under basic conditions, it was considered desirable to use ammonium acetate in preference to aqueous ammonia. Ammonium acetate liberates ammonia on slow heating at a low temperature and the reaction mixture remains slightly acidic due to the acetic acid. The use of ammonium acetate in place of ammonia has been reported in such condensations leading to the synthesis of heterocyclic ring systems by a number of workers.[6–11]

Preliminary studies to arrive at the optimum conditions were first undertaken with benzaldehyde, urea and ammonium acetate in the molar ratio 2:1:1 respectively. The reaction products were found to be (1) 2-keto-4, 6-diphenyl-hexahydro-*s*-triazine, (2) 1, 3-*bis*-(benzylidene) urea and (3) hydrobenzamide. The results of the condensation under varying conditions are presented in Table I.

TABLE I

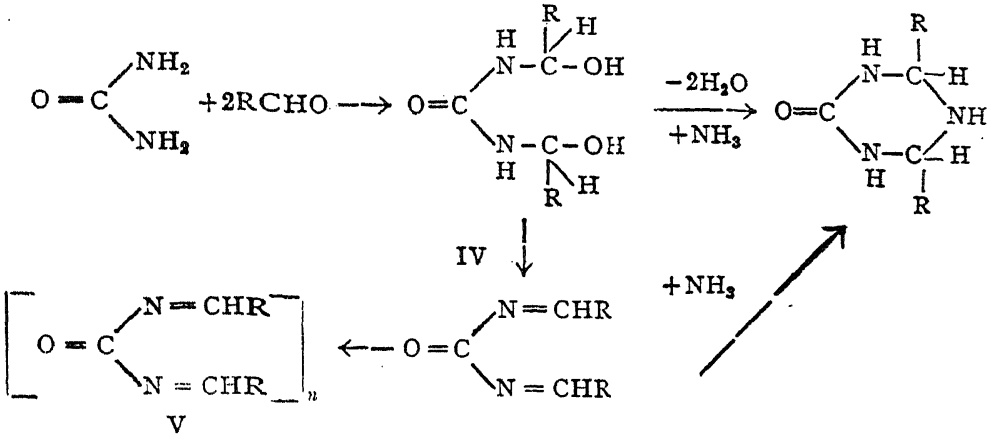
Reaction between benzaldehyde (two moles), urea (one mole) and ammonium acetate (one mole)

(Time of reaction: 6 hours)

No.	Reaction conditions	Percentage yield of		
		Keto-triazines	1, 3-*Bis*-(benzylidene) urea	Hydro-benzamide
1	95% ethanol as solvent	13·8	47·4†	..
2	Glacial acetic acid as solvent	4·3	5·1†	..
3	95% ethanol as solvent pH 7–8 with ammonia	..	..	59·1
4	95% ethanol as solvent pH 8–9 with ammonia	8·3	5·1†	59·1
5	95% ethanol as solvent pH 9–10 with ammonia	..	..	85·7
6	95% ethanol as solvent pH 8–9 (5% NaOH)	..	18·2*	11·7
7	95% ethanol as solvent excess of sodium acetate as buffer	..	..	..

* Polymeric. † Trimeric.

The formation of the keto-triazine and the benzylidene urea in the reaction may be explained on the basis of the following scheme. The unstable intermediate (IV) postulated in the mechanism could not be isolated in any of the condensations.



It could be inferred from the results given in Table I that the dehydration to 1, 3-*bis*-(benzylidene) urea is more readily facilitated in the presence of a strong alkali than the formation of triazine. The cyclisation with ammonia leading to keto-triazine seems to be favoured under the conditions of experiment (1) in 95% ethanol, although dehydration could not be prevented. Using these conditions, the condensation with eight representative aromatic aldehydes containing hydroxy, methoxy, chloro and nitro substituents has been studied. In all the cases, the two types of compounds, namely, 2-keto-4, 6-diarylhexahydro-*s*-triazines and 1, 3-*bis*-(arylidene) ureas could be isolated by fractionation with suitable solvents. 1, 3-*bis*-(arylidene) ureas have been found to be trimeric in the case of benzaldehyde and anisaldehyde condensations, whereas in the other cases they appear to be monomeric in view of their solubility in common solvents and crystalline nature. Eight new 2-keto-4, 6-diaryl-hexahydro-*s*-triazines and 1, 3-*bis*-(arylidene) ureas have been obtained as a result of these studies. The results are summarised in Table II. *p*-Hydroxy benzaldehyde and *p*-di-methylaminobenzaldehyde did not react under these conditions.

Since the conditions are the same, the yield of the products may be expected to depend mainly on the reactivity of the aldehyde to form the dimethylol urea type of compounds and on their stability. The highest yield of keto-triazine has been obtained with *o*-chloro-benzaldehyde, whereas benzaldehyde gave the highest yield of the trimeric benzylidene urea.

In order to characterise the two types of compounds, the ultra-violet and infra-red absorption characteristics of some of these newly prepared

TABLE II

Products of condensation of urea with aromatic aldehydes and ammonium acetate

(Time of reaction: 6 hours.)

No.	Name of aldehyde	Percentage yield of 2-Keto-4, 6-disubstituted hexahydro-*s*-triazine	Percentage yield of 1, 3-*Bis*-(benzylidene) urea
1	Benzaldehyde ..	13·8	47·4
2	Salicylaldehyde ..	35·5	8·3
3	Anisaldehyde ..	12·6	11·8
4	*o*-Nitrobenzaldehyde ..	11·1	14·7
5	*m*-Nitrobenzaldehyde ..	15·3	21·1
6	*p*-Nitrobenzaldehyde ..	25·3	27·3
7	*o*-Chlorobenzaldehyde ..	72·0	27·6
8	2, 4-Dichlorobenzaldehyde ..	10·2	29·0

compounds have been recorded. The ultra-violet absorption spectra of 1, 3-*bis*-(benzylidene) ureas exhibit two maxima, one at 255 mμ (log $\epsilon_{max.}$ = 4·01) and another at 265 mμ (log $\epsilon_{max.}$ = 3·58). In the case of keto hexahydro-*s*-triazines, the absorption maximum at 255 mμ is less intense and the band at 265 mμ is absent. The infra-red absorption spectrum of 2-keto-4, 6-diphenyl hexahydro-*s*-triazine exhibits a medium intensity band at 1675 cm.$^{-1}$ (5·97 μ). This has been assigned to the carbonyl absorption of amide I band. It is supported by the fact that Edward and Singh[12] reported the carbonyl absorption in liquid 2-piperidone at 1670 cm.$^{-1}$, whereas Witkop *et al.*[13] observed the carbonyl absorption in a number of 2-quinolone derivatives at 1667 cm.$^{-1}$ The carbonyl absorption in 1, 3-*bis*-(arylidene) ureas appears between 1621 cm.$^{-1}$ (6·17 μ) and 1634 cm.$^{-1}$ (6·1 μ). Another characteristic absorption band has been observed in the latter type of compounds, which appears between 1546 cm.$^{-1}$ (6·57 μ) and 1587 cm.$^{-1}$ (6·30 μ). These bands are indicative of acyclic conjugated $> C = N -$ in these compounds. The spectrophotometric data may therefore be made use of to

distinguish between these two types of compounds and also support the structures assigned to them from analytical and chemical studies.

Experimental

All m.p.'s are uncorrected. Unless otherwise mentioned, 95% ethanol is the solvent used for recrystallisation.

General procedure for the condensation of urea with aromatic aldehydes and ammonium acetate

Urea (one mole), the aromatic aldehyde (two moles) and ammonium acetate (one mole) were taken together in excess of 95% ethanol, heated slowly on a steam-bath to dissolve the solids and then refluxed for six hours or less in some cases. The reaction mixture was worked up either by cooling it to room temperature or by removing the solvent under reduced pressure. The fractionation of the product was carried out on the basis of the difference in the solubility of the substances in select solvents. The products obtained by such fractionation were purified and characterised.

2-*Keto*-4, 6-*diphenyl hexahydro-s-triazine*.—Urea, benzaldehyde and ammonium acetate were taken in ethanol and refluxed. The reaction mixture was left overnight, when it solidified to a yellowish mass. This was repeatedly washed with hot water to remove unreacted urea and dried. The solid was extracted with boiling alcohol and the alcoholic extracts were concentrated and cooled. This treatment yielded a colourless granular solid which was purified from a mixture of ethyl acetate and petroleum ether. Two more recrystallisations gave colourless silky needles, m.p. 205° (Found: C, 71·0; H, 6·2; N, 16·6; molecular weight, 246; $C_{15}H_{15}N_3O$ requires C, 71·1; H, 5·9; N, 16·6%; molecular weight 253). 2, 4-Dinitrophenyl hydrazone, orange-red needles from ethyl acetate, m.p. 239° (Found: N, 23·0; $C_{21}H_{19}N_7O_4$ requires N, 22·6%).

1, 3-Bis-(*benzylidene*) *urea*.—The alcohol insoluble solid from the above was found to be insoluble in most of the usual organic solvents. It dissolved in hot acetic acid but decomposed when recrystallised from this solvent. It could however be purified from boiling nitrobenzene yielding a colourless amorphous solid, m.p. 239–40° (Found: C, 76·0; H, 5·5; N, 11·7; molecular weight, 703; $C_{15}H_{12}N_2O$ requires C, 76·2; H, 5·1; N, 11·9%; molecular weight of the trimer, 708).

2-*Keto*-4, 6-*di*-(o-*hydroxyphenyl*) *hexahydro*-s-*triazine*.—Urea, salicylaldehyde and ammonium acetate were refluxed resulting in an orange viscous liquid. The solvent was removed under reduced pressure. The dark orange

sticky product thus obtained, on trituration with water, gave an yellow granular solid which was repeatedly extracted with small quantities of cold acetone till no more solid dissolved. The yellow solution was concentrated and the solid precipitated by adding water gradually. The keto-triazine thus obtained crystallised from alcohol in yellow plates, m.p. 290° (charring) (Found: C, 62·9; H, 5·3; N, 14·5; $C_{15}H_{15}N_3O$ requires C, 63·1; H, 5·2; N, 14·7%).

1, 3-Bis-(o-*hydroxy benzylidene*) *urea.*—The acetone insoluble product from the above was recrystallised from ethyl acetate-petroleum ether to give yellow plates, m.p. 162° (decomp.) (Found: C, 66·9; H, 4·3; N, 10·1; $C_{15}H_{12}N_2O_3$ requires C, 67·1; H, 4·4; N, 10·4%).

2-*Keto*-4, 6-*di*-(p-*methoxyphenyl*) *hexahydro*-s-*triazine.*—Anisaldehyde, urea, ammonium acetate and ethanol were condensed and the reaction mixture on keeping overnight deposited a pale-yellow solid. The solid was extracted with ethanol. On concentration and cooling, a colourless solid was deposited which after four recrystallisations gave light silky needles, m.p. 179° (Found: C, 65·0; H, 6·3; N, 13·3; molecular weight, 308; C, 65·2; H, 6·1; N, 13·4%; molecular weight, 313).

1, 3-Bis-(p-*methoxy benzylidene*) *urea.*—The solid insoluble in ethanol was dissolved in boiling nitrobenzene, cooled and to the clear solution an excess of petroleum ether was added. A thick precipitate of an amorphous solid, m.p. 268°, was obtained. (Found: C, 68·6; H, 5·1; N, 9·1; molecular weight 878; $C_{17}H_{16}N_2O_3$ requires C, 68·9; H, 5·4; N, 9·4; molecular weight of the trimer, 888).

2-*Keto*-4, 6-*di*-(o-*nitrophenyl*) *hexahydro*-s-*triazine.*—Urea, *o*-nitrobenzaldehyde and ammonium acetate together with ethanol were refluxed. The reactants dissolved first and then a pale-yellow solid started separating slowly. After six hours, the flask was cooled in an ice-salt mixture. The solid was subjected to steam distillation to remove any unreacted *o*-nitrobenzaldehyde. The residue left after steam distillation was treated with an excess of boiling acetone. The acetone insoluble portion on recrystallisation from boiling nitrobenzene gave yellow plates, m.p. 200–01° (Found: C, 52·7; H, 4·0; N, 20·4; $C_{15}H_{13}N_5O_5$ requires C, 52·4; H, 3·7; N, 20·4%).

1, 3-Bis-(o-*nitrobenzylidene*) *urea.*—The acetone soluble part from the above condensation was isolated as an yellow solid by concentration. Two more recrystallisations from the same solvent gave pale-yellow needles, m.p. 187° (Found: C, 55·1; H, 3·0; N, 16·9%; $C_{15}H_{10}N_4O_5$ requires C, 55·2; H, 3·1; N, 17·1%).

2-*Keto*-4, 6-*di*-(m-*nitrophenyl*) *hexahydro*-s-*triazine*.—Urea, *m*-nitrobenzaldehyde and ammonium acetate were condensed in ethanol. The solvent was removed under reduced pressure, leaving a semi-solid brown mass which could be converted to a granular yellow solid by the addition of water with slow agitation. The solid was filtered, dried and extracted with an excess of ethyl acetate. The ethyl acetate-insoluble part on recrystallisation from acetone gave pure *s*-triazine, yellow square plates, m.p. 239–40° (Found: C, 52·6; H, 3·4; N, 20·2; $C_{15}H_{13}N_5O_5$ requires C, 52·4; H, 3·7; N, 20·4%).

1, 3-Bis-(m-*nitrobenzylidene*) *urea*.—The ethyl acetate soluble part from the previous experiment on the addition of petroleum ether deposited an yellow solid which was purified by further recrystallisation from ethyl acetate, tiny yellow rods, melting point 221° (Found: C, 55·4; H, 3·2; N, 16·9; $C_{15}H_{10}N_4O_5$ requires C, 55·2; H, 3·1; N, 17·1%).

1, 3-Bis-(p-*nitrobenzylidene*) *urea*.—Urea, *p*-nitrobenzaldehyde and ammonium acetate were condensed in ethanol. A dark orange solid separated during refluxing. The reaction mixture was cooled in an ice-salt mixture, the orange product that separated was filtered and recrystallised from ethyl acetate and then from acetone (animal charcoal). Yellow rectangular plates were thus obtained, m.p. 114–15° (Found: C, 55·3; H, 3·1; N, 16·8; $C_{15}H_{10}N_4O_5$ requires C, 55·2; H, 3·1; N, 17·1%).

2-*Keto*-4, 6-*di*-(p-*nitrophenyl*) *hexahydro*-s-*triazine*.—The mother liquor from the above experiment was treated with an excess of petroleum ether, the solid that separated was filtered and purified by recrystallisation from ethyl acetate-petroleum ether, orange plates, m.p. 229° (Found: C, 52·1; H, 3·6; N, 20·1; $C_{15}H_{13}N_5O_5$ requires C, 52·4; H, 3·7; N, 20·4%).

2-*Keto*-4, 6-*di*-(o-*chlorophenyl*) *hexahydro*-s-*triazine*.—Urea, *o*-chlorobenzaldehyde, ammonium acetate and ethanol were slowly heated till the reactants dissolved and after 10–15 minutes of refluxing the whole thing solidified to a colourless mass. This was washed with hot water and dried. The solid was repeatedly extracted with small portions of ethanol till no more solid dissolved. The combined alcoholic extracts were concentrated to nearly one-third of its volume and cooled when an ice-like mass separated out. On two recrystallisations from acetone it yielded tiny colourless rods, m.p. 116° (Found: C, 55·6; H, 3·9; N, 13·1; $C_{15}H_{13}Cl_2N_3O$ requires C, 55·9; H, 4·0; N, 13·0%).

1, 3-Bis-(o-*chlorobenzylidene*) *urea*.—The alcohol-insoluble part, after recrystallisation, twice from acetone, yielded needles, m.p. 214° (Found: C, 59·1; H, 3·2; N, 8·9; molecular weight 301; $C_{15}H_{10}Cl_2N_2O$ requires C, 59·0; H, 3·2; N, 9·1; molecular weight 305).

2-Keto-4, 6-di-(2', 4'-dichlorophenyl) hexahydro-s-triazine.—Urea, 2, 4-dichlorobenzaldehyde, ammonium acetate and ethanol were refluxed for three hours when copious solid separated. This was filtered, washed repeatedly with hot water and dried. It was extracted with glacial acetic acid to remove the unreacted 2, 4-dichlorobenzaldehyde and then with an excess of ethanol. The alcoholic extracts were concentrated and the solid that separated was recrystallised twice from alcohol, light brown plates, m.p. 148° (Found: C, 46·1; H, 2·5; N, 10·5; $C_{15}H_{11}Cl_4N_3O$ requires C, 46·0; H, 2·7; N, 10·7%).

1, 3-Bis-(2', 4'-dichlorobenzylidene) urea.—The alcohol-insoluble part from the above experiment on recrystallisation from nitrobenzene yielded thick rods, m.p. 232° (Found: C, 48·3; H, 2·1; N, 7·2; $C_{15}H_8Cl_4N_2O$ requires C, 48·1; H, 2·1; N, 7·4%).

SPECTROPHOTOMETRIC DETERMINATIONS

(*a*) *Ultra-violet Absorption Spectra*

The compounds were repeatedly recrystallised prior to the determination of spectra. Ethyl alcohol (95%) was used as solvent. The readings were recorded in the ultra-violet region on a Unicam Spectrophotometer Model S.P. 500. Quartz Cell of one cm. thickness and narrow slit width (0·12 mm.) were used.

(i) *2-Keto-4, 6-diphenyl hexahydro-s-triazine.*—

$\lambda_{max.}$ 255 mμ (log $\epsilon_{max.} = 3 \cdot 84$).

(ii) *2-Keto-4, 6-di-(p-methoxyphenyl) hexahydro-s-triazine.*—

$\lambda_{max.}$ 281–86 mμ (log $\epsilon_{max.} = 4 \cdot 28$).

(iii) *1, 3-Bis-(o-chlorobenzylidene) urea.*—

$\lambda_{max.}$ 255 mμ (log $\epsilon_{max.} = 4 \cdot 01$); $\lambda_{max.}$ 265 mμ (log $\epsilon_{max.} = 3 \cdot 58$).

(*b*) *Infra-red Absorption Spectra*

The absorptions were recorded on a Perkin-Elmer Model 21, double beam infra-red spectrophotometer. Rock-salt prism was used. The compounds were admixed with nujol to get a mull. The characteristic absorptions are given in wave-numbers. The letter in the bracket indicates the intensity of the bands.

(I) *2-Keto-4, 6-diphenyl hexahydro-s-triazine.*—2941 (m), 2841 (m), 1675 (m), 1515 (w), 1499 (m), 1460 (m), 1439 (m), 1377 (m), 1351 (m), 1305 (m), 1266 (m), 1207 (w), 1196 (w), 1157 (w), 1140 (w), 1057 (w), 1024 (w), 892 (w), 845 (m), 765 (m), 742 (w), 698 (m), 668 (w).

(II) 1, 3-Bis-(2, 4-*dichlorobenzylidene*) *urea.*—2899 (w), 1634 (m), 1587 (w), 1471 (w), 1379 (w), 1258 (w), 1099 (w), 1075 (w), 866 (w), 820 (w), 791 (w).

(III) 1, 3-Bis-(o-*chlorobenzylidene*) *urea.*—3311 (w), 1621 (w), 1546 (w), 1271 (w).

Summary

Optimum conditions have been worked out for the condensation of urea with aromatic aldehydes and ammonium acetate. 2-Keto-4, 6-diaryl-hexahydro-*s*-triazines and 1, 3-*bis*-(arylidene) ureas have been prepared using eight substituted benzaldehydes in the condensations. Their ultra-violet and infrared absorption data are recorded for characterisation.

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