

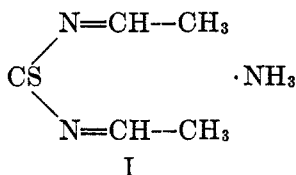
NEW REACTIONS AND DERIVATIVES OF UREA SYNTHESIS OF TRIAZINES¹

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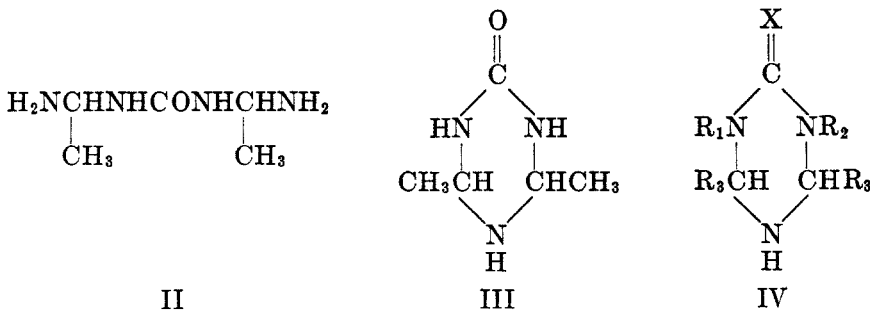
Investigations dealing with the reaction of urea with alcohols (1), with ketones and formaldehyde (2), with diamines, alkylene oxides and certain unsaturated compounds (3) have been described elsewhere. Likewise the formation of new complex compounds of urea with metals, ammonia, and amines has been reported (2). In the present communication the results of a study of the reaction of urea and related compounds on aldehyde-ammonia and aldehyde-amine derivatives is presented.

Nencki (4) described the formation of a crystalline substance to which he assigned the structure of an ammoniated complex of diethylidenethiourea (I) from the reaction of one mole of thiourea with two moles of acetaldehyde-ammonia.



Dixon (5) confirmed the formation of Nencki's compound, but was unable to prepare the analogous compound from urea.

It has now been found that, under proper conditions, urea does indeed react with acetaldehyde-ammonia, and that the nature of the product is dependent on the conditions of the experiment. When moist acetaldehyde-ammonia is intimately mixed with dry urea, immediate liquefaction accompanied with a slight evolution of heat occurs. Extraction of the cooled melt with ether gave a substance assigned the structure of N,N'-bis-(1-aminoethyl)urea (II)



¹The work reported in this paper was done in the laboratories of the I. G. Farbenindustrie at Hoechst-am-Main, Germany. Due to the author's political exclusion from the laboratories in the summer of 1944, the investigations could not be completed, and certain details are no longer available.

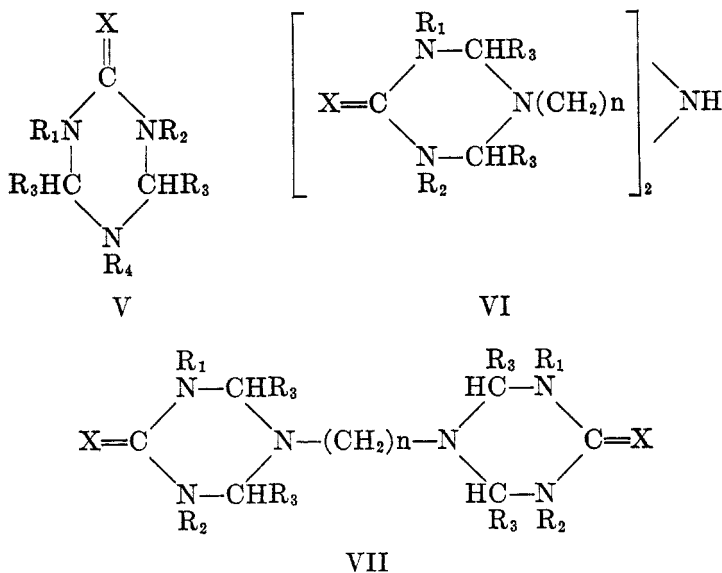
on the basis of elementary analysis. II readily lost ammonia, even at the boiling point of ether, to yield the triazine III, with the result that preparations of II were always somewhat contaminated by III. By carrying out the reaction in water or alcohol at 40–50°, satisfactory yields of III can be obtained directly. The triazine is a weak base. It forms salts with strong acids, a characteristic difficultly soluble picrate, and a well crystallizing double salt with silver nitrate. Aqueous solutions of the triazine decompose slowly on boiling, particularly when slightly acidified, with the formation of ammonia, acetaldehyde, and urea. Analogous triazines of the general type of IV have been prepared by reaction of thiourea, guanidine, and N, N'-disubstituted ureas with ammonia compounds of various aldehydes. The triazines in general melt above 150° when pure. However when moist or impure they undergo decomposition at temperatures of about 100°, with elimination of ammonia and formation of resins.

It is not necessary to prepare the aldehyde-ammonia derivatives separately, as under the proper conditions the triazines may be obtained directly from the urea compound, ammonia, and aldehyde.

Formaldehyde forms an exception to the above general reactions. Hexamethylenetetramine was the only product formed when urea is used in the reaction. With thiourea the product was the double salt of two moles of thiourea and one mole of hexamethylenetetramine.

By substituting aliphatic amines for ammonia in the reaction, triazines of the type of V result. In this reaction, the use of formaldehyde leads to a triazine.

The triazines prepared from diamines on heating lose ammonia to yield bis-triazines of the type of VI.



By the reaction of one mole of diamine with two moles of urea compound and four moles of aldehyde, bis-triazines of type VII may be prepared.

TABLE I
 SUBSTITUTED HEXAHYDROTRIAZINES (FORMULA V). $R_1 = R_2 = R_3 = H$

X	R_4	YIELD %	M.P. °C.	SOLVENT FOR CRIST.	CALC'D				FOUND				M.W. ²	
					% C	% H	% N	% S	% C	% H	% N	% S		
O	CH ₃	68	199 d.	ethanol	41.0	7.7	35.9		115	40.6	7.6	35.8		108, 117, 124
O	<i>n</i> -C ₃ H ₇	62	182	ethanol	50.3	9.1	29.4		143	50.7	9.3	29.7		148, 154, 159
O	<i>iso</i> -C ₄ H ₉	51	194	ethanol ^a	53.5	9.5	26.8		157	53.2	9.4	27.2		134, 141, 154
O	C ₆ H ₁₁	64	205 d.	ethanol ^a	59.1	9.3	22.9		183	59.2	9.4	22.6		186, 191, 196
S	CH ₃	63	169 d.	ethanol-benzene (1:1)	36.6	6.9	32.0	24.4	131	36.6	7.0	32.0	24.3	126, 129, 136
S	<i>iso</i> -C ₄ H ₉	68	142	ethanol	48.6	8.7	24.3	18.5	173	48.7	8.6	24.1	18.3	152, 161, 170
S	C ₆ H ₁₁	72	176	ethanol	54.2	8.5	21.0	16.1	199	54.0	8.6	20.9	15.9	192, 197, 202
O	CH ₂ CH ₂ NH ₂	68	176-7	25% ethanol ^a	41.7	8.3	38.8		144	41.5	8.4	38.7		139, 146, 151
S	CH ₂ CH ₂ NH ₂	54-88	140 d.	water	37.3	7.5	35.0	20.0	160	37.0	7.6	35.3	19.8	151, 158, 164
O	CH ₂ CH ₂ OH			Non-cryst.										

^a It was necessary to heat to 135° to secure crystallization.

EXPERIMENTAL

4-Keto-2,6-dimethylhexahydro-1,3,5-triazine. V. $X = O, R_1 = R_2 = R_4 = H, R_3 = CH_3$. A mixture of 60 g. of urea, 149 g. of freshly prepared acetaldehyde-ammonia (containing 18% of water) and 30 g. of water was heated with stirring at 55–60° until a clear liquid resulted. The temperature was then raised to 75° during half an hour. Evolution of ammonia occurred and the product began to crystallize from the melt. After cooling to 0° the semi-solid crystalline mass was filtered and recrystallized from alcohol-acetone (4:1) yielding 71% of the triazine which melted at 190° (dec.).

Anal. Calc'd for $C_8H_{11}N_3O$: C, 46.5; H, 8.5; N, 32.5; M.W., 129.

Found: C, 46.5; H, 8.6; N, 32.5; M.W.,² 123, 127, 132.

The substance is soluble in cold water and ethanol. It forms an insoluble phosphate and picrate and a well-crystallizing double salt with silver nitrate.

The same substance may be prepared alternatively as follows. To 136 g. of 25% aqueous ammonia cooled to 5° was added slowly through a dropping-funnel extending to the bottom of the flask 88 g. of acetaldehyde cooled to 0°. The mixture was stirred and cooled so that the temperature did not exceed 15°. After half an hour a solution of 60 g. of urea in 60 g. of water was added and the mixture was heated gradually to 70–75°. The triazine was isolated as above.

4-Thio-2,6-dimethylhexahydro-1,3,5-triazine. V. $X = S, R_1 = R_2 = R_4 = H, R_3 = CH_3$. This was prepared as above, from 76 g. of thiourea, and 149 g. of 82% acetaldehyde-ammonia in 420 g. of water at 65–70° for twenty minutes. The yield of material melting at 180° (dec.) after recrystallization from water was 87%. The substance is slightly soluble in cold water and alcohol.

Anal. Calc'd for $C_8H_{11}N_3S$: C, 41.4; H, 7.6; N, 28.9; S, 22.0; M.W., 145.

Found: C, 41.4; H, 7.6; N, 28.8; S, 21.9; M.W.,² 142, 148, 153.

4-Imino-2,6-dimethylhexahydro-1,3,5-triazine. V. $X = NH, R_1 = R_2 = R_4 = H, R_3 = CH_3$. This was prepared from 122 g. of guanidine nitrate, 149 g. of 82% acetaldehyde-ammonia in 70 g. of water at 70–75° for twenty-five minutes. The yield of material melting at 156–157° (dec.) after recrystallization from aqueous ethanol was 54%.

Anal. Calc'd for $C_8H_{12}N_4$: C, 46.8; H, 9.4; N, 43.7; M.W., 128.

Found: C, 46.8; H, 9.5; N, 43.7; M.W.,² 124, 128, 133.

4-Keto-2,3,5,6-tetramethylhexahydro-1,3,5-triazine. V. $X = O, R_1 = R_2 = R_3 = CH_3, R_4 = H$. This was prepared as above from 88 g. of *N,N'*-dimethylurea, 149 g. of 82% acetaldehyde-ammonia, and 80 g. of water at 70–75° for thirty minutes. The yield was 55%.

Anal. Calc'd for $C_{12}H_{18}N_3O$: C, 53.4; H, 9.6; N, 26.6; M.W., 157.

Found: C, 53.5; H, 9.6; N, 26.8; M.W.,² 142, 148, 154.

4-Keto-2,6-di-n-propylhexahydro-1,3,5-triazine. V. $X = O, R_1 = R_2 = R_4 = H, R_3 = C_3H_7$. This was prepared as above from 60 g. of urea, 212 g. of 84% butyraldehyde-ammonia and 50 g. of water at 70–75° for twenty-five minutes. The yield of material recrystallized from alcohol was 74%.

Anal. Calc'd for $C_{20}H_{32}N_3O$: C, 58.4; H, 10.3; N, 22.7; M.W., 185.

Found: C, 58.3; H, 10.3; N, 22.6; M.W.,² 174, 182, 191.

4-Keto-2,6-dibenzylhexahydro-1,3,5-triazine. V. $R_1 = R_2 = R_4 = H, R_3 = CH_2C_6H_5$. This was prepared in 68% yield from 60 g. of urea, 299 g. of 91% phenylacetaldehyde-ammonia in a mixture of 70 g. of water and 160 g. of ethanol at 70–75° for thirty-five minutes. It was recrystallized from ethanol.

Anal. Calc'd for $C_{17}H_{19}N_3O$: C, 72.6; H, 6.8; N, 14.9; M.W., 281.

Found: C, 72.5; H, 6.9; N, 14.8; M.W.,² 286, 289, 294.

N,N'-bis-(1-aminoethyl)urea. II. A mixture of 60 g. of urea and 149 g. of freshly prepared acetaldehyde-ammonia containing 18% of water was ground in a mortar. Liquefaction occurred and the temperature of the mixture rose to about 37°. After ten minutes

² Ebullioscopic in ethanol.

the mixture was cooled to 20° and shaken with ether several times. After drying and removal of the ether at the water-pump, a substance melting at 41–46° was obtained. The material apparently was contaminated with the triazine III, since repeated analysis at best approximated the values demanded for the urea II.

4-Keto-1-methylhexahydro-1,3,5-triazine. V. $X = O, R_1 = R_2 = R_3 = H, R_4 = CH_3$. To a solution of 60 g. of urea in 125 g. of 25% aqueous methylamine was added 150 g. of 40% formaldehyde solution at 10–15° with stirring and cooling. After stirring with cooling for an additional hour, the mixture was heated to 55° during half an hour. After distillation of the water at reduced pressure, the crystalline residue was recrystallized from ethanol. Analytical data for this and similar compounds prepared by the same general procedure are given in Table I.

β,β' -Bis-(4'-keto-1,3,5-hexahydro-1-triazinyl)ethylamine. VI. $X = O, R_1 = R_2 = R_3 = H, n = 2$. When 4-keto-1-aminoethylhexahydro-1,3,5-triazine was heated to its melting point, loss of ammonia occurred. This process was completed by heating at 155–160° until evolution of ammonia ceased. Analyses proved the structure of the compound, but these are not at hand.¹ A similar reaction took place when the analogous sulfur compound was heated.

1,2-Bis-(4'-thio-1,3,5-hexahydro-1-triazinyl)ethane. VII. $X = S, R_1 = R_2 = R_3 = H, n = 2$. To a solution of 76 g. of thiourea in 200 g. of water, 40 g. of 76% ethylenediamine and 200 g. of 30% formaldehyde were added simultaneously through two dropping-funnels at 20–25°. The mixture was stirred and cooled. A white powder which changed gradually into an opaque soft resinous mass separated. This crystallized after a short time. Recrystallization from ethanol gave 75% of material melting at 209–210° (dec.).

Anal. Calc'd for $C_8H_{16}N_6S_2$: C, 36.6; H, 6.8; N, 32.0; S, 24.4; M.W., 260.

Found: C, 37.0; H, 6.7; N, 32.3; S, 24.7; M.W.,² 248, 256, 263.

The analogous oxo-compound may be similarly prepared from urea.

SUMMARY

Aldehydes forming stable ammonia addition compounds react with urea and its derivatives to form 1,3,5-triazines having an NH group at the 1-position. The same reaction may be realized with urea derivatives, aldehydes and ammonia. Intermediates in these reactions are N,N'-bis-(amino-alkyl or -aryl) ureas.

1,3,5-Triazines with an alkyl or aryl substituted 1-imino group may be prepared from the corresponding amines and aldehydes, including formaldehyde. Amines with a hydroxyl group give rise to triazines containing a reactive hydroxyl, suited to further substitutions.

Reaction of diamines with one mole of urea compound gives triazines with a free amino group, which may condense to a bis-compound with loss of ammonia.

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