dilute alcohol 0.18 g. of 3-anilino-7-nitro-2-phenyl-4-quinazolone, colorless needles, m.p. 151°.

Anal. Calcd. for $C_{20}H_{14}N_4O_3$: C, 67.04; H, 3.91. Found: C, 66.83; H, 3.85.

A few *o*-acylaminobenzanilides were obtained from 4-nitro-benzoylanthranil (IIb) and aromatic amino compounds (Table I). These gave the corresponding quinazolone derivatives when heated about 30° above their melting points (Table II).

3-Amino-7-nitro-2-phenyl-4-quinazolone (IV). A solution of IIb (0.5 g.) in glacial acetic acid (10 ml.) and hydrazine hydrate (4.0 ml.) was refluxed for 1 hr. On cooling pale yellow crystals separated which on recrystallization from dilute acetic acid gave 0.46 g. of IV, lemon-yellow needles, m.p. 249°

Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.54; N, 19.85. Found: C, 59.25; H, 3.50; N, 20.00.

Benzoyl derivative of IV. Colorless cubes from alcohol and ethyl acetate mixture, m.p. 295°.

Anal. Calcd. for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.62. Found: C, 64.81; H, 3.60.

Acetyl derivative of IV. Colorless plates from alcohol, m.p. 149°.

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.70. Found: C, 58.92; H, 3.67.

3-Hydroxy-7-nitro-2-phenyl-4-quinazolone (V). Prepared by the procedure given for compound IV by using hydroxylamine hydrochloride and sodium acetate. Recrystallization from dilute acetic acid gave 70% of V, colorless cubes, m.p. 246°.

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.36; H, 3.18. Found: C, 59.01; H, 3.16.

Benzoyl derivative of V. Light brown needles from dilute alcohol, m.p. 273°.

Anal. Calcd. for $C_{21}H_{13}N_3O_5$: C, 65.11; H, 3.35. Found: C, 64.92; H, 3.30.

Acetyl derivative of V. Colorless cubes from dilute acetic acid, m.p. 157°.

Anal. Calcd. for $C_{16}H_{11}N_3O_5$: C, 59.07; H, 3.38. Found: C, 58.86; H, 3.39.

6-Nitro-2-phenylindazole (VI). Compound I (0.5 g.) and aniline (4 ml.) were heated at 140° for 3 hr. On cooling orange yellow cubes separated which on recrystallization from acetic acid gave 0.30 g. of VI, orange-yellow needles, m.p. 325°

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.76. Found: C, 64.89; H, 3.70.

6,6'-Dinitro-2,2'-bisindazolyl (VII). Compound I (0.5 g.) in glacial acetic acid (10 ml.) and hydrazine hydrate (4 ml.) were refluxed for 2 hr. On cooling reddish brown needles separated which on recrystallization from ethyl acetate gave 0.35 g. of VII, orange needles, m.p. 324°.

Anal. Calcd. for $C_{14}H_8N_6O_4$: C, 51.85; H, 2.47; N, 25.93. Found: C, 51.48; H, 2.81; N, 25.80.

6-Nitro-2-anilinoindazole (VIII). Compound I (0.5 g.) and phenylhydrazine (3 ml.) were heated on water bath for 3 hr. The product after washing with dilute hydrochloric acid, alcohol, and recrystallizing from acetic acid gave 0.41 g. of VIII, reddish brown needles, m.p. 190°.

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.42; H, 3.94. Found: C, 61.20; H, 4.00.

MEERUT, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, MEAD JOHNSON RESEARCH CENTER, MEAD JOHNSON AND CO.]

Syntheses Pertaining to the Carbamoylation of Cyclic 1,3-Dicarbonyl Compounds with Urea

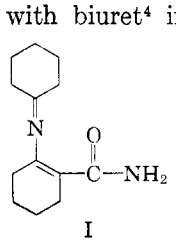
HOMER C. SCARBOROUGH

Received March 1, 1961

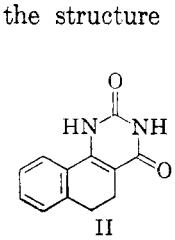
The mechanism of carbamoylation of cyclic 1,3-dicarbonyl compounds with urea is discussed with respect to the reactions of urea and derivatives with carbonyl compounds. These are the reactions of cyclohexanone and 2-methyl cyclic 1,3-dicarbonyl compounds with urea and the reactions of 1,3-dimethylbarbituric acid with urea and derivatives. A bicyclic transition state mechanism is suggested as a possibility by which these results may be interpreted.

The carbamoylation of some cyclic 1,3-dicarbonyl compounds with urea has been reported as has been a rationale for the use of urea as a source of the elements of cyanic acid in this reaction.[1,2] As the synthesis is accomplished at elevated temperatures, it was felt that free cyanic acid might be an actual reacting species and a cyclic transition state was suggested.[1] A number of active methylene compounds were treated with urea; however, only cyclic 1,3-dicarbonyl compounds gave simple carbamoyl derivatives. Cyclohexanone furnished a carbamoyl compound in which the keto carbonyl was replaced by imine function.[2,3]

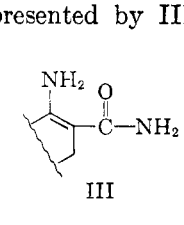
The formation of cyclohexylidene 2-carbamoylcyclohex-1-enylamine, I, from the reaction of cyclohexanone[2,3] or 1(*N*-morpholino)cyclohexene[2] and urea would appear to be analogous to the preparation of compound II which has been reported by the fusion of α-tetrolone with urea or with biuret[4] if the structure represented by III



I



II



III

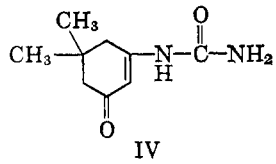
(1) H. C. Scarborough, *J. Org. Chem.*, **26**, 2579 (1961).

(2) H. C. Scarborough and W. A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).

(3) A. F. McKay, E. J. Tarlton, and C. Podesva, *J. Org. Chem.*, **26**, 77 (1961).

(4) K. Dziewonski and J. Schoen, *Bull. intern. acad. polon. sci., Classe sci. mathl nat.*, Ser. A. 101 (1950); *Chem. Abstr.*, **47**, 136h (1953).

were considered to be a common intermediate in each reaction. Compound I could be formed by condensation with a second mole of cyclohexanone and compound II by reaction with a second mole of urea. Cyclohexenylamine and cyanic acid have been postulated as intermediates for I.[3] A ureido derivative formulated as IV could be isolated in low yield from urea-5,5-dimethyl-1,3-cyclohexane-



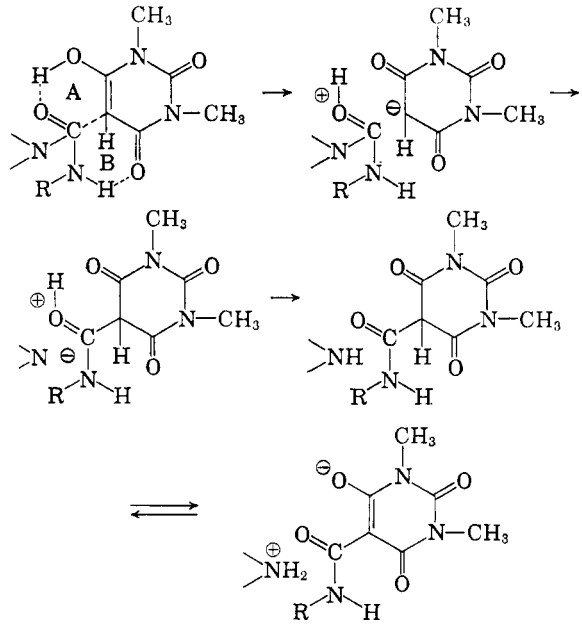
IV

dione reaction mixtures. The ureido derivative could conceivably be a precursor of either III or of a β-oxocyclohexenenylamine and cyanic acid. Careful fusion of pure IV or fusion of IV with urea failed to yield any trace of 2-carbamoyl-5,5-dimethyl-1,1-cyclohexanedione, however. In any event, the production of products containing structure III from reaction of cyclic monofunctional ketones (and their enamines) with urea indicates that these reactions occur by a different mechanism than the carbamoylation of cyclic 1,3-dicarbonyl compounds.

Evidence supporting a cyclic transition state interpretation was obtained from the reactions of 2-methyl-1,3-cyclopentanedione, 2,5,5-trimethyl-1,3-cyclohexanedione and 1,3,5-trimethylbarbituric acid with urea. All of these compounds furnished carbamoyl derivatives with urea if the active methylene carbon were unsubstituted.[1,2] Molecular models have shown that a 2-hydrogen of an enolized 1,3-dicarbonyl system imparts some steric hindrance to a cyclic transition state and thus a larger substituent as methyl would be expected to prevent carbamoylation, even though the acidic compound may still donate a proton for decomposition of urea *via* cyanic acid. All of the aforementioned methyl compounds reacted vigorously with urea when heated, but were recovered unchanged after neutralization. Direct evidence of interaction was obtained by the isolation of the ammonium salt of 1,3,5-trimethylbarbituric acid in 89% yield if the reaction mixture were not acidified. The introduction of a methyl group in these instances did not block the decomposition of urea but did prevent the incorporation of cyanic acid into the molecule.

As a further elaboration of the nature of the reaction, it was considered of interest to investigate the reactions of some methyl substituted ureas and of biuret. 1,3-Dimethylbarbituric acid proved especially useful as the 1,3-dicarbonyl component since it possessed a high degree of thermal stability. 1,3-Dimethylbarbituric acid was recovered unchanged after being heated to 360°. This work together with a representation of a possible cyclic transition state is presented in Table I.

TABLE I



Urea Derivative	Temp.	Product R	Product Yield, %
1-Methylurea	135	H	46.5
1-Methylurea	225	H	24
1,3-Dimethylurea	225	CH_3	45
		CH_3	92
1,1-Dimethylurea	220	H	73.5
Biuret	220	H	83
1,1,3,3-Tetramethylurea	220–205[a]	No reaction	

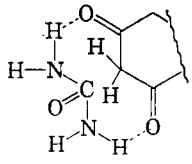
[a] Temperature at which the reaction mixture refluxes.

It may be noted that while the yield of 5-(*N*-carbamoyl)-1,3-dimethylbarbituric acid was 92% at a temperature of 225°, yields were substantially less at lower temperatures. As few cyclic 1,3-dicarbonyl compounds would lend themselves to such high reaction temperatures the reaction is probably not of general preparative value.

These results are believed to support a bicyclic transition state as shown. The existence of a simple isocyanate reaction is believed improbable in view of the ease of polymerization of methyl isocyanate, the high temperature employed and the high yield of 5-(*N*-methylcarbamoyl)-1,3,dimethylbarbituric acid. A 93% recovery of 1,3-dimethylbarbituric acid from attempted reaction with tetramethylurea eliminates an unlikely amide-displacement mechanism, as tetramethylurea can furnish neither an associated transition state nor an isocyanate intermediate. A monocyclic transition state involving only the single six-membered ring A could be formulated. However, in the reactions of 1,1-dimethylurea and biuret the leaving groups [$(CH_3)_2N$— and $NH_2C(=O)NH$—] were ones which cannot be satisfactorily incorporated into ring B. In addition, the dissimilar carbamoylation of mono functional cyclic ketones with urea implicates the participation of both functions in 1,3-dicarbonyl

compounds. Molecular models show that the σ-electrons of the ketone oxygen of ring B would be properly oriented for bonding with an amino hydrogen.

A transition state can be constructed from a 1,3-diketo form as shown. However, such a state does not accommodate proton transfer to urea for



initiation of reaction. A reactive 1,3-diketo species which is not associated with urea should furnish carbamoyl derivatives with 2-methyl compounds, as proton transfer was shown to occur.

These reactions occur at lower temperatures than other reactions such as the pyrolysis of esters,[5] β-hydroxy olefins,[6] and amides[7] which are formulated by cyclic six-membered transition state mechanisms. The lower temperature requirement might be the result of increased hydrogen bonding forces. These are possible in the interpretations proposed for the urea-diketone reaction.

EXPERIMENTAL[8]

Ureido derivative of 5,5-dimethyl-1,3-cyclohexanedione (IV). A mixture of 14 g. (0.1 mole) 5,5-dimethyl-1,3-cyclohexanedione and 6 g. (0.1 mole) of urea was heated at 130° for 25 min. The cooled reaction mixture was dissolved with agitation in a mixture of 200 ml. of ether and 100 ml. of water. The ether was separated and washed with water. The aqueous portions were combined and the *p*H adjusted to 5. Cooling overnight gave 2.3 g. (12.6%), m.p. 203–205° dec. Recrystallizations from methanol and from ethyl acetate furnished pure material, m.p. 211–211.5° dec.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.51; H, 7.78; N, 15.18.

The residue obtained by concentration of ether was recrystallized from methanol to furnish 2 g. (11%) of 2-carbamoyl-5,5-dimethyl-1,3-cyclohexanedione.[1]

The ureido compound decomposed extensively when heated at 220° either alone or with urea. None of the fusion products was found to contain 2-carbamoyl-5,5-dimethyl-1,3-cyclohexanedione. The fusion product did not give the characteristic pale blue precipitate which was formed on treatment of 2-carbamoyl-5,5-dimethyl-1,3-cyclohexanedione fusion mixtures with methanolic cupric acetate.

Fusion of 1,3,5-trimethylbarbituric acid with urea. Ammonium 1,3,5-trimethylbarbiturate. A powdered mixture of 4.25 g. (0.025 mole) of 1,3,5-trimethylbarbituric acid[9] and 3.0 g. (0.05 mole) of urea was heated at 125° for 12 min. A vigorous reaction ensued to furnish a semisolid which was triturated with 25 ml. of cold water and collected and recrystallized from aqueous acetone to furnish 4.2 g. (89%), m.p. 248° dec.

Anal. Calcd. for $C_7H_{13}N_3O_3$: C, 44.91; H, 6.99; N, 22.45. Found: C, 45.06; H, 6.68; N, 22.42.

A small amount of the ammonium salt was suspended in cold water. The mixture was acidified with dilute hydrochloric acid to furnish 1,3,5-trimethylbarbituric acid, m.p. 85–88°, no depression with authentic material. The infrared spectra of recovered 1,3,5-trimethylbarbituric acid and authentic material were identical.

The same ammonium salt as above was obtained by concentration of a solution of 1,3,5-trimethylbarbituric acid in concentrated ammonium hydroxide.

Fusion of 2,5,5-trimethyl-1,3-cyclohexanedione with urea. A pulverized mixture of 4 g. (0.026 mole) of 2,5,5-trimethyl-1,3-cyclohexanedione[10] and 3.12 g. (0.052 mole) of urea was heated at 137° for 11 min. A brick reaction ensued from the start of the heating period. The cooled reaction melt was dissolved in 15 ml. of methanol and cold 0.1*N* hydrochloric acid added to furnish a white solid, softened 145°, m.p. 156–161°. Recrystallization from 65 ml. of isopropyl acetate furnished 3.3 g. (82%) of 2,5,5-trimethyl-1,3-cyclohexanedione (no depression on admixture of melting point and identical infrared spectra with starting material).

Fusion of 2-methyl-1,3-cyclopentanedione[11] with urea as above gave 86% of recovered 2-methyl-1,3-cyclopentanedione.

Fusion of 1,3-dimethylbarbituric acid with 1-methylurea. A. *Fusion at 137°.* A powdered mixture of 3.9 g. (0.025 mole) of 1,3-dimethylbarbituric acid[12] and 3.7 g. (0.05 mole) of 1-methylurea was heated at 137° for 15 min. The reaction mixture was purified by recrystallizations from methanol and from butanone to furnish 2.3 g. (46.5%) of 5-carbamoyl-1,3-dimethylbarbituric acid, m.p. 217–219°, no depression on admixture with authentic material.[2] Examination of the residues obtained by concentration of the organic solvents by their infrared spectra did not reveal the presence of any 5-(*N*-methylcarbamoyl)-1,3-dimethylbarbituric acid.

B. *Fusion at 225°.* A mixture as above was heated at 225° for 5 min. The reaction products were separated from starting 1,3-dimethylbarbituric acid and 1-methylurea by recrystallization from methanol, m.p. 146–153°, 3.9 g. Infrared analysis of this mixture showed that an overall yield of 24% of 5-carbamoyl-1,3-dimethylbarbituric acid and 45% of 5-(*N*-methylcarbamoyl)-1,3-dimethylbarbituric acid had been obtained.[13]

Reaction of 1,3-dimethylbarbituric acid with 1,3-dimethylurea. 5-(N-Methylcarbamoyl)-1,3-dimethylbarbituric acid. A mixture of 4.66 g. (0.03 mole) of 1,3-dimethylbarbituric acid and 5.28 g. (0.06 mole) of 1,3-dimethylurea was heated at 225° for 5 min. Crystallization of the reaction mixture from 450 ml. of methanol furnished 4.2 g. (92%), m.p. 174°. The melting point was unchanged upon recrystallization from butanone. The reaction product was soluble in 0.1*N* sodium hydroxide and gave a precipitate with methanolic cupric acetate. $\lambda_{max}^{0.1N\ NaOH}$ 257 mμ (ϵ 17,900); $\lambda_{max}^{0.1N\ HCl\ in\ CH_3OH}$ 262 mμ (ϵ 21,900).

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.11; H, 5.28; N, 19.57.

Fusion of 1,3-dimethylbarbituric acid with 1,1-dimethylurea. A mixture of 4.66 g. (0.03 mole) of 1,3-dimethylbarbituric acid and 5.3 g. (0.06 mole) of 1,1-dimethylurea[14] was heated at 220° for 6 min. The cooled melt was triturated with 50 ml. of warm water and the insoluble material separated to furnish 4.1 g. of 5-carbamoyl-1,3-dimethylbarbituric acid,

(5) C. D. Hurd and F. H. Blunck, *J. Am. Chem. Soc.*, **60**, 2419 (1938).

(6) R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, **81**, 6443 (1959).

(7) W. J. Bailey and C. N. Bird, *J. Org. Chem.*, **23**, 996 (1958).

(8) All melting points are uncorrected. Microanalyses are by Mr. Clarence Kennedy of the Mead Johnson Research Center.

(9) A. C. Cope *et al.*, *J. Am. Chem. Soc.*, **63**, 356 (1941).

(10) R. D. Desai, *J. Chem. Soc.*, 1079 (1932).

(11) M. Orchin and L. W. Butz, *J. Am. Chem. Soc.*, **65**, 2296 (1943).

(12) H. Biltz and H. Wittels, *Ber.*, **54**, 1035 (1922).

(13) Infrared analyses were by Mr. John Schmidt of the Mead Johnson Research Center.

(14) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1790 (1929).

m.p. 220–221°, no depression on admixture with authentic material. Acidification of the aqueous liquor furnished 1 g., m.p. 191–200°. Recrystallization of this second crop from acetic acid gave another 0.3 g. of 5-carbamoyl-1,3-dimethylbarbituric acid for a total yield of 73.5%.

The aqueous solution was concentrated to dryness and the residue suspended in acetone. The acetone-insoluble material was recrystallized from ethanol to furnish 0.2 g. of recovered 1,1-dimethylurea. The acetone liquor was concentrated. The residue furnished 0.3 g. (6.5%) of 1,3-dimethylbarbituric acid on recrystallization from benzene.

Fusion of 1,3 - dimethylbarbituric acid with biuret. A powdered mixture of 3.9 g. (0.025 mole) of 1,3-dimethylbarbituric acid and 3.09 g. (0.03 mole) of biuret was heated at 220° for 5 min. The vigorous reaction stopped after 4.5 min. of heating. The reaction mixture was suspended in 60 ml. of boiling glacial acetic acid and a little insoluble material removed with the aid of charcoal. The liquor was diluted to 300 ml. of water and cooled to furnish a white solid which was collected and recrystallized from 80 ml. of isopropyl alcohol to furnish 4.1 g. (83%) of 5-carbamoyl-1,3-dimethylbarbituric acid, m.p. 219–221°. The infrared spectra of this product and of material prepared by the reaction of urea with 1,3-dimethylbarbituric acid were identical. There was no depression in a mixed melting point determination.

Attempted reaction of tetramethylurea with 1,3-dimethylbarbituric acid. A solution of 3.9 g. (0.025 mole) of 1,3-dimethylbarbituric acid in 6.5 g. (0.05 mole) of tetramethylurea[15] was heated at 220–230° for 15 min. The internal reaction temperature was 200–205°. No apparent reaction occurred and the cooled mixture was dissolved in 50 ml. of hot benzene. Cooling gave 3.6 g. (92%) of unchanged 1,3-dimethylbarbituric acid.

Acknowledgment. The author is grateful to Dr. Richard T. Arnold for his suggestions regarding the mechanism proposed.

EVANSVILLE 21, IND.

(15) W. Michler and C. Escherich, *Ber.*, 12, 1164 (1879). A sample of intermediate dimethylcarbamoyl chloride was supplied by the Ott Chemical Co., Muskegon, Mich.

[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, MEAD JOHNSON RESEARCH CENTER, MEAD JOHNSON AND CO.]

The Reaction of Urea with Cyclic 1,3-Dicarbonyl and Other Active Hydrogen Compounds

HOMER C. SCARBOROUGH AND WILLIAM A. GOULD

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A number of 2-carbamoyl cyclic 1,3-dicarbonyl compounds have been prepared by the reaction of urea and cyclic 1,3-dicarbonyl compounds. Other active methylene compounds failed to give simple carbamoyl derivatives.

The thermal reactions of some cyclic 1,3-dicarbonyl compounds with urea to form their 2-carbamoyl derivatives has been reported.[1] This work has been extended and some additional examples of the reaction are given. Urea was also heated with other active hydrogen compounds in an effort to prepare carbamoyl derivatives. While reactions did occur, simple carbamoyl derivatives could only be obtained from cyclic 1,3-dicarbonyl compounds.

The 2-carbamoyl cyclic 1,3-dicarbonyl compounds of Table I were prepared by heating one equivalent of the dicarbonyl compound with 1.5 to 2 equivalents of urea, either by simple fusion (Method F) or by refluxing in a suitable solvent (Method S).

In general, the fusion method was employed for those reactants giving a homogeneous melt at 132–150°. Fusion times varied from two to thirty minutes. Time-temperature relationships were determined experimentally for each reaction, but as a rule the lowest temperature yielding a homogeneous melt and evidence of interaction as determined visually and by evolution of acrid or ammoniacal gas was employed. The appearance of a precipitate when a sample in methanol was treated with methanolic cupric acetate was also useful in determining initiation of reaction.

The solvent method was generally used for those high melting 1,3-dicarbonyl compounds which did not give a homogeneous melt at fusion temperatures. The use of a solvent was preferred if the 1,3-dicarbonyl compound and formed product were stable to heat during the longer reaction time employed. The reaction time varied from one to twenty-four hours depending on the solvent, but was typically one to four hours using chlorobenzene as solvent. The solvents employed are given in Table I, chlorobenzene being particularly useful because of its solvent ability for urea and the 1,3-dicarbonyl compound at its boiling point which was sufficiently high to effect reaction. 1-Methyl-2-pyrrolidone could be employed for highly insoluble materials.

There appear to be two principal restrictions on the introduction of a carbamoyl moiety by this method. Since the reaction is run at elevated temperatures, thermal instability of the starting 1,3-dicarbonyl compound or of the formed carbamoyl compound is a serious preparative hindrance. Thus, 1,3-indandione gave anhydrobisdiketohydrinden when heated with urea, the latter also

(1) H. C. Scarborough, *J. Org. Chem.*, 26, 2579 (1961).