BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1246—1247 (1970)

Intramolecular Cyclization of *N*-(Phenylcarbamoyl)anthranilic Acid Derivatives

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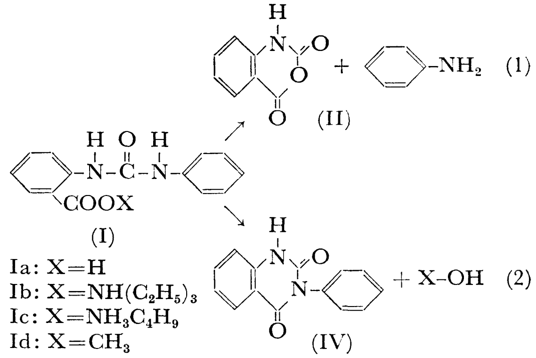
(Received May 16, 1969)

The thermal dissociation of urea derivatives under various conditions has been reported.[1,2] Iwakura and Nagakubo described the thermal decomposition of 1,3-di-*p*-phenetylurea in aliphatic alcohol solution to give *p*-phenetidine and phenyl isocyanate.[3] So far, no studies have been reported on the thermal dissociation of *ortho*-substituted *N*-(phenylcarbamoyl)aniline derivatives in polar organic solvents.

In connection with the study of cyclopolycondensation reactions[4] of aromatic diamino dicarboxylic acids with various active carbonyl compounds, we noted that several open-chain precursors of aromatic heterocyclic polymers such as polyurea acids[5] were sensitive to elevated temperatures in usual cyclodehydration. By the cyclodehydration reactions of *ortho*-substituted *N*-(phenylcarbamoyl)aniline derivatives, two condensation products, isatoic anhydride and 3-phenyl-2,4(1*H*,3*H*)-quinazoline-dione were isolated.

In this paper, we wish to report the new intramolecular cyclization reactions and the mechanism of the formation of isatoic anhydride (II) and 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione (IV) from *N*-(phenylcarbamoyl)anthranilic acid derivatives (I). When *N*-(phenylcarbamoyl)anthranilic acid (Ia), its ammonium salts (Ib,c) and methyl ester (Ia) were treated either (A) in organic solvent such as *N*-methylpyrrolidone at 100°C or (B) in an inert gas at 220°C, the following two types of reactions were found to occur depending upon the reaction conditions.

The results of the cyclization reaction in *N*-methylpyrrolidone are summarized in Table 1.



Ia: X=H
Ib: X=NH$(C_2H_5)_3$
Ic: X=NH$_3C_4H_9$
Id: X=CH$_3$

TABLE 1. PRODUCTS OF CYCLIZATION REACTION EN *N*-METHYLPYRROLIDONE (mol % yield)

Product	Compound Ia	Ib	Ic	Id
II*	50	30	28	0
IV**	50	70	72	0
I (starting material recovered)	0	0	0	100

* mp 242°C. Found: C, 58.60; H, 3.12; N, 8.42%. Calcd for $C_{18}H_5O_2N_5$: C, 58.90; H, 3.09; N, 8.59%.

** mp 282°C. Found C, 70.36; H, 4.17; N, 11.45%. Calcd for $C_{14}H_{10}O_2N_2$: C, 70.58; H, 4.22; N, 11.48%.

TABLE 2. YIELD OF IV PRODUCED BY THE REACTION IN NITROGEN ATMOSPHERE

	Ia	Ib	Ic	Id
Yield of IV (mol%)	64	77	76	72

The reaction product obtained in nitrogen was found to be solely 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione (IV). The yields of IV are shown in Table 2.

The formation of isatoic anhydride by the elimination of aniline is a new intramolecular cyclization reaction which has not been reported. For this cyclization reaction, two types of reaction mechanism are considered: (a) an intramolecular cyclization takes place directly by nucleophilic attack of carboxyl group on carbonyl group of ureido linkage to eliminate aniline as shown in Eq. (3),

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3) Y. Iwakura and K. Nagakubo, *Bull. Tokyo Inst. Technol.*, **18**, 25 (1948).

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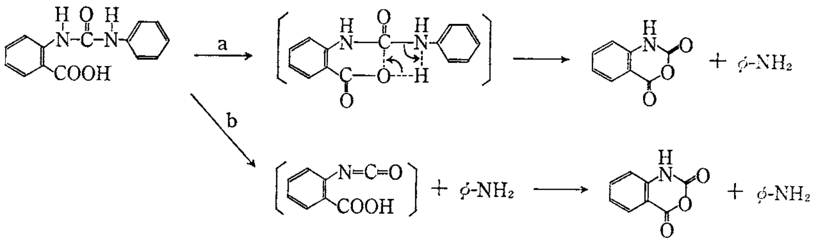

or (b) the dissociation of ureido group forms isocyanate as a reaction intermediate (Eq. (4)).

When *N*-methyl-*N*-(phenylcarbamoyl)anthranilic acid was treated in *N*-methylpyrrolidone under the same reaction conditions, *N*-methylisatoic anhydride was obtained. In this case the formation of isocyanate as an intermediate (Eq. (4)) is impossible, and it should inevitably involve the participation of carobxyl group in the reaction process. Furthermore, reaction path (a) is favored by the fact that *N*-(phenylcarbamoyl)anthranilic acid (Ia) and its ammonium salts (Ib,c) afforded isatoic anhydride, whereas methyl ester (Id) did not give isatoic anhydride in organic solvent as shown in Table 1. The fact suggests that only the species which easily dissociate to give carboxylate anion respond to path (a).

When methyl *N*-(phenylcarbamoyl)anthranilate was fused in nitrogen atmosphere, it affords quinazolinedione as a sole product by intramolecular cyclization.

Experimental

***N*-(phenylcarbamoyl)anthranilic Acid.** Phenyl isocyanate (4.0 g, 1/300 mol) dissolved in benzene (20 m*l*) was added slowly at 30°C into a solution of anthranilic acid (4.6 g, 1/300 mol) in benzene (40 m*l*). After stirring for 3 hr, the precipitate was collected and recrystallized from ethanol: mp 185—186°C. Found: C, 65.51; H, 4.65; N, 10.65%. Calcd for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.72; N, 10.93%.

***N*-Methyl-*N*-(phenylcarbamoyl)anthranilic Acid.** A 3.02 g (0.02 mol) portion of *N*-methylanthranilic acid (mp 186—187°C, recrystallized from aqueous ethanol) was dissolved in 100 m*l* of benzene at 60°C. To this solution was added 2.38 g (0.02 mol) of phenyl isocyanate (bp 46—47°C/7 mmHg) in 10 m*l* of benzene, and the mixture was refluxed at 80°C for 2.5 hr. After the mixture had been allowed to cool to room temperature, the precipitate was filtered, washed several times with distilled water, and dried. It was then recrystallized twice from ethyl acetate to obtain colorless needles in a 43% yield. Mp 252—253°C. It was identified to be *N*-methyl-*N*-(phenylcarbamoyl)anthranilic acid on the basis of infrared spectrum and elemental analysis.

The infrared spectrum (KBr) shows absorption bands at 3300 cm^{-1} (N-H), and 1650 cm^{-1} (ureido carbonyl). Ultraviolet spectrum: $\lambda_{\max}=210\ \mathrm{m}\mu$ (ε, 29200), 257 mμ (ε, 33600). Found: C, 66.87; H, 5.35; N, 10.41%. Calcd for $C_{15}H_{14}O_3N_2$: C, 66.81; H, 5.08; N, 10.58%.

Methyl *N*-(Phenylcarbamoyl)anthranilate. To a solution of methyl anthranilate (5.0 g, 1/300 mol) in 30 m*l* of benzene was added phenyl isocyanate (4.0 g, 1/300 mol) dissolved in 20 m*l* of benzene. After stirring for 3 hr at 30°C, benzene was removed and the residue was recrystallized from ethanol: mp 138—139°C. Found: C, 66.65; H, 5.22; N, 10.32%. Calcd for $C_{15}H_{14}O_3N_2$: C, 66.81; H, 5.08; N, 10.58%.

Cyclization Reaction in *N*-Methylpyrrolidone. A solution of *N*-(phenylcarbamoyl)anthranilic acid or its derivatives (1/300 mol) in 20 m*l* of *N*-methylpyrrolidone was kept at 100°C for 3 hr with stirring. After removal of the solvent under reduced pressure, the residue was separated by fractional recrystallization from ethanol.

Cyclization Reaction in Nitrogen Gas. *N*-(Phenylcarbamoyl) anthranilic acid derivative (0.1 g) was introduced into a test tube in a nitrogen atmosphere. The test tube was sealed and placed in an oven and heated at 220°C for 2 hr. In every case, the product was identified to be 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione (IV) from its IR spectrum and melting point (282°C).