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ISATOIC ANHYDRIDE. II. REACTIONS OF ISATOIC ANHYDRIDE WITH AMMONIA

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Reactions of isatoic anhydride with primary and secondary amines (1) in general yield either the corresponding *o*-aminobenzamides or, by continued reaction of isatoic anhydride with the amino group exposed by each such condensation, the so-called "abnormal" products shown to be mixtures of polyanthranoylanthranilamides, in both cases with loss of carbon dioxide. Ammonia and isatoic anhydride have long been known to yield anthranilamide (2), but Sheibley (3) reported that action of hot ammonia-water on dihalogenoisatoic anhydrides yielded none of the corresponding dihalogenoanthranilamide but only dihalogenobenzoylene urea and dihalogenoanthranilic acid, and represented the results by the equation: 5 di-X-isatoic anhydride $+ 2NH_3 + H_2O \rightarrow$ 2 di-X-benzoylene urea + 3 di-X-anthranilic acid $+ 3CO_2$. Using ethylamine instead of ammonia Sheibley obtained results only partially analogous, the products being the corresponding benzoylene urea and the substituted anthranilamide. The formation of benzoylene ureas, which was not observed by Clark and Wagner during reactions of isatoic anhydride and amines,[1] indicates that the reactions can follow another course which leads to ring-closure without loss of carbon dioxide. This paper reports the findings of a study to seek an explanation for the seemingly conflicting claims outlined above, and especially to learn the course by which benzoylene ureas are formed. The simplest case, that of isatoic anhydride and ammonia, was selected for examination; other cases will be studied later.

Comparison of the experimental conditions used by Clark and Wagner and those used by Sheibley reveal that the former took the reactants generally in about equivalent amounts but that Sheibley used both ammonia (as strong ammonia water) and ethylamine in enormous initial excess.[2]

Experiments to test the importance of this difference in conditions showed that the proportions of isatoic anhydride and ammonia, and the concentration of the latter, are factors which determine the proportions of two obtainable products,

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[1] Benzoylene urea was obtained by interaction of isatoic anhydride with ethyl carbamate and with urea, as a result of expected reactions. Otherwise no search was made for benzoylene urea in the reaction mixtures.

[2] Clark and Wagner used amine in large excess only when the 1:1 ratio yielded "abnormal" products, indicating presumably an unfavorable ratio of the speeds of the normal and "abnormal" reactions. This was the case with some primary aromatic amines and five of the seven secondary amines tested. By use of amine in large excess the disadvantage mentioned was overcome to some extent in the case of *p*-bromoaniline and to greater extents with the secondary amines, showing that large excesses of these amines present throughout the reactions operated to decrease the incidence of the "abnormal" reaction. The failure of secondary amines to yield benzoylene ureas by this procedure has no bearing on the inquiry, for secondary amines are clearly incapable of providing a nitrogen atom for the diazine ring of benzoylene urea.

viz., anthranilamide and benzoylene urea. Using ammonia in amount and concentration near the minima required for involvement of all the isatoic anhydride (2.5 equivalents of ammonia at 1-molar concentration) there resulted no benzoylene urea but only anthranilamide amounting to over 90% of the theoretical yield. Benzoylene urea first appeared as a product (10%) with 5 equivalents of ammonia at 2-molar concentration, and was accompanied by 90% of anthranilamide. As the concentration and excess of ammonia were increased the yields of benzoylene urea increased steadily to a maximum of about 42% (40 equivalents of ammonia at 16-molar concentration), while those of amide decreased to 55%. The data for these experiments appear in Table I, the significant features of which are immediately obvious in Figure 1.

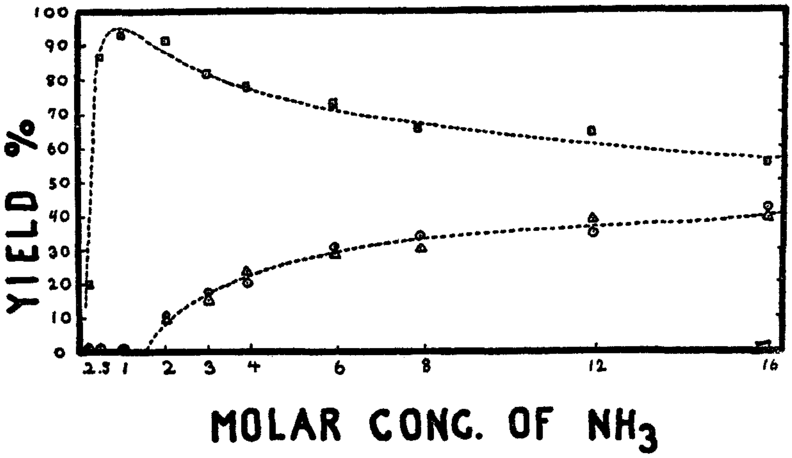
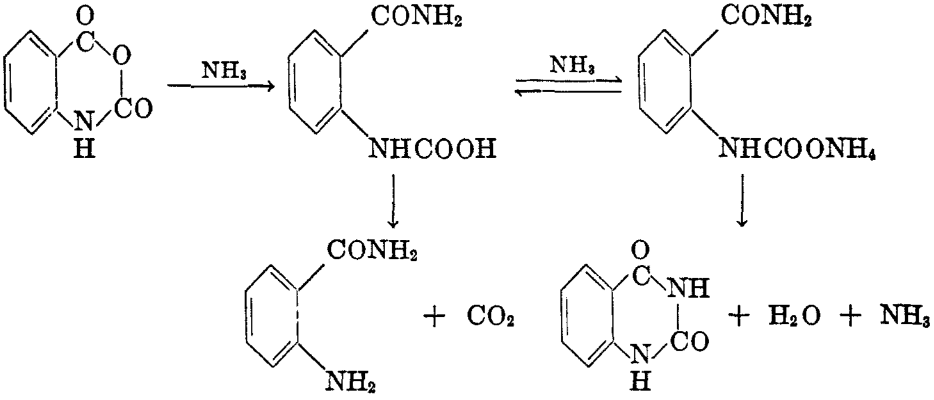


FIG. 1. INTERACTION OF ISATOIC ANHYDRIDE AND AMMONIA

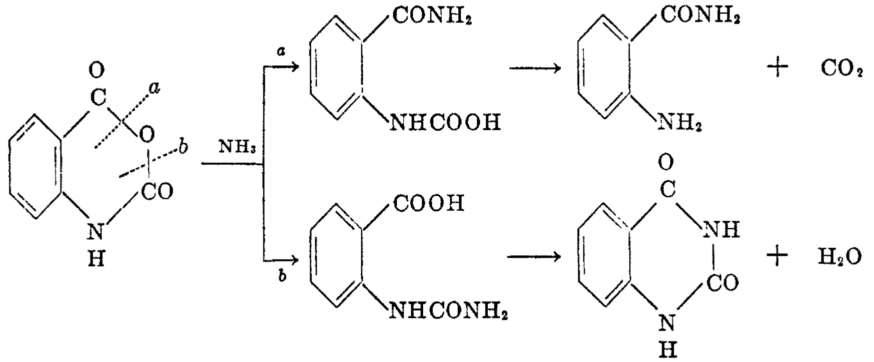
□ anthranilamide
△ uramido benzoic acid
⊙ benzoylene urea

It was conjectured at first that the effect of high concentration of ammonia in favoring the formation of benzoylene urea might be a stabilization of isatoic acid as its ammonium salt, sufficient to delay decarboxylation and permit ring closure:



This view proved untenable, for experiments to test it by use of large amounts of added ammonium salt yielded the result that with the liquid nearly saturated with ammonium acetate no benzoylene urea was found at any concentration of ammonia from 4-molar to 12-molar, at which concentrations but in absence of ammonium acetate the yields of benzoylene urea are 20% and 40% respectively. In the presence of ammonium acetate, the isolable product was anthranilamide in high yield.

The surmise was then tested that two separate and competitive reactions lead to formation of anthranilamide and of benzoylene urea, involving two different cleavages of the mixed anhydride grouping of isatoic anhydride (see reaction scheme below). This proved to be correct, for under conditions known to yield benzoylene urea it was found that, after the initial reaction with ammonia in large excess, acidification of the chilled mixture caused the separation of a compound identified as *o*-uramidobenzoic acid, which is the primary product to be expected by cleavage at *b* (reaction scheme), and which is convertible with the greatest ease to benzoylene urea (4). It is significant that the amounts of uramidobenzoic acid (determined in separate experiments) paralleled closely those of benzoylene urea at all concentrations of ammonia (Figure 1), leaving little reason to doubt that uramidobenzoic acid is the precursor of benzoylene urea. The filtrates always contained anthranilamide in quantity, but no anthranilic acid formed by hydrolysis of anthranilamide, which in separate tests was found to be apparently unaffected by concentrated ammonia water at room temperature. Experiments to test the effects of temperature and time, with the concentration of ammonia constant, showed clearly that the determining variable is the concentration of ammonia. The two reactions appear to be independent except as both consume isatoic anhydride. The interaction of isatoic anhydride and ammonia may be represented as shown in the reaction scheme:



For the present there is withheld speculation as to the reason why cleavage of isatoic anhydride at *b* requires a higher concentration of ammonia than cleavage at *a*. In the experiments there was found no "abnormal" product (formed by condensation of anthranilamide with isatoic anhydride), indicating that the action of ammonia was so rapid as to exclude this secondary condensation. The "abnormal" reaction appeared to occur when isatoic anhydride was treated with only one-half equivalent of ammonia, the product being an amorphous material similar to that reported previously (5) as formed from anthranilamide and isatoic anhydride.

These findings for the interaction of isatoic anhydride and ammonia parallel Sheibley's findings for reactions of dihalogenoisatoic anhydrides with ethylamine but not with ammonia. It may be suspected that Sheibley's equation for the interaction of ammonia and dihalogenoisatoic anhydrides represents a composite of several concurrent reactions and that the stoichiometric relationships on which it is based are valid in an over-all sense for the somewhat indefinite conditions used, *viz.*, concentrated aqueous ammonia in large initial excess which decreased rapidly as the mixture was heated.

EXPERIMENTAL

Action of aqueous ammonia on isatoic anhydride. General procedure. In the experiments represented in Table I, 1.63 g. (0.01 mole) of powdered isatoic anhydride was added with stirring to 25 ml. of water containing ammonia in concentrations from 0 to 16 molar, corresponding to molar ratios (with respect to isatoic anhydride) of 0 to 40, and obtained by diluting the requisite concentrated aqueous ammonia with water as required. Reaction was allowed to occur at room temperature (about 23°); the negligible effect of temperature upon the essential results is shown later. When the concentration of ammonia was molar or greater the isatoic anhydride dissolved more or less promptly. The solution was then examined for anthranilamide and for either uramidobenzoic acid or benzoylene urea by the procedure outlined below; the negligible effect of reaction time upon the essential results is shown later. When the concentration of ammonia was (or became) 0.4 molar or less the isatoic anhydride did not dissolve completely. In such cases the suspension was stirred at regular intervals during periods of six hours or more, and the mixture was examined by the procedure given below.

Procedure for analysis of reaction mixtures. If isatoic anhydride did not dissolve completely after about six hours the mixture was filtered through a tared Gooch crucible, and the collected isatoic anhydride was washed with cold water, dried at 110° and weighed. As shown by the complete recovery of isatoic anhydride in the experiment with pure water the compound is practically insoluble in water, and is not hydrolyzed by it under the conditions used. The filtrate from the recovered isatoic anhydride (or the original reaction liquid if this was clear) was examined as follows.

Determination of benzoylene urea and anthranilamide. The sensible solubility of anthranilamide in water made its approximately quantitative recovery as such impracticable. Therefore in most cases it was converted to anthranilic acid by hydrolysis with aqueous sodium hydroxide and this was precipitated and determined as cupric anthranilate. The validity of this procedure is based upon the facts (a) that aqueous ammonia, under the conditions used, does not hydrolyze either isatoic anhydride or anthranilamide, so that no anthranilic acid is present from these sources; (b) that aqueous alkali converts uramidobenzoic acid to the sodium salt of benzoylene urea, which is not decomposed by alkali, so that no benzoylene urea is lost during the treatment with alkali; and (c) that in solutions which are neutral or slightly acid with acetic acid cupric acetate in excess precipitates anthranilic acid as the cupric salt (6). An experiment to test the completeness of hydrolysis and precipitation by the procedure described below showed recovery of cupric anthranilate from 0.5000 g. of anthranilamide to be 0.6190 g. or 100.4%.

Procedure. To the clear reaction liquid was added 0.5 g. of solid sodium hydroxide, and the solution was evaporated to a thick paste on a hot plate. The residue was dissolved in 50 ml. of water, and the solution was acidified with acetic acid and was chilled in an ice-bath. Any benzoylene urea present separated and was collected in a tared Gooch crucible, washed with cold water, dried at 110°, and weighed. This product was identified as benzoylene urea by conversion to the dimethyl derivative (m.p. 167°) by shaking with methyl sulfate and aqueous sodium hydroxide. The filtrate from the benzoylene urea was neutralized with sodium hydroxide solution, and the solution was chilled in an ice-bath and treated with a moderate excess of cupric acetate solution (about 1 *M*). The green precipitate of cupric anthranilate was collected in a tared Gooch crucible, washed with cold water, dried at 110°, and weighed. (A brown color or a brown amorphous precipitate accompanying the cupric anthranilate appeared after about thirty minutes if the hydrolysis of anthranilamide was incomplete.)

Uramidobenzoic acid was determined either in separate experiments as follows or along with anthranilamide as outlined in the succeeding procedure. Following reaction of isatoic anhydride with ammonia the clear solution was cooled to somewhat below room temperature and was gradually acidified by addition of cold 1:1 sulfuric acid. Any separated uramidobenzoic acid was collected in a tared Gooch crucible, washed with cold water, dried at 110°, and weighed. This product was identified as uramidobenzoic acid by melting point (*ca.* 140°) and by its ready conversion to benzoylene urea upon treatment with hot 1:1 sulfuric acid, or by dissolving it in strong aqueous sodium hydroxide and then acidifying.

TABLE I

ACTION OF AMMONIA ON ISATOIC ANHYDRIDE

(0.01 Mol. isatoic anhydride, conc'd $NH_4OH + H_2O$ to 25 cc. Temp. 23°)

CONC'D AMMONIA MOLAR	0.0 H_2O	0.2	0.4	1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0
Molar Ratio: NH_3 to Isatoic Anhydride	0.0	0.5	1.0	2.5	5.0	7.5	10.0	15.0	20.0	30.0	40.0
Undissolved Isatoic Anhydride, %	100.0	79.6	20.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Anthranilamide, %	0.0	19.8	86.0	92.5	91.0	81.6	78.2	72.0	65.3	63.9	55.4
Uramidobenzoic Acid, %	0.0	0.0	0.0	0.0	9.1	15.0	23.5	28.5	30.0	38.5	39.0
Benzoylene Urea, %	0.0	0.0	0.0	0.0	10.4	17.2	20.4	30.0	34.1	34.5	41.8
Total Isatoic Anhydride Accounted for	100.0	99.4	106.0	92.5	101.4	98.8	98.6	102.0	99.4	98.4	97.2

To determine *uramidobenzoic acid and anthranilamide* the clear ammoniacal reaction liquid was evaporated to dryness at or below 50°. The residue was stirred with 25 ml. of water, and any undissolved anthranilamide was collected in a tared Gooch crucible, washed sparingly with cold water, air-dried at room temperature, and weighed. The filtrate was chilled in an ice-bath and was acidified with acetic acid. After two hours in the ice-bath any uramidobenzoic acid was collected in a tared Gooch crucible and was determined. The anthranilamide in the filtrate was converted to anthranilic acid by adding 20% sodium hydroxide solution to strong alkalinity and by boiling for an hour. The solution was acidified with acetic acid and the anthranilic acid was precipitated and determined as outlined above.

Table I records results obtained by the foregoing procedures.

Effect of time. For each experiment there were used ammonia and isatoic anhydride in the molar ratio 10:1, a temperature of 25°, the general procedure given above, and reaction periods of five to forty-five minutes counted from the moment the isatoic anhydride was completely dissolved. The extent of reaction was inferred in each case from the amount of benzoylene urea isolated by the procedure described. The results were as follows:

Time, minutes	5	15	30	45
Benzoylene urea, %	21.8	20.0	21.6	20.4

It appears that reaction occurs promptly, and probably within the interval required to dissolve the isatoic anhydride.

Effect of temperature. Experiments similar to the foregoing, but with a uniform reaction period of ten minutes and with temperatures ranging from 10° to 50°, yielded these results:

Temperature °C	10	20	40	50
Benzoylene urea, %	23	22	20.6	18.5

Temperatures above room temperature appear to be without advantage; at 50° rapid change in the concentration of ammonia occurs because of volatilization.

Stability of anthranilamide toward aqueous ammonia. Anthranilamide (0.5 g.) was added to 16 *M* ammonia water (15 ml.) and the suspension was allowed to stand for twelve hours. The mixture was evaporated to dryness below 70°. The residue was treated with water and the undissolved anthranilamide was collected on a filter; the recovery was about 75%, but this value is not significant owing to the solubility of anthranilamide in water. The filtrate was adjusted to neutrality (bromocresol purple) with acetic acid and sodium hydroxide, and an excess of cupric acetate solution was added. No precipitate of cupric anthranilate appeared even after the mixture was cooled, indicating no hydrolysis of the amide by aqueous ammonia.

Reaction of aqueous ammonia and isatoic anhydride in presence of ammonium acetate. In each of the following experiments 1.63 g. (0.01 mole) of isatoic anhydride was added to aqueous ammonia previously saturated with ammonium acetate: (a) with 5 cc. of conc'd ammonia-ammonium acetate solution anthranilamide (60%) precipitated; (b, c) with 25 cc. of ammonia-ammonium acetate solution, either 4-molar or 16 molar in ammonia, no precipitate appeared, and upon acidification in the cold by addition of dilute sulfuric acid no uramidobenzoic acid separated; (d) no benzoylene urea was obtained when the reaction mixture (4-molar in ammonia) was examined for the compound by the procedure given previously; the further operations to determine anthranilamide showed presence of 90.5% of the product, a value probably somewhat low, as the solubility of cupric anthranilate is increased by presence of salts (6).

Preparation of uramidobenzoic acid or benzoylene urea from isatoic anhydride. The preparation of either of the compounds named by action of concentrated ammonia upon isatoic anhydride is easier and more rapid than by any other available method, though the yields do not exceed 40% and the process is not economical. For rapid preparation of small amounts the following procedure will serve. Isatoic anhydride is dissolved in concentrated (16 *M*) aqueous ammonia, using 15 ml. per gram of isatoic anhydride. To obtain uramidobenzoic acid the solution is chilled and then acidified slowly by addition of cold dilute sulfuric acid. To obtain benzoylene urea the reaction liquid is warmed and acidified with conc'd sulfuric acid, after which the mixture is cooled. In each case the product precipitates at once.

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