[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

ISATOIC ANHYDRIDE. I. REACTIONS WITH PRIMARY AND SECONDARY AMINES AND WITH SOME AMIDES[1]

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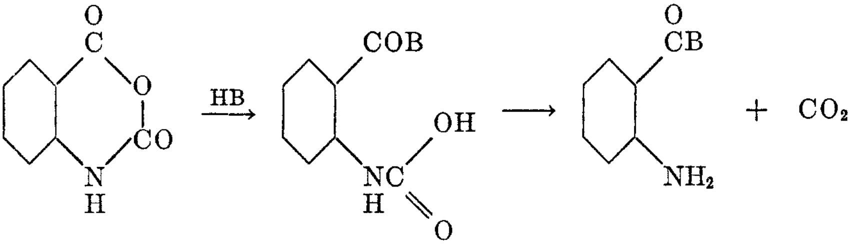
Received October 1, 1943

Isatoic anhydride is a convenient reagent for certain anthranoylations, serving instead of the unknown anthranoyl chloride and similarly to anthranil (1), which at present is not conveniently obtainable. Isatoic anhydride has been used recently in syntheses of substituted dihydroquinazolones (2) and tetrahydroquinazolones (3), but its usefulness in synthesis is limited because its chemistry has been studied only partially and in some directions not very successfully. This paper describes the initial work in the study of its preparation and reactions. The previously reported reactions with compounds containing reactive hydrogen atoms (ammonia, primary amines, alcohols, phenols) may be regarded as anthranoylations, in general:



B = —NH$_2$, —NHR, —NHAr, —OR, —OAr

The liberation of carbon dioxide is characteristic of these reactions, which are those of a cyclic mixed anhydride of a simple carboxylic acid and a carbamic acid.

The interaction of isatoic anhydride and ammonia or common primary amines (4, 7, 8) proceeds readily, but it was found that some primary and secondary amines react to liberate carbon dioxide but yield the expected amides in small amounts or not at all, the principal products being amorphous solids of refractory character and ill defined properties. For convenience these reactions and their products will be referred to as "abnormal". The nature of these materials, the manner of their formation, and procedures by which their formation to some extent may be controlled or avoided, are discussed below. Alcohols and phenols were reported to yield esters of anthranilic acid (4, 6, 9) but preliminary results have indicated that their reactions with isatoic anhydride may be in part abnormal. The reactions of isatoic anhydride with amides (acetamide, urea) were reported by Meyer (9) to be slow and to yield only amorphous and poorly defined products. This finding has been verified for acetamide, but both urea and ethyl

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[1] This paper is constructed from the doctoral thesis submitted by Robert H. Clark to the Graduate School of the University of Pennsylvania, 1943.

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carbamate were found to yield also benzoylenurea. It was found possible to use isatoic anhydride in a simplified quinazolone synthesis, eliminating the necessity of preparing separately the intermediate substituted anthranilamide. These results are discussed later.

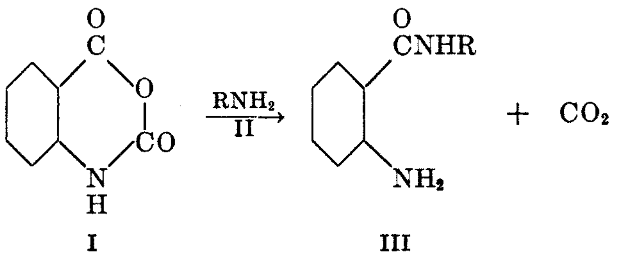
Isatoic anhydride is a minor by-product of the preparation of anthranilic acid from phthalimide (10), and has been prepared from anthranilic acid by action of either ethyl chlorocarbonate or phosgene. The chlorocarbonic ester method (5) proved to be only moderately satisfactory, requiring prolonged heating and producing isatoic anhydride in yields usually not above fifty per cent, accompanied by relatively large amounts of monoethyl isatoate or (and) diethyl isatoate. Erdmann's phosgene method (5), involving maintenance of relatively low acidity by occasional introduction of sodium carbonate, appears to be equally uncertain, and was abandoned when a final trial yielded almost wholly an amorphous product, not identified. A patented procedure (11) by which phosgene is passed into a strongly acid solution of anthranilic acid with no subsequent regulation of the increasing acidity, a favorable temperature being maintained by the rate at which phosgene is introduced, was found consistently to give good yields of substantially pure isatoic anhydride and no undesirable by-product. This method, in the form developed in the course of numerous trials, is described in the experimental section.

I. REACTIONS OF ISATOIC ANHYDRIDE WITH PRIMARY AMINES

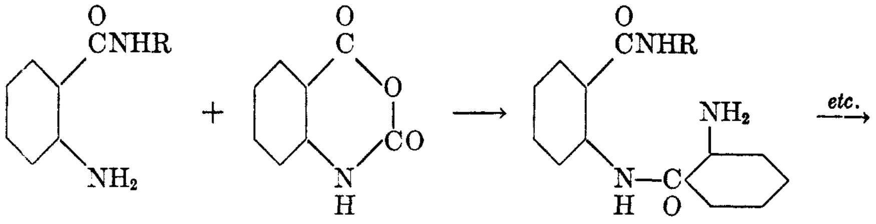
Strongly basic primary amines react readily with isatoic anhydride at low or moderate temperatures (room temperature to 130° in most cases), and some even in water solution. Aromatic primary amines with ortho substituents (*e.g.*, 2,6-dimethylaniline, mesidine) or with negative substituents in ortho or para positions (*e.g.*, *o*-bromoaniline, *o*- and *p*-nitroanilines, methyl and ethyl anthranilates) were found to react less readily and to yield largely or almost wholly the abnormal products. The essential results of the reactions of thirty-one primary amines are collected in Table I.

The *abnormal reaction* occurs with evolution of carbon dioxide in amounts that indicate the involvement of isatoic anhydride to be quantitative or nearly so. The probable course of the abnormal reaction becomes obvious when it is noted that the product formed by the normal reaction (equation 1) contains a free amino group, and is therefore capable of reaction with isatoic anhydride (equation 2):

1.

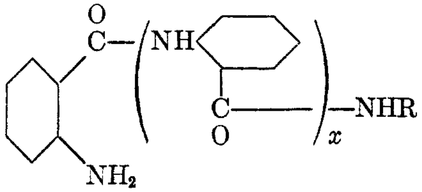


2.



III IV

If the reactivity of the amino-hydrogen of compound III approaches or exceeds that of the amino-hydrogen of compound II, then some or all of III will react with isatoic anhydride to form IV. This product likewise contains a free amino group, and if the reactivity of II is for any reason low the condensation may continue, yielding products representable by the general formula V.



V

The conditions which favor abnormal reaction probably prevail not beyond the second or third stage (x = 1 or 2). It may be concluded that mixtures of products result, and that the average value of x is not integral and is not large. Such molecules, because of their jagged structures and multipolar characters may well associate or aggregate to form macromolecular polyamides analogous to proteins, nylon, etc. The abnormal products show characteristics consistent with this view: they are amorphous, refractory, and practically insoluble in the common solvents, including acids and bases. In no case was it possible to isolate a single compound of type IV or V from the intractable mixtures obtained. This excluded identification of any abnormal product with an anthranoylanthranilamide of type IV synthesized from *o*-nitrobenzoyl chloride as described by Meyer (12), though the superficial properties of the two are unmistakably similar.

The essential correctness of the foregoing conception of the abnormal reaction was established by the following experimental findings. (A) The interaction of equivalent amounts of isatoic anhydride and *o*-bromoaniline yielded no isolable normal product, but when *o*-bromoaniline was used in large excess some N-(*o*-bromophenyl)anthranilamide was formed. It may be inferred that the excess of amine in part overcame the disadvantage inherent in a relatively high rate for reaction 2 as compared with reaction 1. (B) The interaction of equivalent amounts of isatoic anhydride and aniline is normal, but when two equivalents of isatoic anhydride were used the product was amorphous and entirely unlike anthranilanilide obtained from equivalent weights of the reactants. The amount of carbon dioxide evolved showed all the isatoic anhydride (two equivalents) to have reacted. (C) When pure anthranilanilide (a normal product) was heated with an equivalent of isatoic anhydride the theoretical amount of carbon dioxide was disengaged and the abnormal product resulted. (D) Hydrolytic cleavage of the abnormal product obtained from isatoic anhydride and anthranilamide was effected by heating under pressure with concentrated hydrochloric acid. The hydrolytic products were anthranilic acid and ammonia, as required by a structure of type V, and the quantity of ammonia indicated the average value of x to be 2. From the evidence just reviewed it is concluded that the abnormal products are mixtures of polyanthranoylanthranilamides as represented by formula V.

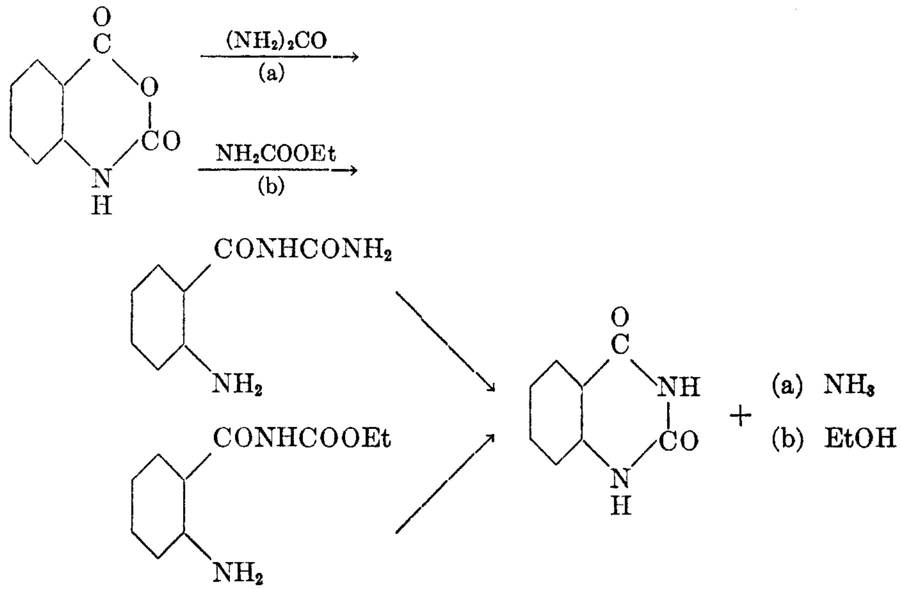
II. REACTIONS OF ISATOIC ANHYDRIDE WITH SECONDARY AMINES

The interaction of isatoic anhydride and secondary amines has not been studied previously. When equivalent amounts were heated together, reaction occurred and carbon dioxide was evolved, but the N,N-disubstituted anthranilamides which would be the normal products were obtained usually in small amounts or not at all, the reaction mixtures in most cases being resinous, gummy masses, from which no well-defined compounds could be isolated. It was found however that moderately good yields of normal products resulted when the secondary amines were maintained in considerable excess throughout the reaction, in order to impose a statistical disadvantage on the abnormal reaction (equation 2). This was done in each case by adding finely-divided solid isatoic anhydride slowly to a two- to five-fold excess of the amine while the mixture was kept at a temperature which ensured rapid reaction as indicated by prompt evolution of carbon dioxide. By this procedure normal condensations were effected using N-alkylanilines, but results with several strongly reactive secondary amines (*e.g.*, diethylamine) were not materially improved, the low yields of the normal products (which in these cases are liquids or low-melting solids) by either procedure being due apparently to difficulties in the isolations. Table II presents the essential results with secondary amines. The structures of the new compounds were established by independent synthesis of each compound by condensing with *o*-nitrobenzoyl chloride the amine represented and by reduction of the product (12, 13).

III. REACTIONS OF ISATOIC ANHYDRIDE WITH AMIDES (PRELIMINARY)

Acetamide and isatoic anhydride reacted slowly above 180° to yield an amorphous product with the characteristics of a mixture, confirming the result reported by Meyer and Bellmann (9). An abnormal condensation seems likely with acetamide, whose feebly basic amino group presumably cannot compete advantageously with the basic amino group of the first-formed product, so that interaction of this and isatoic anhydride occurs, yielding products of type V. In contrast with this behavior of acetamide it was found that urea and also ethyl carbamate reacted with isatoic anhydride to yield benzoylenurea, as well as considerable amorphous material. The formation of benzoylenurea was anticipated, for it was known to be obtainable by interaction of anthranilic acid and urea (14) and also ethyl carbamate (15). It is concluded that the initial reactions of these amides are normal, and that incidence of the abnormal reactions is in part excluded because of the ease of ring closure:

3.

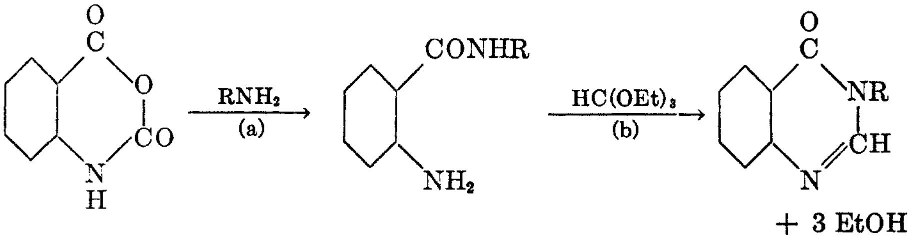


The formation of benzoylenurea from isatoic anhydride and urea may occur also by an alternate course, for the ammonia liberated during the ring closure would react with isatoic anhydride to form anthranilamide, which on heating with urea is known to yield benzoylenurea (16).

IV. THE SYNTHESIS OF 3-SUBSTITUTED-4-KETO-3,4-DIHYDROQUINAZOLINES

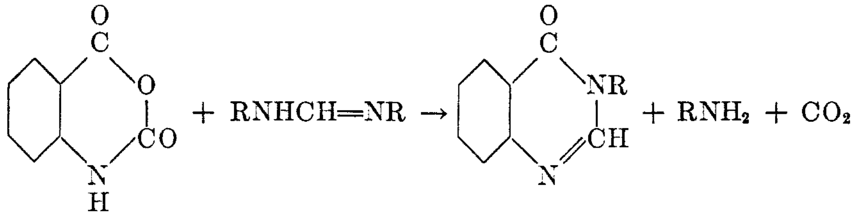
This synthesis, by interaction of isatoic anhydride, primary amines, and ethyl orthoformate, was found to be feasible, and constitutes a simplification of the conventional ring closure using the preformed substituted anthranilamide and orthoformic ester. The course of the reaction is not clear, as there may be involved primary interaction of isatoic anhydride and amine to form the substituted anthranilamide, followed by ring closure with orthoformic ester (equation 4), or (and) primary interaction of amine and orthoformic ester to yield the corresponding formamidine (17), which has been shown (2) to react with isatoic anhydride to form the quinazolone (equation 5):

4.



5. (a) $2\,RNH_2 + HC(OEt)_3 \longrightarrow RNHCH{=}NR + 3\,EtOH$

(b)



Reaction 5b, however, required temperatures 20° to 30° higher than sufficed for reactions 4a,b and also for reaction 4a and 4b when effected separately. The formation of dihydroquinazoline from isatoic anhydride, amine, and ethyl orthoformate therefore appears to follow the course represented by equations 4a, b.

An attempted quinazolone synthesis using ethyl orthoacetate instead of ethyl orthoformate was unsuccessful, as was an attempt to effect synthesis of a tetrahydroquinazolone by interaction of isatoic anhydride, aniline, and methylal (105° in sealed tube), the reaction proceeding only to the anthranilamide stage.

EXPERIMENTAL

Unqualified melting point values were obtained with a Fisher-Johns apparatus. Corrected values were determined in a Hershberg apparatus (22). Nitrogen analyses were made by a semimicro Kjeldahl procedure (23).

Preparation of isatoic anhydride (*11*). One mole (137 g.) of anthranilic acid was dissolved in a mixture of 150 g. (125 ml.) of conc'd hydrochloric acid and 1 liter of water. The solution was filtered into a three-liter three-necked flask fitted with a sealed mechanical stirrer, an inlet tube reaching to the bottom of the flask, and an outlet tube connected to a safety flask, followed by a Drechsel absorber charged with ammonium hydroxide. The mixture was stirred mechanically and phosgene was passed through an empty safety bottle and then into the solution of anthranilic acid at such rate (about two bubbles per second) that bubbles of gas escaped only slowly at the surface of the liquid (hood). The temperature rose, but was readily maintained near 50° by regulation of the rate at which the phosgene was introduced. The rate of absorption of phosgene was found to be increased as the rate of stirring was increased. Separation of isatoic anhydride began soon after the stream of phosgene was started. The process was continued during several (2 to 4) hours or until the absorption of phosgene was much decreased. The flask was disconnected and a stream of air bubbled through its contents to remove phosgene. The white solid was collected, washed several times with cold water, and dried at 110°. Yields from a number of runs ranged from 115 g. to 125 g. (71–77%) of material melting at 240–243°, pure enough for use. Further purification may be effected by crystallization from 95% ethanol (30 ml. per gram) or from hot dioxane (10 ml. per gram).

I. Reactions of isatoic anhydride with primary amines

A. Procedures (*Cf. Table I*). 1. *Aliphatic monoamines* (*ethyl, propyl, butyl, amyl*). Powdered isatoic anhydride (2.04 g.; 0.0125 mole) was added gradually to a solution of slightly more than an equivalent amount of amine in 10 ml. (or the minimal larger volume) of water. Evolution of carbon dioxide was spontaneous and vigorous. When action ceased the solid product was washed by decantation with three 25-ml. portions of cold water, dried, and crystallized from dilute alcohol or benzene, a second crop being obtained by concentration of the mother liquor.

2. *Aliphatic diamines* (*ethylenediamine and propylenediamine*). Powdered isatoic anhydride (8.15 g.; 0.05 mole) was added gradually to a solution of a slight excess of the di-

amine in 15 ml. of water. Reaction started upon warming the mixture gently, and became vigorous. The mixture was allowed to stand overnight. After partial drying it was crystallized from dioxane-water mixture, two crops being obtained.

3. *Cyclohexylamine.* Isatoic anhydride (4.08 g.; 0.025 mole) was sifted slowly into 4.94 g. (0.05 mole) of cyclohexylamine. Reaction occurred cold; the mixture was finally heated to 100° to complete the action. The hot mixture was treated with 15 ml. of alcohol and was chilled in ice. The crystalline product was recrystallized from 50% ethanol.

4. *Benzylamine* (5.6 g.; 0.05 mole) was poured upon 4.08 g. (0.025 mole) of isatoic anhydride. When the spontaneous reaction had subsided the mixture was heated to 165°. The brown, fluid mass solidified upon cooling. It was washed well with cold water on the filter, dried, and crystallized from benzene, a second crop being recovered from the mother liquor.

5. *Aromatic amines* (excepting *o*-bromoaniline, 2,6-dimethylaniline, mesidine, *o*- and *p*-nitroaniline, anthranilamide, and anthranilic esters; see later procedures). Isatoic anhydride (2.04–8.15 g.; 0.0125–0.05 mole) and a 3% excess of amine were heated to reaction temperature (50° to 130°) in a water-bath or oil-bath until evolution of carbon dioxide ceased. The solid residual mass was dissolved in hot benzene and two crops of crystals were isolated. The product from anthranilic acid was isolated by extraction in *N* sodium hydroxide solution and was reprecipitated by acetic acid. The products from (a) 2-aminopyridine, (b) 2-amino-3-methylthiazole (24) and (c) 2-amino-6-methylbenzothiazole (25) were crystallized respectively from (a) 40% ethanol, (b) 95% ethanol, and (c) benzene (twice) then alcohol (twice).

6. *Phenylhydrazine* (9) and isatoic anhydride in 95% ethanol reacted at 70°. On chilling the solution in an ice-salt bath, yellow crystals separated; a second crop was obtained from the filtrate.

7. *Hydroxylamine* (*9*). To a solution of 6.9 g. (0.10 mole) of hydroxylamine hydrochloride in 250 ml. of water was added an equivalent amount of sodium carbonate. To the solution was added 8.15 g. (0.05 mole) of isatoic anhydride; reaction was spontaneous. The mixture was allowed to stand overnight, and the solid product was crystallized from water at 40°, dried briefly in the air and then completely in a vacuum desiccator. This compound decomposed rapidly upon exposure to moist air.

8. *o-Bromoaniline.* Interaction of equivalent amounts of *o*-bromoaniline and isatoic anhydride yielded 90% or more of the theoretical carbon dioxide (collected and weighed in an Ascarite absorber), but the product was amorphous and obviously of the abnormal type. A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and two equivalents of *o*-bromoaniline (8.60 g.; 0.05 mole) heated at 130° gave off 90% of the theoretical carbon dioxide. Excess amine was removed by steam distillation. Extraction of the solid residue with 100 ml. of hot 1:1 alcohol left undissolved 0.9 g. of material melting 175–220°, not examined further. The alcohol solution was chilled, yielding 0.96 g. of material which softened slowly above 116°. Addition of water to the filtrate precipitated 1.97 g. of material melting near 106°. This was extracted four times with 1:1 hydrochloric acid, and the filtered extracts were made alkaline with ammonium hydroxide. The combined precipitates were crystallized from dilute ethanol, two crops of N-anthranoyl-*o*-bromoaniline being obtained.

9. *2,6-Dimethylaniline* and isatoic anhydride, the former in 5% excess, reacted slowly during four hours at 125–130°. Extraction of the mass with hot benzene left undissolved a gray material without definite melting point. No identifiable solid could be recovered from the benzene extract.

10. *Mesidine* (4.25 g.; 0.0315 mole) and isatoic anhydride (4.08 g.; 0.025 mole) reacted slowly at 125–130°, and in seven hours liberated 80% of the theoretical carbon dioxide. A small part of the mass dissolved in hot benzene; the residue (3.96 g.) melted indefinitely above 250°. No well defined product could be isolated from the benzene extract.

11. *Ethyl anthranilate.* A mixture of 8.30 g. (0.05 mole) of ethyl anthranilate and 8.15 g. (0.05 mole) of isatoic anhydride, heated at 140–150° until gas evolution ceased, yielded 93% of the theoretical carbon dioxide. The sticky reaction mixture was extracted with two 200-ml. portions of boiling 95% ethanol, most of the mass remaining undissolved as an

amorphous material without definite melting point. On cooling the combined alcohol extracts, 1.45 g. of crystalline material melting at 136–140° separated. This was crystallized from 95% ethanol in three portions, the first melting at 139–143°, and the second and third at 157–158°. The filtrate from the crude substance of m.p. 136–140° was heated nearly to boiling, and water was added to incipient turbidity. After treatment with Norit the mixture was filtered and the filtrate was chilled, causing separation of an oil which solidified on standing. It was broken up, dried in the air (2.06 g.; m.p. 50–70°) and crystallized from 60% alcohol in two crops melting at 93.5–94.5° corr. This compound was found to be the normal product, ethyl N-anthranoylanthranilate. For its identification, ethyl anthranoylanthranilate was made synthetically from *o*-nitrobenzoyl chloride and ethyl anthranilate, which condensed in presence of aqueous sodium hydroxide. The product was crystallized from dilute alcohol and was then reduced in alcohol solution in an Adams and Vorhees apparatus using Raney nickel catalyst. The resulting ethyl N-anthranoylanthranilate separated from the filtered liquid upon addition of water. It melted at 94–94.5°, corr. A mixture of this compound and the compound obtained from isatoic anhydride and ethyl anthranilate melted at 93.5–94.5°, corr. The product of m.p. 157–158° mentioned above, possibly dianthranoylanthranilic ester, could not be identified with a specimen of this compound made synthetically from ethyl N-anthranoylanthranilate by condensing with *o*-nitrobenzoyl chloride in presence of aqueous alkali and reduction of the resulting N-(*o*-nitrobenzoyl)anthranoylanthranilic ester (m.p. 161–162° after crystallization from 95% alcohol). The ethyl dianthranoylanthranilate melted at 121–122.5°, a value not changed by crystallization from 60% ethanol.

12. *Methyl anthranilate.* Equimolecular amounts (0.10 mole) of isatoic anhydride and methyl anthranilate were heated at 170° until gas evolution ceased. Extraction of the reaction mixture with 200 ml. of hot methanol left undissolved most of the solid, which did not melt up to 285°. The methanol extract was concentrated by slow evaporation, with occasional removal of the solid which separated in small amount; this material showed no definite m.p. Finally a crystalline compound separated: 1.20 g. (4.5%); m.p. 114.5–115.5° corr. Meyer (12) reported methyl N-anthranoylanthranilate, made *via* *o*-nitrobenzoyl chloride, to melt at 119°.

13. *Anthranilamide.* A mixture of 5.40 g. (0.0397 mole) of anthranilamide and 6.47 g. (0.0397 mole) of isatoic anhydride was heated at 105–108° for two hours and then at 130° for one hour. The reaction yielded 81% of the theoretical carbon dioxide. The brown, glassy reaction mixture dissolved almost wholly in hot alcohol. Concentration of the extract yielded 4.38 g. of solid material which softened and melted from 150° to 165°; it was examined as described in section B. No normal product was obtained.

14. o-*Nitroaniline and* p-*Nitroaniline.* A mixture of 1.75 g. (0.0127 mole) of nitroaniline and 2.04 g. (0.0125 mole) of isatoic anhydride was heated at 155–160° until the slow evolution of carbon dioxide appeared to cease. The mass was extracted with 140 ml. of boiling benzene. Concentration of the benzene extract yielded only some unchanged nitroaniline. The yellow amorphous materials not soluble in benzene weighed 1.50 g. and 1.42 g. respectively. That from *o*-nitroaniline did not melt up to 285°; that from *p*-nitroaniline softened around 230° (unchanged isatoic anhydride).

B. Abnormal reactions and products. 1. *Aniline and excess isatoic anhydride* (Cf. *Section A, Procedure 5*). A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and 1.16 g. (0.0125 mole) of aniline was heated at 110–120° until evolution of carbon dioxide ceased. The evolved carbon dioxide was 90% of the theoretical based on all the isatoic anhydride taken. The mass was extracted with 100 ml. of 95% ethanol, leaving undissolved 0.72 g. of amorphous material which melted at 250° and was found to be not isatoic anhydride. The alcohol extract upon concentration yielded 1.35 g. of a solid which melted from 180° to 195°. These products are abnormal; the m.p. of anthranilanilide is 125°.

2. *Conversion of normal to abnormal compound* (*Equation 2*). A mixture of 2.04 g. (0.0125 mole) of isatoic anhydride and 2.65 g. (0.0125 mole) of anthranilanilide was heated at 120° until no more carbon dioxide escaped; the carbon dioxide was 82% of the theoretical. The

TABLE I

REACTIONS OF ISATOIC ANHYDRIDE WITH PRIMARY AMINES

AMINE	PROCEDURE; TEMPERATURE °C.	REF.	M.P. °C[c]	PRODUCT YIELD,[a,b] %	NITROGEN, (KJELDAHL)[d]	
					Calc'd, %	Found, %
Ethylamine	1; room	18	102–103 obs.	87.7	—	—
n-Propylamine	1; room	—	98.5–100	100	15.74	15.30, 15.36
n-Butylamine	1; room	—	83–84	83.6	14.58	14.32, 14.40
n-Amylamine	1; room	—	80.0–81.0	88.3	13.60	13.25, 13.30
Isoamylamine	1; room	—	69.0–70.0	91.4	13.60	13.35, 13.26
Ethylenediamine	2; room	19	242.0–243.0 obs.[e]	59.1	—	—
Propylenediamine	2; room	—	183.0–184.0[e]	50.2	17.95	17.81, 17.62
Cyclohexylamine	3; room, then 100	—	155.5–156.5	70.2	12.84	12.77, 12.92
Benzylamine	4; room, then 165	—	123.0–123.5	69.0	12.39	12.33, 12.42
Aniline	5; water-bath	8a	125.5–126.5	79.0	—	—
p-Toluidine	5; 85–90	20	150.0–151.0	83.2	—	—
p-Anisidine	5; 125–130	3	125.0–126.0	64.0	—	—
m-Bromoaniline	5; 120–130	—	147.5–149.0	60.5	9.63	9.54, 9.52
p-Bromoaniline	5; 120–130	3	148.0–149.0	70.0	—	—
m-Chloroaniline	5; 125–130	—	130.0–131.5	74.5	11.36	11.10, 11.35
p-Chloroaniline	5; 110–120	—	140.0–141.5	72.3	11.36	11.05, 11.28
2,4-Dimethylaniline	5; 120–130	20	137–138 obs.	56.9	—	—
Anthranilic acid	5; 50	21	205.5–206.5	54.0	—	—
2-Aminopyridine	5; 130	—	132.0–133.0	56.0	19.70	19.56, 19.66
2-Amino-4-methylthiazole	5; 100	—	117.5–118.5	68.8	18.01	17.76, 17.76
2-Amino-6-methylbenzothiazole	5; 130–140	—	186.0–187.0	20.4	14.80	14.48, 14.41
Phenylhydrazine	6; 70	9	172.0–173.0 obs.	78.6	—	—
Hydroxylamine	7; room	9	78 obs.	57.9	—	—
o-Bromoaniline	8; 130	—	115.5–116.0	9.6[f]	9.63	9.67, 9.69
2,6-Dimethylaniline	9; 125–130	—	—	[f]	—	—
Mesidine	10; 125–130	—	—	[f]	—	—
Ethyl anthranilate	11; 140–150	—	93.5–94.5	9.5[f]	Ident. by synthesis	
Methyl anthranilate	12; 170	12	114.5–115.5	4.5[f]	—	—
Anthranilamide	13; 130	—	—	[f]	—	—
o-Nitroaniline	14; 155–160	—	—	[f]	—	—
p-Nitroaniline	14; 155–160	—	—	[f]	—	—

[a] The products are the N-monosubstituted anthranilamides corresponding to the amines used.

[b] Only definite compounds (not abnormal products) are listed.

[c] Melting points are corrected unless designated "obs."

[d] Compounds for which analytical data are given have not been reported previously.

[e] This product is the *sym*-bis-anthranoyl diamine.

[f] Reaction largely abnormal.

reaction mixture was extracted with 100 ml. of boiling 95% ethanol, leaving undissolved 0.91 g. of material which melted 230–245° and was found to be not isatoic anhydride. The alcohol extract, when concentrated by evaporation, yielded in two crops 1.23 g. of amorphous material melting from 180° to 195°.

3. *Composition of abnormal product as shown by cleavage.* In these experiments the product of m.p. 150–165° obtained from anthranilamide and isatoic anhydride (Section A, procedure 13) was used. Attempts to decompose it by refluxing with aqueous hydrochloric acid were unsuccessful, and hydrolysis by aqueous alkali yielded some ammonia but no anthranilic acid or other identifiable product. Nearly complete cleavage resulted when 1.0 g. of substance was heated with 5 ml. of conc'd hydrochloric acid in a sealed tube at 125–135° for 4.5 hours. The clear liquid was evaporated to dryness; the yellow granular residue weighed 1.29 g. The presence of anthranilic acid was shown by dissolving 0.25 g. of the residue in 10 ml. of 5% sodium hydroxide solution and shaking with benzenesulfonyl chloride, filtering, acidifying to precipitate N-(benzenesulfonyl)anthranilic acid, which was crystallized from 50% ethanol. The m.p. was 212–214°, and a mixture of this compound and an authentic specimen of benzenesulfonylanthranilic acid melted at 211–212°. The quantity of ammonia produced by the hydrolysis was determined by heating with strong sodium hydroxide solution 1.00 g. of the hydrolysis residue (equivalent to 0.78 g. of the original substance), distilling the ammonia into 50 ml. of 0.1 *N* hydrochloric acid and titrating the excess acid. The ammonia found (equivalent to 29.18 ml. of decinormal acid) was 0.0453 g. The amounts required by formula V when $x = 1, 2, 3$ are 0.0660 g., 0.0452 g., 0.0344 g. The substance examined had an average composition corresponding to the requirements of formula V when $x = 2$; the close agreement is fortuitous, since the material was not a single compound.

TABLE II

REACTIONS OF ISATOIC ANHYDRIDE AND SECONDARY AMINES

AMINE	PROCEDURE	PRODUCT[a]			NITROGEN, (KJELDAHL)	
		B.P., °C.	M.P., °C.[b]	YIELD, %	Calc'd, %	Found, %
Diethylamine	1	147–148 (1 mm.)	70.0–70.5 obs.	28.7	14.58	14.42, 14.40
	2	158–160 (4 mm.)	70.0–70.5 obs.	31.6		
Di-*n*-propylamine	2	174–177 (4 mm.)	Oil	29.3		
			Picrate: 104–104.5		15.59	15.39, 15.28
Piperidine	1	160–163 (1–2 mm.)	73.0–74.0	63.3	13.73	13.50, 13.55
Methylaniline	2	—	127–127.5	41.0	12.39	12.00, 12.11
Ethylaniline	2	—	102.5–103	33.3	11.66	11.37, 11.41
n-Propylaniline	2	—	75.5–76.5	11.5[c]	11.02	10.79, 10.75

[a] The products are the N,N-disubstituted anthranilamides corresponding to the amines used. Excepting methylphenylanthranilamide they are new compounds.

[b] Melting points are corrected unless designated "obs."

[c] Evolved carbon dioxide was 90% of the theoretical.

II. Reactions of isatoic anhydride with secondary amines

A. Procedures (Cf. *Table II*). 1. *Amine and isatoic anhydride in equivalent amounts.* The amine (diethylamine 3.65 g., 0.05 mole; piperidine 2.13 g., 0.025 mole) was dissolved in 10 ml. of 95% ethanol, and an equivalent amount of powdered isatoic anhydride was added. Reaction was vigorous at room temperature. When evolution of carbon dioxide ceased the reaction mixture was distilled fractionally under reduced pressure. Essential data for the two products appear in Table II.

2. *Amine in excess.* To the amine, taken in three to five times the theoretical amount (0.063 to 0.15 mole), referred to isatoic anhydride, was added gradually and in small portions, finely divided isatoic anhydride (0.0125 to 0.05 mole), the mixture in each case being kept at such temperature that prompt evolution of carbon dioxide followed each addition. Diethylamine and di-*n*-propylamine reacted without warming; the experiments with alkylanilines were run at 120–130°. To isolate the N,N-dialkylanthranilamides the mixtures were distilled *in vacuo*. Excess amine distilled first, after which the products passed over as 2° to 3° fractions. N,N-di-*n*-propylanthranilamide did not solidify, and for identification and analysis was converted into its 1:1picrate (m.p. 103–104°), made in alcohol solution. To isolate the alkylarylanthranilamides the mixtures were first subjected to steam distillation to remove excess amine. In each case the residue in the flask was treated with 25 ml. of 1:1 hydrochloric acid, and the mixture was extracted with benzene. The acid layer was chilled and made alkaline with ammonium hydroxide. The precipitated product (in the experiment with propylaniline oily at first) was crystallized from dilute alcohol. Essential data for individual compounds appear in Table II.

3. *Identification of products.* Of the compounds listed in Table II only N-methyl-N-phenylanthranilamide has been reported previously. All were identified by mixed m.p. tests using the same compounds made by independent syntheses by the method of Meyer (12) and Pictet and Gonset (13). *Procedure:* To 0.025–0.05 mole of secondary amine and 0.025–0.05 mole of *o*-nitrobenzoyl chloride was added slowly 20–50 ml. of 20% sodium hydroxide solution, and the mixture was shaken. The product which separated was washed with water, and was then dissolved in 40 ml. of 95% ethanol and hydrogenated in presence of Raney nickel in an Adams and Voorhees apparatus. The filtered solution was heated on a water-bath to remove alcohol, and the residue was distilled under reduced pressure. The main fraction solidified on cooling, excepting the one composed of N,N-dipropylanthranilamide, which was converted to its picrate (*cf.* procedure 2). The determined constants of the products so obtained from the several secondary amines are as follows: N-anthranoyldiethylamine, b.p. 144–146° (1 mm.); m.p. 69.5–71.0° corr.; N-anthranoyldi-*n*-propylamine, an oil, b.p. 154–156° (1 mm.); picrate, m.p. 104.0–104.5°; N-anthranoylpiperidine, m.p. 73.0–74.5° corr.; N-anthranoyl-N-methylaniline, m.p. 126.5–127.5° corr.; N-anthranoyl-N-methylaniline, m.p. 102.0–103.0° corr.; N-*o*-nitrobenzoyl-*n*-propylaniline, m.p. 92–92.5°; N-anthranoyl-*n*-propylaniline, m.p. 75.5–76.5° corr. Mixtures of the solid products with corresponding compounds made from secondary amines and isatoic anhydride showed no significant depressions in the like melting points of the single compounds.

III. Reactions of isatoic anhydride with amides

1. *Acetamide (9).* A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and 7.40 g. (0.125 mole) of acetamide was heated at 180–190° until the slow evolution of carbon dioxide ceased. The cooled mixture was extracted with 20 ml. of warm water to remove excess acetamide. The undissolved residue (2.25 g.) was amorphous and yellow. It softened slowly above 250° but showed no m.p.

2. *Ethyl carbamate; formation of benzoylenurea.* A mixture of 8.15 g. (0.05 mole) of isatoic anhydride and 22.3 g. (0.25 mole) of ethyl carbamate was heated under return condenser for two hours at 220–240°. The cooled mass was ground and extracted with 30 ml. of 95% ethanol; the undissolved residue weighed 10.92 g. Five grams of this material was dissolved in 50 ml. of warm 0.5 *N* sodium hydroxide solution and the solution was chilled. The precipitate (the disodium salt of benzoylenurea) was removed and dissolved in 75 ml. of hot water, and the solution was acidified with 1:1 sulfuric acid. The precipitated benzoylenurea was collected on a filter, washed with water, and crystallized from glacial acetic acid. The product (1.26 g.; 34%) did not melt at 280°. It was identified by conversion of the disodium salt to the N,N-dimethyl derivative by action of dimethyl sulfate. From 0.40 g. of the supposed benzoylenurea and excess dimethyl sulfate was obtained, by shaking the mixture which was kept somewhat alkaline by addition to sodium hydroxide solution at intervals, 0.44 g. of crystalline dimethylbenzoylenurea, m.p. 166°. A mixture of this com-

pound with an authenic specimen of dimethylbenzoylenurea melted at the same temperature.

3. *Urea; formation of benzoylenurea.* A mixture of 8.15 g. (0.05 mole) of isatoic anhydride and 15.0 g. (0.025 mole) of urea was heated at 140° (the lowest temperature at which gas evolution was noticeable) for two hours. Excess urea was removed from the cooled mixture by leaching with 35 ml. of warm water, leaving a yellow residue (5.16 g.). Of this material 1.5 g. was treated as described in 2 for isolation of benzoylenurea, of which 0.75 g. (31.8%) was obtained. It did not melt at 280°, and was identified as the dimethyl derivative (m.p. 167°) by mixed m.p. test (166–167°).

IV. Synthesis of 3-substituted-4-keto-3,4-dihydroquinazolines

A mixture of 0.025 mole each of aniline, *p*-toluidine or *p*-anisidine, isatoic anhydride, and ethyl orthoformate was heated under a return condenser for the periods and temperatures noted below; in each case alcohol began to reflux at about 80°. The alcohol was removed by distillation (3.1 ml.), and the solid crystalline residue was crystallized from alcohol. The data for each of these experiments are recorded herewith in the following sequence: the amine used, the duration of the heating, the temperature of heating, and with respect to the substituted dihydroquinazolone the solvent used for crystallization, the yield, and the m.p. Aniline; 6 hrs.; 120–125°; 1:1 ethanol; 72.1%; 136–136.5° (ref. 16). *p*-Toluidine; 1.5 hr.; 115–120°; 65% ethanol; 66%; 144–145° (ref. 16). *p*-Anisidine; 1.5 hr. 110°; 95% ethanol 72.2%; 194–195° (ref. 3). The compound obtained from *p*-toluidine was identical with 3-*p*-toyl-3,4-dihydroquinazolone-4 as made in 73.2% yield by heating N-anthranoyl-*p*-toluidine with ethyl orthoformate at 110° for four hours. The m.p. was 144–145°; a mixed m.p. test showed no depression.

Attempts to extend this synthesis by use of ethyl orthoacetate instead of ethyl orthoformate were unsuccessful. Equivalent amounts (0.025 mole) of amine (aniline, *p*-anisidine), isatoic anhydride, and ethyl orthoacetate were heated under return condenser at 110° for three hours. At about 70° gas was evolved, and at about 80° slow refluxing was in progress. The reaction mixtures were viscous, and yielded no substituted quinazolone.

An attempted analogous synthesis of a tetrahydroquinazolone was unsuccessful. A mixture of 4.08 g. (0.025 mole) of isatoic anhydride, 2.35 g. (0.0253 mole) of aniline and 4.0 ml. (an excess) of methylal was sealed in a tube and heated at 100–105° for two hours. The ether-soluble material weighed 3.12 g., and proved to be anthranilanilide (m.p. 119–120°).

SUMMARY

Studies of certain reactions of isatoic anhydride led to the following conclusions: 1. primary amines without obstructing substituents condense to yield the corresponding substituted anthranilamides with evolution of carbon dioxide; 2. when the normal condensation referred to is in some way retarded, isatoic anhydride reacts also with the free amino group of the substituted anthranilamide to form a dianthranoyl compound, and by successive repetitions of this reaction polyanthranoyl compounds result, obtained as amorphous mixtures (the abnormal reaction); 3. secondary amines condense normally but with an increased tendency to yield in part amorphous products; 4. the abnormal reaction can be limited to some extent by use of amine in excess, and especially by adding isatoic anhydride gradually to an excess of amine, the mixture being held at a temperature at which reaction is rapid; 5. the polyamide character of the abnormal products was demonstrated for polyanthranoylanthraniline and polyanthranoylanthranilamide by conversion of the normal to the abnormal product and by the results of cleavage; polyanthranoylanthranilamide appears to have an average composition which approximates that of dianthranoylanthranilamide; 6. isatoic anhydride reacts with acetamide to form amorphous products, but condenses with urea or ethyl carbamate to yield also benzoylenurea; 7. interaction of isatoic anhydride, primary amine and ethyl orthoformate yields the corresponding 3-substituted 4-keto-3,4-dihydroquinazolines; under the same conditions the analogous reaction with ethyl orthoacetate does not occur.

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