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ISATOIC ANHYDRIDE. III. REACTIONS WITH PRIMARY AND SECONDARY AMINES[1]

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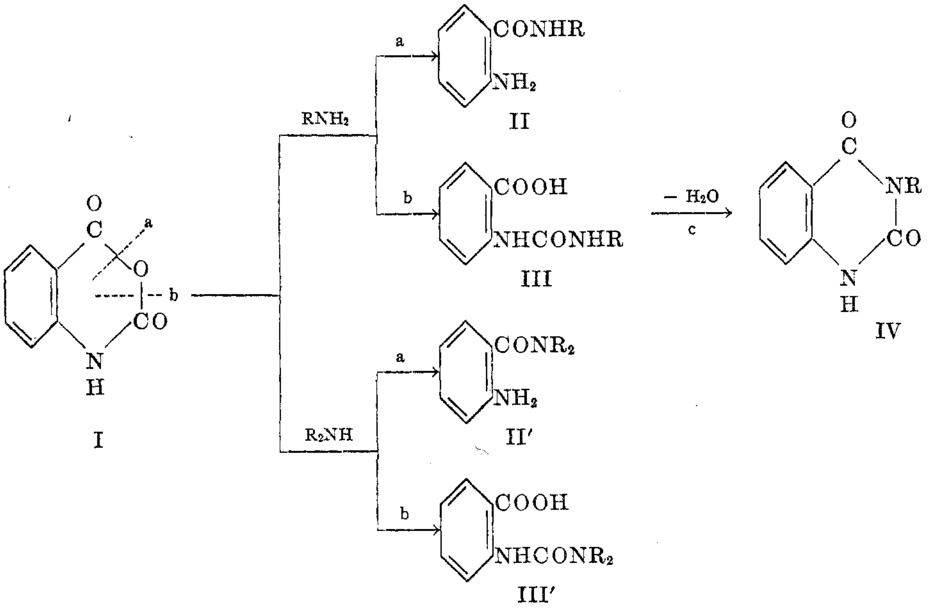
The condensations of isatoic anhydride (I) with primary and secondary amines, like its condensation with ammonia (1–3) have been found to yield the corresponding substituted anthranilamides (II), earlier believed to be the sole normal products of this reaction (4, 5) and, concurrently, the corresponding ω-substituted *o*-uramidobenzoic acids (III). The latter, if derived from primary amines, may undergo cyclization to form the 3-substituted benzoylene ureas (IV). The initial reactions involve two different cleavages of isatoic anhydride, which is a mixed anhydride. The conversion of uramidobenzoic acids to substituted benzoylene ureas is a familiar reaction (6), which is necessarily excluded when the amine represented is secondary.



Both III and III′ appear to be potentially capable of an alternate ring closure, *via* the imidol forms, to yield derivatives of 3,1,4*H*-benzoxazine, but this reaction was not observed to occur under the conditions employed.

Formation of the primary products II, II′ and III, III′ is rapid, and in most cases studied occurs on contact of the reactants and without application of

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[1] Paper constructed from the Ph.D. dissertation of Roger P. Staiger, University of Pennsylvania, 1953.

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TABLE I

Products and Percentage Yields for the Reactions of Primary Amines with Isatoic Anhydride at Various Molar Ratios

	AMINE *Molar* CONC.	0.2	0.4	1.0	2.0	3.0	4.0	6.0
	MOLAR RATIO AMINE TO I.A.	0.5	1.0	2.5	5.0	7.5	10	15
AMINE		PRODUCTS, %						
Methyl	U.B.A.	4.1	3.8	6.7	8.2	8.9	8.3	6.8
	I.A. recovered	61.8	35.6					
Ethyl	Amide	15.1	38.0	35.9	30.4	18.6	24.3	25.6
	U.B.A.	0.2	0.6	21.1	27.0	35.5	41.4	48.5
	I.A. recovered	69.2	50.2					
n-Propyl	Amide	15.5	40.6	45.0	52.0	40.8	44.2	36.8
	U.B.A.			7.9	22.8	24.0	35.9	37.6
	I.A. recovered	75.0	37.3	2.7				
Isopropyl	Amide	23.4	57.5	65.0	34.2	13.7	21.2	16.3
	U.B.A.			30.9	55.5	68.0	77.2	89.2
	I.A. recovered	76.0	40.3					
n-Butyl	Amide	29.8	58.5	72.0	46.3	50.4	45.6	47.1
	U.B.A.			14.3	46.4	38.2	41.1	39.5
	I.A. recovered	67.6	39.0					
sec-Butyl	Amide	10.9	29.8	33.6	9.6	7.3	1.4	2.0
	U.B.A.		0.3	24.2	77.9	98.6	81.4	86.0
	I.A. recovered	72.6	40.2	9.1				
tert-Butyl	Amide	3.5	6.6	17.9	7.7	9.0	9.2	9.7
	U.B.A.	0.9	4.3	42.1	75.5	86.0	88.5	93.0
	I.A. recovered	70.0	44.8					
Allyl	Amide	45.2	64.5	93.2	86.0	63.6	76.4	85.5
	U.B.A.			2.1	7.5	13.0	15.1	17.5
	I.A. recovered	60.3	36.8					
Cyclohexyl	U.B.A.	1.1	1.9	33.4	62.4	73.5	69.5	65.7
	I.A. recovered	60.5	37.7					
Benzyl	U.B.A.	0.7	1.2	4.1	14.5	15.0	22.7	26.8
	I.A. recovered	51.7	31.8					
Aniline	U.B.A.				2.4	5.0	7.4	8.7
	I.A. recovered	69.0	63.5	30.6	2.0			

heat; aniline and methylaniline required heat to involve all of the isatoic anhydride. Hydrolyzing conditions may lead to conversion of substituted anthranilamide to anthranilic acid (3).

The primary amines tested are methylamine, ethylamine, *n*-propylamine, isopropylamine, *n*-butylamine, *sec*-butylamine, *tert*-butylamine, allylamine, cyclohexylamine, benzylamine, and aniline. All of these yielded both substituted anthranilamides and substituted uramido-benzoic acids. Ring closure of the latter to 3-substituted benzoylene ureas, by action of warm aqueous sulfuric acid, occurred when R was methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, cyclohexyl or benzyl, but was not observed to occur when *R* was *sec*-butyl, allyl or phenyl; in these cases the uramidobenzoic acids survived prolonged heating with aqueous acid. The obstruction to cyclization is probably steric, but is not satisfactorily rationalized from the evidence at hand. A special behavior was shown by *tert*-butyluramidobenzoic acid, which yielded benzoylene urea itself, with loss of the *tert*-butyl group. The structures of R affected also the proportions of II and III formed in the initial reactions, as well as the ease of cyclization of III to IV.

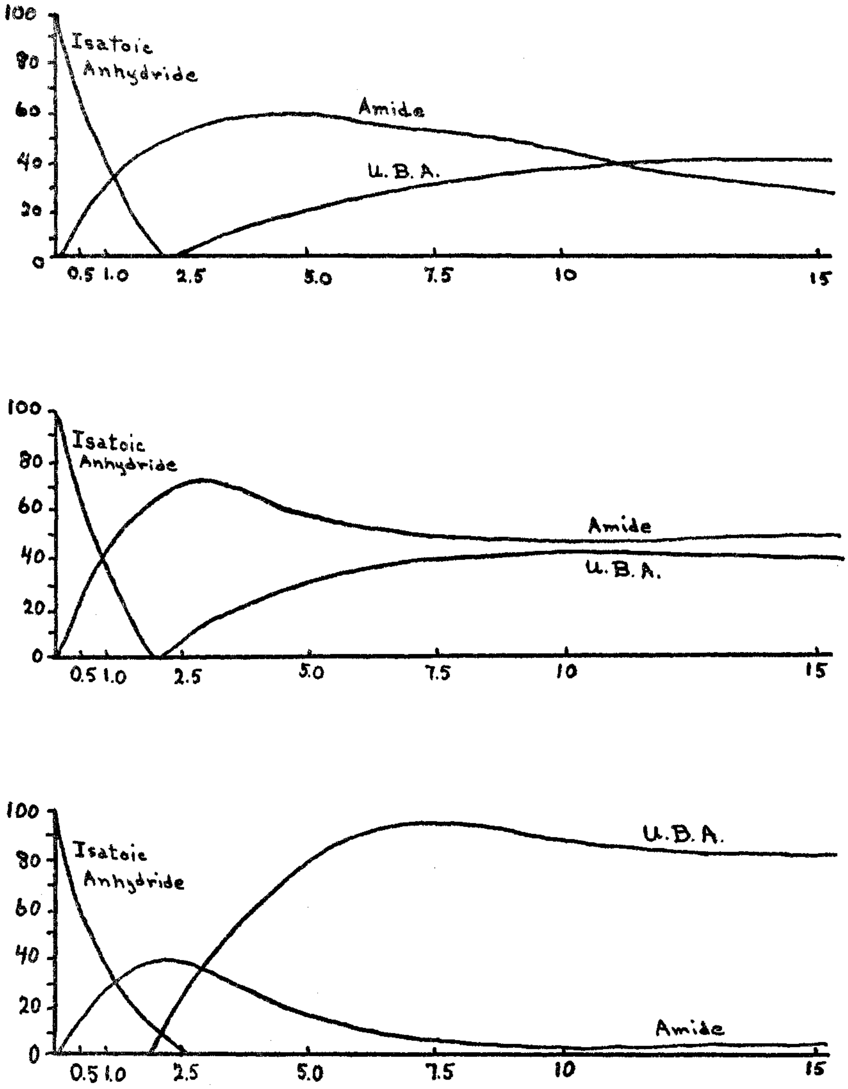
TABLE II

PRODUCTS AND PERCENTAGE YIELDS FOR THE REACTIONS OF SECONDARY AMINES WITH ISATOIC ANHYDRIDE AT VARIOUS MOLAR RATIOS

	AMINE *Molar* CONC.	0.2	0.4	1.0	2.0	3.0	4.0	6.0
	MOLAR RATIO AMINE TO I.A.	0.5	1.0	2.5	5.0	7.5	10	15
AMINE		PRODUCTS, %						
Diethyl	U.B.A.	0.2	8.7	73.0	80.4	80.0	80.0	80.4
	I.A. recovered	64.0	44.5					
Di-*n*-propyl	U.B.A.	0.0	16.9	44.5	64.4	76.6	80.8	87.5
	I.A. recovered	26.8	8.0					
Piperidine	U.B.A.	1.2	4.1	44.6	50.8	54.0	56.7	43.2
	I.A. recovered	60.4	42.0					
Morpholine	U.B.A.	0.0	0.3	14.7	24.2	22.6	20.4	11.4
	I.A. recovered	67.6	55.2	8.6				
Methylaniline	U.B.A.	2.9	1.5	8.4	22.0	43.4	48.5	48.4
	I.A. recovered	69.7	71.4	61.0	34.5			

The secondary amines tested are diethylamine, di-*n*-propylamine, piperidine, morpholine, and methylaniline, which yielded as end-products II′ and III′, the latter incapable of cyclization to 3-substituted benzoylene urea.

The effects of the ratios and concentrations of I and the amine (for concentrations of amine from 0.2 to 6.0 *molar*, and for ratios of amine to isatoic anhydride ranging from 0.5 to 15) upon the distribution of products between II, II′ and III, III′ were determined by isolation of the products. Using the procedures described in the experimental section isolations of the uramidobenzoic acids were nearly quantitative. Isolations of the anthranilamides were in many cases good but never quantitative; the anthranilamides were invariably identified. The

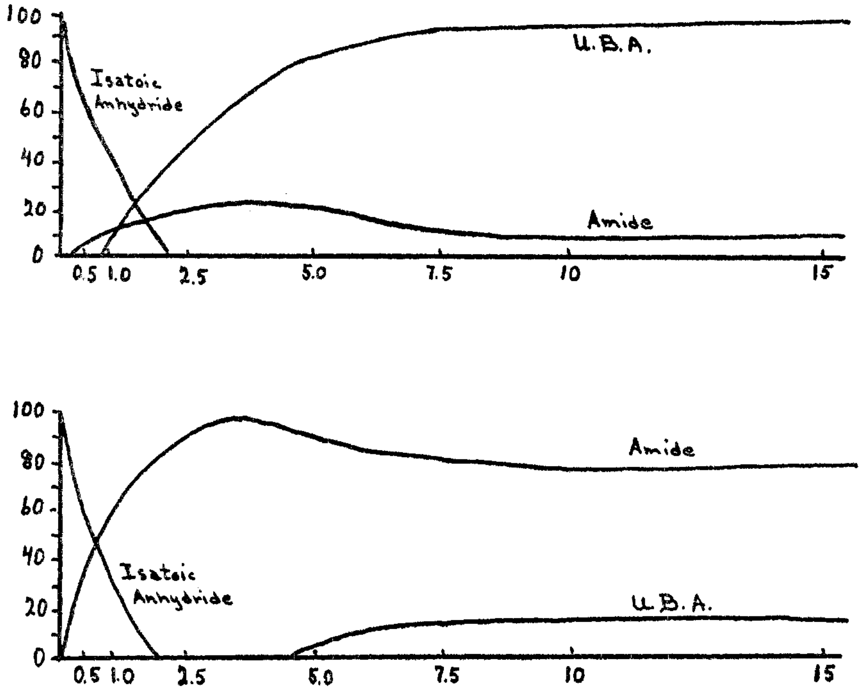


FIGS. 1–3

FIG. 1. *n*-PROPYLAMINE (upper graph).
FIG. 2. *n*-BUTYLAMINE (center graph).
FIG. 3. *sec*-BUTYLAMINE (lower graph).
In each case, *Ordinate*, yield in %; *Abscissa*, molar ratio of respective amine to isatoic anhydride.

results of experiments to test the effects of the molar ratios of reactants are collected into Table I (primary amines) and Table II (secondary amines). When in the tables no values are given for II or II′, the amounts formed can be estimated roughly by difference, and for some conditions can be ascertained from results published previously (5). The data for several amines are plotted in Figures 1, 2, 3, 4, and 5.

The extents to which cleavages *a* and *b* occur were found to be determined by the molar ratios of amine to isatoic anhydride. At low ratios (*ca.* 1) not all the isatoic anhydride reacts, and polyamides (the so-called "abnormal" products) may form. Cleavage *a* (yielding amide) reacts the maximum in the neighborhood of ratio 2.5. As the ratio increases above this value cleavage *b* (to uramidobenzoic acid) is progressively favored, though amide-formation is not excluded; similar results were reported for ammonia (1). Chain-branching in R increases the tendency to yield III, which is especially noticeable with *tert*-butylamine (Figure 4). From the data in Tables I and II the optimum conditions for obtaining compounds II and III can be ascertained.



Figs. 4–5

Fig. 4. *tert*-Butylamine (upper graph).

Fig. 5. Allylamine (lower graph).

In each case, *Ordinate*, yield in %; *Abscissa*, molar ratio of respective amine to isatoic anhydride.

The *effect of time* was found to be slight, as with ammonia (1). Most of the reactions were apparently complete by the time the isatoic anhydride had dissolved. The reaction between ethylamine and I at 5:1 ratio for intervals from

0.5 to 30 minutes gave yields of ethyluramidobenzoic acid within the narrow range 28 to 31%.

Effect of temperature. Reactions that start at room temperature are thereafter accelerated only slightly by heat, doubtless because they are already virtually complete. In experiments using ethylamine and I at 5:1 ratio and for a 10-minute reaction period the yields of III ranged from 22% at 10° to the maximum of 27.5% at 25° and then decreased to 13% at 65°; the decrease may be attributed to loss of amine (b.p. 16.6°) while warming initially to the higher temperatures. Aromatic amines require heat to start reaction and to bring it to completion; the product is mostly II.

Effect of solvent. Water was used as solvent for the water-soluble amines, and ethanol for aniline and methylaniline. A series of experiments, using *n*-propylamine and I at ratios of 0.5 to 15 in water, ethylene glycol, and 95% ethanol, yielded III in greatest amount in water and in least amount in ethanol. For ratio 5.0 the relative amounts were respectively 1.0:1.0:0.3, and at ratio 15 the relative amounts were 1.0:0.79:0.57. The highest yield, at ratio 15 in water, was 37.6%. Results are collected into Table III. Ethanol does not react appreciably with isatoic anhydride, and may be used as a crystallizing solvent. Isatoic anhydride is capable of interaction with alcohols, phenols, etc., but such reactions have not been thoroughly studied (5, 7, 9).

TABLE III

EFFECT OF SOLVENT UPON THE REACTION OF ISATOIC ANHYDRIDE WITH *n*-PROPYLAMINE

Molar ratio, amine to I.A.	0.0	0.5	1.0	2.5	5.0	7.5	10	15
Water as solvent, yield U.B.A., %	0.0	0.0	0.0	7.9	22.8	24.0	35.9	37.6
Ethylene glycol, yield U.B.A., %	0.0	0.0	0.0	5.9	22.8	27.4	30.0	29.8
95% Ethanol, yield U.B.A., %	0.0	0.0	0.0	0.0	7.2	12.8	17.8	21.4

The experiments produced fourteen new uramidobenzoic acids, which were characterized by melting points, neutral equivalents and analyses; data are presented in Table IV. The cyclizations yielded four new benzoylene ureas, for which melting points and analytical values are reported in Table V. Three benzoylene ureas so obtained are compounds previously known; one was submitted to precautionary analysis. To establish the new compounds as benzoylene ureas, and as a matter of general interest, infrared spectrographs of benzoylene urea itself and of the seven 3-substituted benzoylene ureas were secured, and are presented in Figures 6–13 inclusive. The spectrographs disclose, in addition to indications of the benzene ring, presence of the —NH— linkage (2.9–3.1μ) and of the amide linkage —CONH— (5.95–6.1 μ). Certain other features can be ascribed to the several substituents variously present in position 3. The general similarities are substantial, indicating identity of essential structure.

This path to ω-substituted uramidobenzoic acids and thence to 3-substituted benzoylene ureas should be applicable for preparative purposes, supplementing methods that involve application to anthranilic acid of the extended Wöhler

TABLE IV

CHARACTERIZING DATA FOR ω-SUBSTITUTED URAMIDOBENZOIC ACIDS FORMED BY THE INTERACTION OF PRIMARY AND SECONDARY AMINES AND ISATOIC ANHYDRIDE

ω-SUBSTITUTED URAMIDOBENZOIC ACID	M.P., °C.	NEUT. EQUIV.		ANALYSES					
		Calc'd	Found	Calc'd			Found		
				C	H	N	C	H	N
Methyl	183	195	194	[c]					
Ethyl	189	208	205	[c]					
n-Propyl[a]	164	222	222	[c]					
Isopropyl[a]	183	222	222	[c]					
n-Butyl[a]	164	236	236	[c]					
sec-Butyl[a]	174	236	230	61.02	6.78	11.85	61.01	6.89	11.99
tert-Butyl[a]	174–176	236	239	61.02	6.78	11.85	60.95	6.85	12.00
Allyl[a]	166	220	221	60.00	5.46	12.72	60.05	5.54	12.79
Cyclohexyl[a]	180	262	257	[c]					
Benzyl[a]	192	270	273	[c]					
Phenyl[a, b]	183	256	252	65.63	4.69	10.93	65.46	4.77	11.05
Di-ethyl[a]	151	236	236	61.02	6.78	11.85	61.07	6.91	11.97
Di-*n*-propyl[a]	146	264	265	63.65	7.57	10.60	63.65	7.60	10.71
Piperidine[a]	137–138	248	248	62.92	6.45	11.28	61.94	5.59	10.41
Morpholine[a]	164	250	249	57.60	5.60	11.20	57.68	5.68	11.15
Methyl phenyl[a, b]	161	270	268						

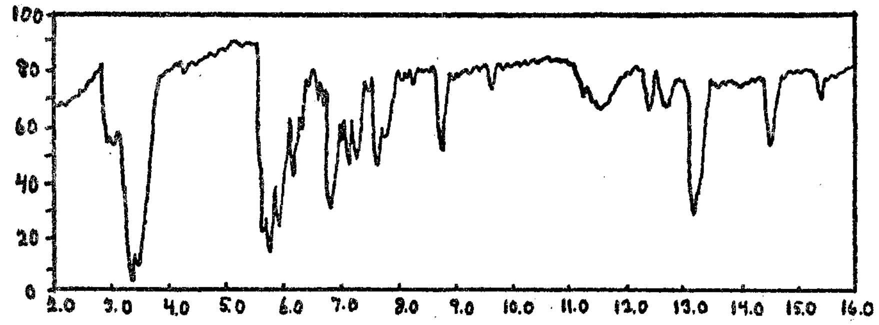
[a] Compounds not reported previously. [b] Prepared by procedure 2 as described in the experimental section. [c] Compounds cyclized to 3-substituted benzoylene ureas and analyzed if not previously reported; see Table V.

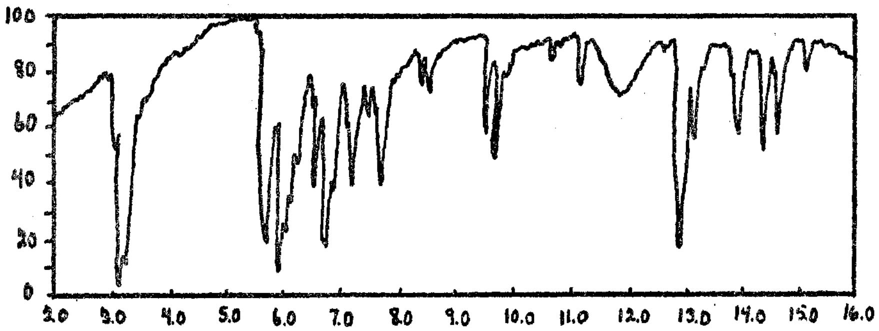
TABLE V

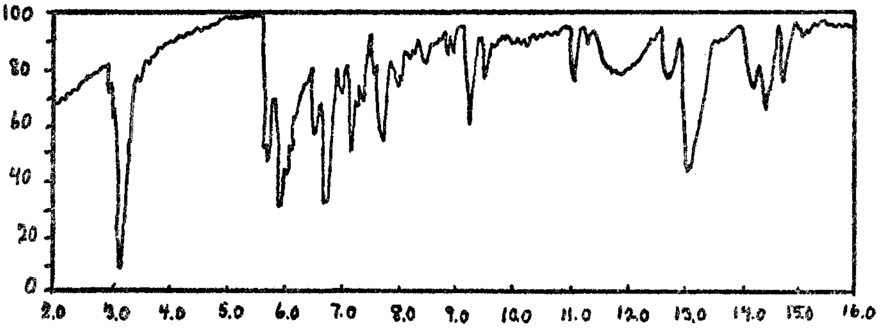
CHARACTERIZING DATA FOR 3-SUBSTITUTED BENZOYLENE UREAS FORMED BY CYCLIZATION OF THE CORRESPONDING URAMIDOBENZOIC ACIDS

3-SUBSTITUTED BENZOYLENE UREAS	M.P., °C.	YIELD, %	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
Methyl	241	61						
Ethyl	198	73						
n-Propyl	186–187	82	64.70	5.87	13.70	64.72	5.73	13.67
Isopropyl[a]	188	41	64.70	5.87		64.74	5.85	
n-Butyl[a]	156	87	66.04	6.43	12.85	66.11	6.46	12.96
Cyclohexyl[a]	270–271	48	68.85	6.56	11.48	68.85	6.74	11.67
Benzyl[a]	227	70	71.43	4.76	11.11	71.38	4.80	10.98

[a] Compounds not reported previously.

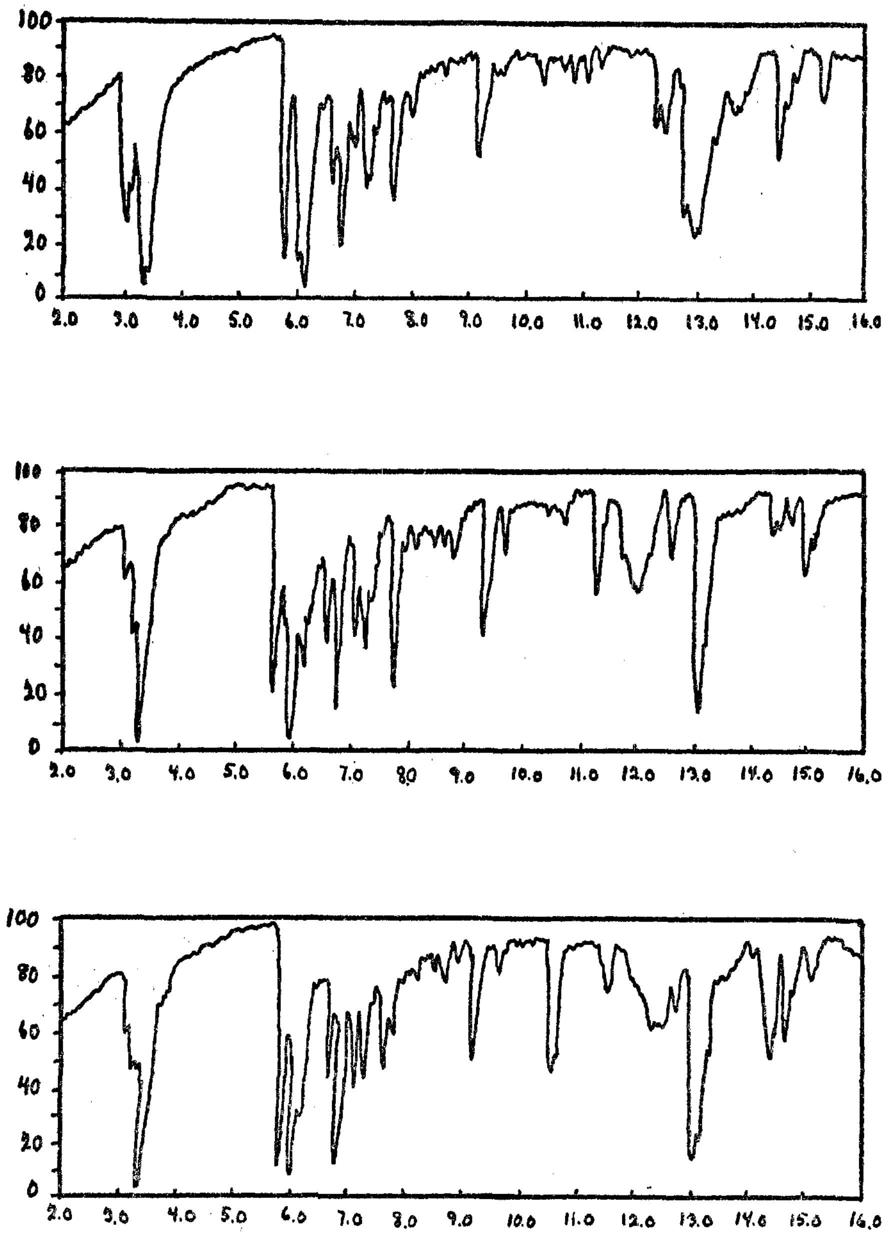






FIGS. 6–8

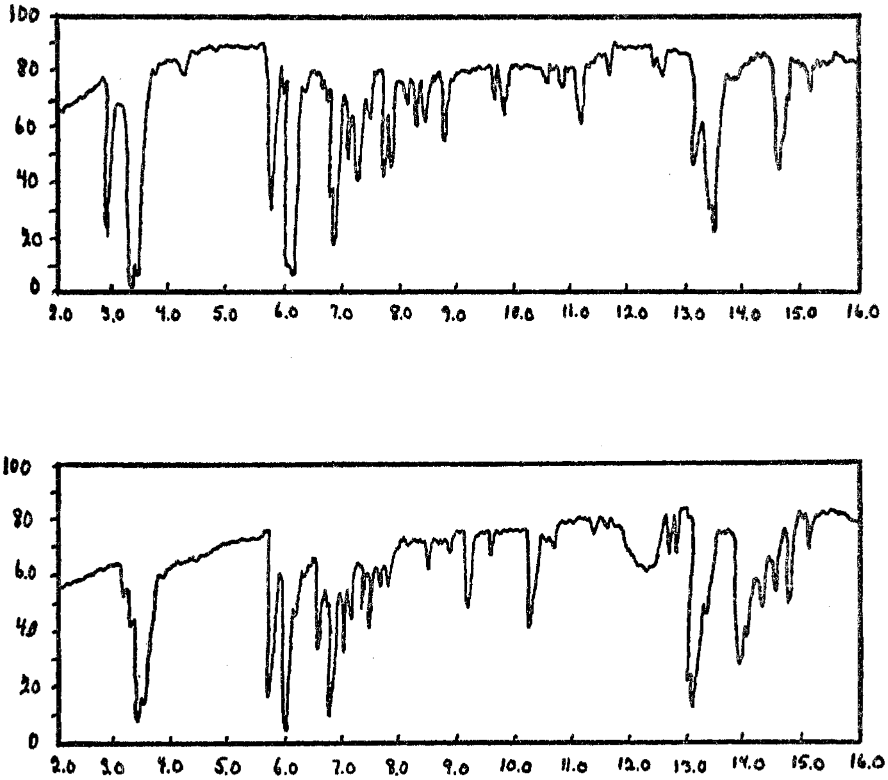
FIG. 6. BENZOYLENE UREA (upper graph).
FIG. 7. 3-METHYLBENZOYLENE UREA (center graph).
FIG. 8. 3-ETHYLBENZOYLENE UREA (lower graph).
In each case, *Ordinate*, transmission in %; *Abscissa*, wave length in microns.



FIGS. 9–11

FIG. 9. 3-*n*-PROPYLBENZOYLENE UREA (upper graph).
FIG. 10. 3-ISOPROPYLBENZOYLENE UREA (center graph).
FIG. 11. 3-*n*-BUTYLBENZOYLENE UREA (lower graph).
In each case, *Ordinate*, transmission in %; *Abscissa*, wave length in microns.

reaction (9) or urea fusion (10, 11). Interaction of isatoic anhydride and ammonia or amines is one of the easiest and best methods for preparation of anthranilamide and substituted anthranilamides of types II and II′.



FIGS. 12–13

FIG. 12. 3-CYCLOHEXYLBENZOYLENE UREA (upper graph).
FIG. 13. 3-BENZYLBENZOYLENE UREA (lower graph).
In each case, *Ordinate*, transmission in %; *Abscissa*, wave length in microns.

EXPERIMENTAL

Amines were obtained from Eastman Organic Chemicals Department, and were tested for identity and purity by distillation. *Isatoic anhydride* was prepared by action of phosgene on anthranilic acid (12) and was recrystallized from hot 95% ethanol; m.p. 244° dec. The solubilities of isatoic anhydride in 95% ethanol (g./100 ml.) were found to be 0.273 at 10°, 0.454 at 20°, 0.655 at 30°; within this range the relationship is linear.

In the tables new compounds are designated by a superscript (a). Thermometric values reported are "observed." Analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado.

PROCEDURES FOR INTERACTION OF ISATOIC ANHYDRIDE WITH PRIMARY AND SECONDARY AMINES

1. *Reaction in water.* Reaction mixtures of the desired concentrations of amines and the desired ratios of reactants were prepared by adding 0.815 g. (0.005 mole) of powdered isatoic

anhydride, with stirring, to 12.5 ml. of aqueous solutions of the amines obtained by diluting 6 *M* solutions of the amines. The concentrations used were 0.2, 0.4, 1.0, 2.0, 3.0, 4.0, and 6.0, corresponding to molar ratios (amine:I) of 0.5, 1.0, 2.5, 5.0, 7.5, 10, and 15. Reactions were run at room temperature and for 15 minutes. With amine concentrations *molar* or above, the isatoic anhydride dissolved promptly. At lower concentrations not all the isatoic anhydride dissolved; in such cases the suspension was stirred at regular intervals during 15 minutes, after which any unused isatoic anhydride was removed by filtration and was weighed. The amounts recovered are entered in Tables I and II. At lower concentrations of amines partial separation of crystalline or gelatinous amide occurred in some cases; in others the amide was retained in solution in the clear reaction liquid or in the filtrate from unused anhydride. To isolate the uramidobenzoic acid the liquid or suspension was diluted with 50 ml. of water, and dilute sulfuric acid was added (at room temperature) to acidity. This precipitated the substituted uramidobenzoic acid, which was collected and weighed. The filtrate containing II or II′ was made alkaline by addition of cold aqueous sodium hydroxide, which in some cases caused separation of some of the amide, which was removed and weighed. Further amounts were obtained by ether-extraction of the alkaline liquid, permitting eventually recovery of most of the amide. Isolation of amide was less than quantitative, but in all cases the amide was identified.

2. *Reaction in ethanol.* Amines insoluble in water (aniline and methylaniline) were brought into reaction with isatoic anhydride in 95% ethanol, concentrations and molar ratios being adjusted as outlined above, but using alcohol instead of water. The mixtures were heated on the steam-bath for 15 minutes. The mixture was then treated with 50 ml. of water, and any residual isatoic anhydride was collected and weighed. The filtrate was acidified with dilute sulfuric acid and was allowed to stand until next day, when the substituted uramidobenzoic acid was removed and weighed. The amide was obtained from the filtrate as outlined above.

3. *Effects of solvent. Comparative results in water, ethylene glycol, and ethanol.* Direct comparisons of results in the solvents named were made for the interaction of *n*-propylamine and isatoic anhydride at molar ratios from 0.5 to 15. The procedure was substantially the same as in 1. Reaction occurred at room temperature. After a 15-minute reaction period the mixture was treated with 50 ml. of water, any unchanged I was removed, and the filtrate was acidified to obtain the uramidobenzoic acid. Results appear in Table III. The lower yields obtained with ethanol as solvent may be attributed in part to the solubilities of uramidobenzoic acids in aqueous alcohol.

ω-Uramidobenzoic acids (Table IV). These compounds are crystalline solids with determinable melting points. Heat or acid readily converts some to corresponding 3-substituted benzoylene ureas. They are insoluble in water, but they form water-soluble salts of alkali metals, from which salts the uramidobenzoic acids are recovered by action of mineral acid; this was used in some of the purifications. Incipient ring-closure sometimes impedes purification. Final purification by recrystallization from aqueous alcohol was effective in most cases. Attempts to esterify several substituted uramidobenzoic acids, with alcohol and acid, were unsuccessful; either there was no reaction, or ring-closure occurred. *Neutral equivalents* were determined as follows. A weighed sample of about 0.1 g. of purified III or III′ was dissolved in 100 ml. of neutral 95% ethanol. The solution was stirred mechanically during addition of 0.1 *N* sodium hydroxide, from a 5-ml. "microburet", using a Leeds and Northrup potentiometer (No. 1662-Al) to locate the end-point. The melting points, neutral equivalents, and analytical data for 16 substituted uramidobenzoic acids are collected into Table IV. Uramidobenzoic acids in which R is *n*-propyl, isopropyl, *n*-butyl, cyclohexyl, and benzyl were established by the chemical characteristics mentioned, and indirectly by analysis of the benzoylene ureas (see Table V) obtained by their cyclizations.

Cyclization of ω-substituted uramidobenzoic acids to 3-substituted benzoylene ureas (Reaction c). (Table V). A suspension of the substituted uramidobenzoic acid in 10% sulfuric acid containing a few drops of 95% ethanol was warmed until a clear solution resulted. Upon chilling the solution the 3-substituted benzoylene urea separated in crystalline form. It was recrystallized from hot aqueous ethanol. The 3-methyl, 3-ethyl, and 3-*n*-propyl compounds, reported previously, were identified by melting point (respectively 241°, 198°, and 186–187°), and the propyl compound was submitted to precautionary analysis. Data for this and for the new substituted benzoylene ureas appear in Table V.

Cyclization failed to occur when R was *sec*-butyl, allyl, or phenyl, even when the severity of the conditions was increased by prolonged heating under reflux; the starting compounds remained unaffected. *tert*-Butyluramidobenzoic acid was decomposed, but with cleavage of C_4H_8, for the product was benzoylene urea.

Infrared absorption spectra of benzoylene urea and of some 3-substituted benzoylene ureas (R = methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, cyclohexyl, and benzyl) were determined with a Baird Associates Double Beam recording spectrophotometer, with samples suspended in Nujol. The plotted transmissions appear as Figures 6 to 13 inclusive.

Acknowledgment. The infrared examinations and interpretations were made by Dr. H. C. Beachell and Mr. Thrygve Meeker, of the Department of Chemistry of the University of Delaware, to whom and to which we make grateful acknowledgment.

SUMMARY

The interactions of isatoic anhydride and certain primary and secondary amines were found to involve two different cleavages of the mixed anhydride, yielding respectively and under most conditions simultaneously the corresponding substituted anthranilamide and the ω-substituted uramidobenzoic acid. The proportions of the two products vary with the structures of the amines and with the molar ratios of amine to isatoic anhydride, with respect to which there is revealed for each amine an optimum ratio for maximal yield of each product. Reactions generally occur upon contact and at room temperature and are too rapid to disclose a marked effect due either to temperature or to time. In some cases (aromatic amines) it is necessary to apply heat. Results in water, in ethylene glycol, and in ethanol as solvents showed yields of uramidobenzoic acid to be highest in water and lowest in ethanol, with no very uniform or striking effect attributable to solvent.

Uramidobenzoic acids obtained from primary amines are in most cases readily cyclized to form the corresponding 3-substituted benzoylene ureas by heating in presence of mineral acid, but under the conditions used *sec*-butyl-, allyl- and phenyl-uramidobenzoic acids resisted ring-closure, and *tert*-butyluramidobenzoic acid lost the alkyl group and was converted to benzoylene urea. Uramidobenzoic acids obtained from secondary amines are incapable of cyclization to benzoylene ureas.

The work yielded sixteen substituted uramidobenzoic acids and seven 3-substituted benzoylene ureas, of which fourteen and four, respectively, are compounds not previously reported. The essential identity of the structures of the substituted benzoylene ureas with that of benzoylene urea was established by the infrared absorptions of the eight compounds.

The reactions studied can be used for preparative purposes, yielding as main products, by suitable adjustment of conditions, the substituted anthranilamides,

the ω-substituted uramidobenzoic acids or, from the latter, the corresponding 3-substituted benzoylene ureas.

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