2-heptene was conducted in the previously described manner[8] to give a 74% yield of pure *exo-syn*-bicyclo[2.2.1]-heptane-2,7-diol, m.p. 172–174° (sealed tube), reported[8] m.p. 174–176°. The infrared spectrum (chloroform solution) exhibited a strong 3.03 μ hydrogen-bonded hydroxyl band.

Diacetate. Treatment of the 2,7-diol with acetic anhydride in pyridine gave a colorless diacetate, b.p. 129–131° at 10 mm., $n_D^{23.5}$ 1.4629.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.3; H, 7.6. Found: C, 62.1; H, 7.5.

Dibenzoate, m.p. 106–107° (ether-hexane).

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 74.9; H, 5.8.

B. Tungstic acid catalyzed hydroxylation. To 10 ml. (0.066 mole) of a 6.6*M* solution of hydrogen peroxide in *t*-butyl alcohol, prepared by dilution of 90% hydrogen peroxide with the alcohol, was added 100 mg. of tungstic acid. The faint yellow mixture was stirred until the catalyst dissolved. The pertungstic acid solution was diluted with 22 ml. of *t*-butyl alcohol and 4.71 g. (0.05 mole) of bicyclo-[2.2.1]-2-heptene was added. The homogeneous reaction mixture was heated, with stirring, at 70° in an oil bath. After a few minutes an exothermic reaction ensued which was allowed to subside before heating at 70° was continued. After a total reaction time of 3 hr. at 70°, approximately 90% of the peroxide had been consumed and no further uptake was noted. The reaction mixture was allowed to cool, filtered to remove a small amount of insoluble material, and the solvent was evaporated. The residual oil was treated with 40 ml. of acetic anhydride and one drop of concentrated sulfuric acid. An exothermic reaction followed and the solution was allowed to stand at room temperature for 3 hr. A small amount of calcium carbonate was added to neutralize the catalyst, the mixture was shaken, filtered, and concentrated at 40–50° under reduced pressure. The residue was diluted with 200 ml. of water and the oily layer extracted with three 100-ml. portions of ether. The combined ether extracts were washed with 50 ml. of 10% sodium bicarbonate solution, 200 ml. of water, and then dried over anhydrous magnesium sulfate. Distillation gave 6.02 g. (57%) of *exo-syn*-2,7-diacetoxybicyclo[2.2.1]heptane, b.p. 130–134° at 11 mm., n_D^{25} 1.4620. The infrared spectrum (Neat) was identical with that of an authentic sample. Lithium aluminum hydride reduction of the 2,7-diacetate gave a 76% yield of *exo-syn*-bicyclo[2.2.1]heptane-2,7-diol, m.p. 174–176°, undepressed on admixture with the diol obtained from the performic acid oxidation. The dibenzoate, m.p. 105.5–106.5°, was identical in all respects with an authentic sample.

Tungstic acid catalyzed hydroxylation of crotyl alcohol in oxygen-18 enriched water. A solution of 1.5 ml. of a 35.5*M* aqueous solution of hydrogen peroxide and 20 ml. of enriched water containing approximately 1.3% excess of oxygen-18[15] was equilibrated by shaking with ordinary carbon dioxide for 5 hr. Mass spectrometric analysis of the resultant carbon dioxide indicated that the solvent contained 1.30% excess of oxygen-18. To the hydrogen peroxide-water-O^{18} solution was added 50 mg. of tungstic acid and 3.61 g. (0.05 mole) of crotyl alcohol (b.p. 120–121°). After an initial exothermic reaction the solution was heated at 70° for 2 hr., after which most of the peroxide had been consumed. The reaction mixture was cooled and equilibrated with ordinary carbon dioxide. Analysis of the carbon dioxide indicated that the solvent contained 1.23% excess of O^{18}. Distillation gave 3.9 g. (74%) of butane-1,2,3-triol-O^{18}, b.p. 155–156° at 11 mm.,[16] n_D^{25} 1.4614, containing 1.19 ± 0.01% excess of oxygen-18.

SEATTLE 5, WASH.

(15) Obtained from the Stuart Oxygen Co. on allocation from the Atomic Energy Commission.

(16) Reported b.p. 170° at 20 mm., n_D^{20} 1.4622, ref. 3.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF URSINUS COLLEGE AND THE RESEARCH LABORATORIES OF MAUMEE CHEMICAL CO.]

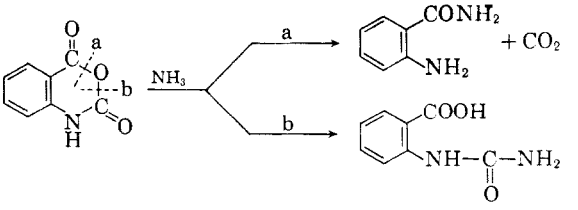
Isatoic Anhydride. IV. Reactions with Various Nucleophiles

ROGER P. STAIGER[1(a)] AND EMERY B. MILLER[1(b)]

Received February 11, 1959

The reactions of isatoic anhydride have been extended to include alcohols, mercaptans, and compounds with active methylene groups forming substituted esters, thio esters, carbamates, and substituted quinolines. A mechanism for the alternate cleavage of the anhydride ring is elucidated.

Reactions of isatoic anhydride (IA) with ammonia, primary and secondary amines, and amides have previously been studied.[2–4] In the latter two references it was reported that the reaction with ammonia followed two competing paths, producing either anthranilamide or *o*-ureidobenzoic acid, or their substituted derivatives with amines. At that time no speculation was made relating the two observed alternate types of cleavage of the anhydride ring:



The present investigators have found that in addition to the amines previously reported, isatoic anhydride reacts readily with the following nucleophilic reagents: primary and secondary alcohols, phenols, thiophenols, mercaptans, and ethyl

(1) (a) Department of Chemistry, Ursinus College, Collegeville, Pa. (b) Maumee Chemical Company, Toledo 5, Ohio.

(2) R. H. Clark, *J. Org. Chem.*, 9, 55 (1944).

(3) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, 13, 347 (1948).

(4) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, 18, 1427 (1953).

acetoacetate. The reactivity and the course of the reaction depend upon the nature of the nucleophile, concentration, and steric hindrance. The reactions with these nucleophiles proceed principally by route (a) to produce esters and thioesters of anthranilic acid.

In reactions with alcohols and phenols, isatoic anhydride has been reported to react with methanol in a tube at 130–135°, yielding methyl anthranilate along with other products,[5] with hot ethanol and HCl to yield ethyl anthranilate,[6] and with phenol in a tube at 180°, to yield phenyl anthranilate.[7] Normally no reaction occurs when isatoic anhydride is warmed with simple aliphatic alcohols at temperatures below 80°, and ethanol is a suitable solvent for the recrystallization of isatoic anhydride.[8]

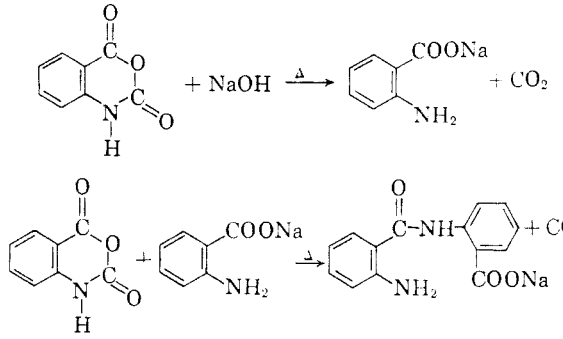
The reaction of isatoic anhydride with anhydrous primary aliphatic alcohols, in the presence of small quantities of NaOH, NaOEt, KOH, $(CH_3)_3N$, or Na_2CO_3 as catalyst occurs readily at temperatures of approximately 65° to give high yields, 95% or better, of the aliphatic ester of anthranilic acid, with the accompanying evolution of carbon dioxide gas. The water present in 95% ethanol causes a secondary reaction consuming I A with the formation of anthraniloylanthranilic acid.

With phenols, employing dioxane as solvent and NaOH as catalyst, the reaction proceeds similarly. The presence of substitutent groups on the benzene ring affects the activity of the hydroxy group. *p*-Nitrophenol and *p*-hydroxybenzoic acid react less readily than phenol, while 2,4-dinitrophenol and salicylic acid resist reaction under the conditions studied. (Glycolic acid also resists reaction.)

Primary aliphatic mercaptans react by route (a) more readily than the corresponding alcohols to yield thio esters of anthranilic acid, which are compounds of new composition. Thiophenols react similarly. In contrast to salicylic acid and glycolic acid, *o*-mercaptobenzoic acid and mercaptoacetic acid react readily with isatoic anhydride to yield the corresponding thioesters of anthranilic acid. This difference in behavior is attributed to hydrogen bonding within the hydroxy compounds, which is negligible in the mercaptans.

A secondary aliphatic alcohol such as isopropanol reacts with isatoic anhydride with difficulty, producing isopropyl anthranilate and isopropyl *N*-*o*-carboxyphenyl carbamate. Isatoic anhydride reacts with itself, in a competing reaction, forming anthraniloylanthranilic acid as a by-product.

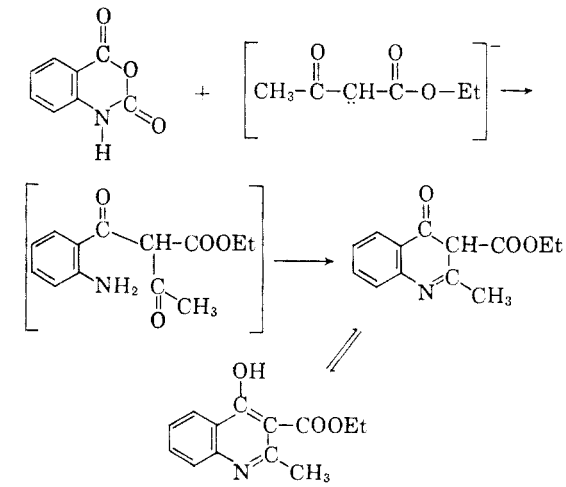
It is also significant that *t*-butyl alcohol and *t*-butyl mercaptan resist reaction with isatoic anhydride. Upon prolonged heating of IA in these two liquids and in the presence of NaOH, the product is the sodium salt of anthraniloylanthranilic acid.



Anthraniloylanthranilic acid is produced in high yield in a water solution containing equimolar ratios of I A, anthranilic acid, and NaOH.

Polyhydroxy compounds and compounds with mixed functional groups react in stages. Ethylene glycol and resorcinol each give a mono- and a dianthranilate. β-Mercaptoethanol and one mole of isatoic anhydride produce the β-hydroxythioester, while two moles of isatoic anhydride give the diester which contains both a thioester and a normal ester grouping. Glucose reacts with one to four moles of isatoic anhydride, liberating CO_2 and yielding a mixture of derivatives. *p*-Aminophenol can give either the ester or the amide, depending upon the proportion of NaOH catalyst employed.

Isatoic anhydride is capable of reacting with active methylene groups, as shown by its reaction with ethyl acetoacetate to produce 3-carbethoxy-4-hydroxy quinaldine:



N-Methylisatoic anhydride has been prepared, and like the unsubstituted compound reacts with nucleophiles to produce amides, normal esters, and thioesters of *N*-methylanthranilic acid. In general the reaction proceeds with slightly more difficulty. It is significant, however, that in the reaction with ammonia and dimethylamine there is no evidence of the ureido derivatives being produced, and with

(5) G. Schmidt, *J. prakt. Chem.*, (2), **36**, 883 (1887).
(6) Kolbe, *J. prakt. Chem.*, (2), **30**, 467 (1884).
(7) G. Schmidt, *J. prakt. Chem.*, (2), **36**, 377 (1887).
(8) E. C. Wagner and M. F. Fegley, *Org. Syntheses*, **Coll. Vol. III**, 488 (1955).

TABLE I

PRODUCTS OF VARIOUS NUCLEOPHILES WITH ISATOIC ANHYDRIDE

Reactant	Procedure	Product	M.P.	Salt	M.P.
Aliphatic Alcohols					
Methanol	1	Methyl anthranilate	24–25	Picrate	103
Ethanol	1	Ethyl anthranilate	13	Picrate	116
n-Propanol	1	*n*-Propyl anthranilate	Colorless oil	Picrate	76–77
Butanol	1	*n*-Butyl anthranilate	Colorless oil	Picrate	83–85
Allyl alcohol	1	Allyl anthranilate	Colorless oil	Picrate	71–73
Cinnamyl alcohol	2	Cinnamyl anthranilate	61	Picrate	108–109
2,2,2-Trichloroethanol	2	2,2,2-Trichloroethyl anthranilate	63	HCl	188–190
2,2,2-Trifluoroethanol	2	2,2,2-Trifluoroethyl anthranilate	44	Picrate	92
Isopropanol	1	Isopropyl *N*-*o*-carboxyphenyl carbamate	149–150		
Aromatic Alcohols					
Phenol	2	Phenyl anthranilate	70	Picrate	113–114
p-Cresol	2	*p*-Tolyl anthranilate	69–70	Picrate	117–118
p-Hydroxybenzoic acid	2	*p*-Carboxyphenyl anthranilate	184–186	Picrate	203–204
p-Aminophenol	2	*p*-Aminophenyl anthranilate	159–160	Picrate	180
p-Nitrophenol	2	*p*-Nitrophenyl anthranilate	109	Picrate	101–102
Thymol	2	Thymyl anthranilate	Colorless oil	Picrate	118
α-Naphthol	2	α-Naphthyl anthranilate	86–87	1,3,5 TNB	119–120
β-Naphthol	2	β-Naphthyl anthranilate	118	1,3,5 TNB	136–137
Mercaptans					
Methanethiol	2	Methyl thioanthranilate	27–28	Picrate	99
Ethanethiol	2	Ethyl thioanthranilate	Yellow oil	Picrate	71–72
Thiophenol	2	Phenyl thioanthranilate	104–105	Picrate	88–89
p-Thiocresol	2	*p*-Tolyl thioanthranilate	96	Picrate	92–93
o-Mercaptobenzoic acid	2	*o*-Carboxyphenyl thioanthranilate	133		
Mercaptoacetic acid	2	Carboxymethyl thioanthranilate	118–120	Picrate	116–117
2-Mercaptoethanol	2	2-Hydroxyethyl thioanthranilate	Yellow oil	Picrate	99–100
Polyfunctional					
Ethylene glycol	2	Ethylene glycol dianthranilate	125–126	Picrate	150–151
p-Aminophenol	2	*o*-Aminobenz-*p* hydroxyanilide	114–115	1,3,5 TNB	164
Piperazine	2	*N*,*N*′-Dianthranoylpiperazine	206–207	Picrate	214
2-Mercaptoethanol	2	2-Mercaptoethyl anthranilate	95	HCl	137–138
Miscellaneous					
Dimethylamine	3	*N*,*N*-Dimethyl-*N*′-*o*-carboxyphenylurea	148		
		o-Aminobenzdimethylamide			
Anthranilic acid	5	Anthraniloylanthranilic acid	203	Picrate	190–191
Ethyl acetoacetate	2	3-Carbethoxy-4-hydroxyquinaldine	228–229		
		3-Carboxy-4-hydroxyquinaldine	247–248		

TABLE II

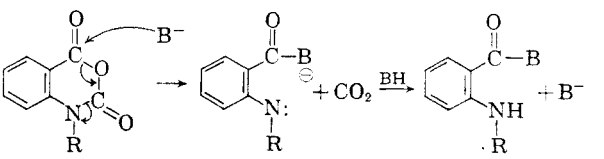
PRODUCTS OF VARIOUS NUCLEOPHILES WITH *N*-METHYLISATOIC ANHYDRIDE

Reactant	Procedure	Product	M.P.	Salt	M.P.
Methanol	1	Methyl *N*-methylanthranilate	19		
Phenol	2	Phenyl *N*-methyl anthranilate	70–71		
Isopropanol	2	Isopropyl *N*-methylanthranilate	23	Picrate	120
Cinnamyl alcohol	2	Cinnamyl *N*-methylanthranilate	71–72	Picrate	109–110
Thiophenol	2	Phenyl *N*-methyl thioanthranilate	76–77	Picrate	83–84
Ammonia	4	*o*-Methylaminobenzamide	159–160		
Aniline	2	*o*-Methylaminobenzanilide	122–123	Picrate	158
Dimethylamine	4	*o*-Methylaminobenzdimethylamide	90–91		

isopropanol there is no evidence of the carbamate derivative being produced, indicating that route (b) is barred.

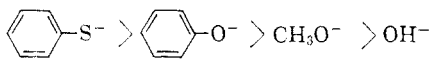
Tables I and II list the reactants and the products of these reactions.

The mechanism proposed for the reaction by route (a) is the attack of the nucleophilic group on the No. 4 carbon atom of the anhydride ring. The NaOH appears to act as a catalyst by ionizing the alcohol or mercaptan. A possible sequence is:



R = alkyl, H

The order of reactivity of the alcohols, phenols, and thiols nearly parallels that observed by Bunnett and Davis[9] for the reaction of 2,4-dinitrochlorobenzene with these same nucleophilic reagents. The order of reactivity with isatoic anhydride is:



This is also substantiated by the noted decrease in the reaction rate of *p*-nitrophenol and 2,4-dinitrophenol, compared with phenol. However, 2,2,2,-trichloroethanol and 2,2,2-trifluoroethanol are found to react readily with isatoic anhydride, yielding the 2,2,2-trichloro and trifluoroethylanthranilates. Possibly this is due to the easier ionization of these alcohols, expected as a result of the strong electronegative substituent effect.

The mechanism proposed for route (b), *i.e.*, the reaction in which ureides or carbamates are the products, is a modification of the above theory. Bulkier groups such as secondary and tertiary amines probably hinder sterically the attack on the No. 4 carbon atom, increasing the likelihood of attack at the No. 2 carbon atom, a less active center, but where steric hindrance should cause less interference. This explanation is supported by the following observations:

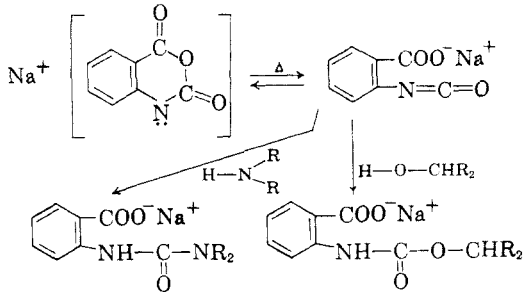
1. Isatoic anhydride with methylamine or ethylamine produces the amide *via* route (a).
2. Diethylamine and *t*-butylamine (a primary amine) both produce predominately the ureido acid.
3. Dimethylamine, whose reaction with isatoic anhydride had not been previously investigated, was found to give approximately equal amounts of the amide and the ureido acid (although the ratio of these two products can be varied somewhat by altering the molar ratios of reactants—Table III).
4. A "handcuffed" secondary amine such as morpholine yields predominately the amide.[4]
5. Increasing the size of the alkyl group in alcohols or its degree of branching near the hydroxyl group increases both the difficulty of reaction and the amount of carbamate formed.

TABLE III

PRODUCTS AND YIELDS FOR THE REACTION OF DIMETHYLAMINE WITH ISATOIC ANHYDRIDE AT VARIOUS MOLAR RATIOS

Products of the Reaction	Molar Ratio of Amine to IA		
	1:1	2.5:1	7.5:1
IA recovered	43.3%	0%	0%
Ureido acid	19.1%	49.7%	45.7%
Amide (by difference)	37.6%	50.3%	54.3%

Ionization of isatoic anhydride followed by cleavage of the anhydride ring may also play an important part under conditions of generally lower reactivity, and produce an intermediate isocyanate which is attacked by the bulkier group to yield the ureido or carbamate derivatives:



Kopple[10] has found evidence in the form of the characteristic —N=C=O infrared absorption, for intermediate isocyanate formation in the reaction of primary amino acid *N*-carboxy anhydrides with amines and sodium methoxide to form ureido and carbamate derivatives. Although our analogous attempts to demonstrate the presence of —N=C=O in dioxane and pyridine solutions of isatoic anhydride and triethylamine did not prove its existence to an observable degree, we believe the isocyanate species to be significant in route (b) because of the *complete* absence of ureido or carbamate derivatives from *N*-methylisatoic anhydride, which has no labile hydrogen atom and cannot form an anion of the anhydride. Kopple found that replacement of the corresponding hydrogen atom in the *N*-carboxy anhydride of glycine by a methyl group precluded formation of ureido or carbamate derivatives. In both cases carbonyl hindrance by the nearby methyl group may help direct attack to the other carbonyl.

Base strength of the nucleophile might well be expected to play a part,[9] but its effect must be relatively small, especially in view of the fact that ammonia and *t*-butylamine represent the weakest of the bases in Table IV, but attack primarily at different respective carbonyls. The other amines also show a much greater correlation with steric hindrance than with base strength.

TABLE IV

Amine	K^{25}	Predominate Route
Ammonia	0.18×10^{-4}	(a)
Methylamine	5.0×10^{-4}	(a)
Ethylamine	5.6×10^{-4}	(a)
Dimethylamine	5.12×10^{-4}	(a) + (b)
Diethylamine	12.6×10^{-4}	(b)
t-Butylamine	2.8×10^{-4}	(b)

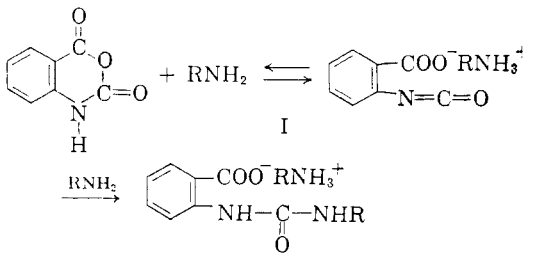
It appears likely that all nucleophiles strong enough to ionize isatoic anhydride bring about some degree of equilibrium with the isocyanato acid anion, the reaction path from this equilibrium mixture being largely dependent upon the steric

(9) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954).

(10) K. Kopple, *J. Am. Chem. Soc.*, **79**, 6442 (1957).

accessibility of the nucleophile, whether this be amine, alkoxide, mercaptide, etc. However, with the most reactive nucleophiles, *e.g.*, phenoxide and mercaptide, such equilibrium probably plays a very small role, because the reaction goes so rapidly with the No. 4 carbon atom before the ring is broken.

Another factor affecting the route of the reaction is the concentration of the nucleophile. With ammonia and amines it has been shown[3,4] that a 1:1 molar ratio with isatoic anhydride produces almost exclusively anthranilamide by route (a), whereas in the same total volume of solution higher molar ratios of ammonia to isatoic anhydride cause route (b) to have greater significance. It has been suggested above that route (b) may proceed from an equilibrium mixture of isatoic anhydride and the corresponding isocyanato anion, shown for ammonia and amines by the equations:



Since the equilibrium (I) lies principally on the left, the over-all rate of formation of (b) products would be:

$$\text{rate} = \frac{k(\text{IA})(\text{RNH}_2)^2}{(\text{RNH}_3^+)}$$

It is seen that the over-all rate by this path alone would be proportional to the *square* of ammonia or amine concentration. On the other hand, the rate of formation of (a) products is undoubtedly proportional to the first power of ammonia or amine concentration. Therefore, the enhancement of route (b) with increasing ammonia or amine concentration seems logically explained by equilibrium (I).

It is believed that *several* factors join in varying degrees to control the route and products in the reaction of isatoic anhydride with any particular nucleophilic reagent, and that the most important of these are nature and activity of the nucleophile, steric hindrance, and concentration.

EXPERIMENTAL

All melting points are uncorrected.

Procedure 1: Isatoic anhydride with low molecular weight liquid aliphatic alcohols. The alcohol was employed as reactant and solvent. The molar ratio of the reactants was 1:3:0.05 of IA to alcohol to NaOH catalyst. The mix was stirred and the temperature raised slowly. Moderate evolution of CO_2 gas occurred at approximately 65°. This temperature was maintained until the IA was consumed and gas evolution had ceased. The mix was cooled and diluted with three times its volume of water. The ester settled out as an immiscible oil which was separated and purified.

TABLE V

REPRESENTATIVE ANALYSIS OF PRODUCTS

	Theoretical C	Theoretical H	Found C	Found H
Cinnamyl anthranilate	75.9	5.97	75.9	5.93
2,2,2-Trichloroethyl anthranilate	40.3	2.98	40.55	3.10
α-Naphthyl anthranilate	77.6	4.94	77.46	5.08
Phenyl *N*-methyl thioanthranilate	69.0	5.39	69.33	5.04
N,N'-dianthranoylpiperazine	66.6	6.19	66.52	6.17
3-Carboxy-4-hydroxyquinaldine	65.5	4.35	65.3	4.46
Anthraniloylanthranilic acid	65.7	4.72	65.75	4.78

Using 95% ethanol as reactant and NaOH as catalyst, the presence of water caused the formation of approximately 20% anthraniloylanthranilic acid. The use of absolute ethanol gave an essentially quantitative yield of ester.

A thick white paste resulted upon warming a mole to mole ratio of IA and NaOH in an excess of isopropyl alcohol. This mixture was heated for approximately 10 min. on a steam bath. Dilution with water caused the paste to dissolve, and some of the ester separated as an oil. Acidification of the solution generated an insoluble precipitate. This was identified as a mixture of unreacted IA, anthraniloylanthranilic acid, and isopropyl *N*-*o*-carboxyphenyl carbamate.

Procedure 2: Isatoic anhydride with higher aliphatic and other alcohols, mercaptans, amines, and ethyl acetoacetate. These compounds were reacted with IA employing dioxane as the solvent. Except in the case of polyfunctional compounds, the molar ratio of the reactants was 1:1:0.05 of IA to nucleophile to NaOH catalyst. The mix was stirred and the temperature raised slowly until a moderate evolution of CO_2 gas occurred. This was usually between 60 and 100°. After the IA was consumed and gas evolution had ceased, the mix was cooled and diluted with three times its volume of water. The product either crystallized or settled out as an immiscible oil which was separated and purified.

Usually hot methanol or a methanol-water mixture was used as the recrystallizing solvent.

Procedure 3: Isatoic anhydride with dimethylamine. Reaction mixtures of the dimethylamine and IA were prepared by adding the amine gas to 25 ml. of water until the solution had increased by the desired weight of amine. To this was added at room temperature and with stirring 0.01 mole (1.63 g.) of IA. Molar ratios of 1:1, 1:2.5, 1:5 and 1:7.5 of IA to amine were prepared. Fifteen min. was allowed for reaction time. With amine concentrations greater than 1:1 molar, the IA dissolved promptly. At the 1:1 molar ratio, not all the IA dissolved, and the unreacted portion was removed, dried, and weighed at the end of the 15-min. reaction period. This filtrate and the other reaction mixes were diluted to 50 ml. with water and acidified with dilute sulfuric acid. The white precipitate that formed was allowed to digest 30 minutes and was then filtered, dried, and weighed. This yield represented the portion of amine converted to the ureidobenzoic acid, and the difference represented the portion converted to *o*-aminobenzdimethylamide, which was water-soluble and not isolated.

Procedure 4: N-methylisatoic anhydride with amines. The *N*-methylisatoic anhydride was reacted with ammonia or dimethylamine by slowly adding the anhydride to an excess of concentrated ammonia or dimethylamine solution. The reactants were allowed to stand for 5 min. Flat plates of amide formed which were separated by filtration. Acidification of the filtrate failed to yield any substituted ureidobenzoic acid derivatives.

Procedure 5: Preparation of anthraniloylanthranilic acid. A reaction mix of 1:1:1.5 molar ratios of anthranilic acid, isatoic anhydride and sodium hydroxide are reacted in water at a temperature of 55° until all the reactants are in solution. The anthraniloylanthranilic acid is separated as an insoluble precipitate by acidification of the reaction mix with acetic acid. A methanol-water (4:1) mixture is used for recrystallization.

Picrate salts were prepared from solutions of absolute methanol or methanol-water mixtures.

Catalysts for the reaction of isatoic anhydride with ethanol. Molar ratios of 10:1 of IA to catalyst were used in an excess of 95% ethanol as reactant and solvent. 2.5 g. of IA (0.0153 mole) was tested in 10 ml. of 95% ethanol with the following substances as catalysts: NaOH, KOH, $(CH_3)_3N$, NaOEt, Na_2CO_3 and CaO. All but the last proved to have catalytic activity.

Acknowledgment. The authors wish to express their appreciation to Dr. Joseph Bunnett of Brown University and Dr. Ernest Eliel of the University of Notre Dame for their assistance and suggestions in developing the theory of these reactions.

COLLEGEVILLE, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SWARTHMORE COLLEGE]

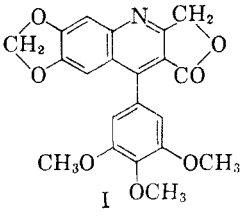
Quinoline Analogs of Podophyllotoxin. III. The Synthesis of a Quinoline Analog of Dehydroanhydropicropodophyllin[1]

EDWARD A. FEHNEL AND JOAN E. STUBER

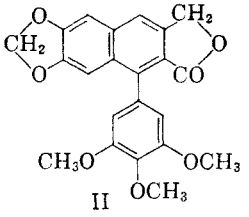
Received February 16, 1959

2-Hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone, a quinoline analog of dehydroanhydropicropodophyllin, has been synthesized by application of the general method described in Part II to 2-amino-4,5-methylenedioxy-3′,4′,5′-trimethoxybenzophenone. The possible tautomeric nature of the product is discussed.

One of the interim objectives of the present series of investigations has been the synthesis of 2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-quinolinecarboxylic acid lactone (I), which may be regarded as a quinoline analog of dehydroanhydropicropodophyllin (II). Compound I is of interest both because it bears a much closer



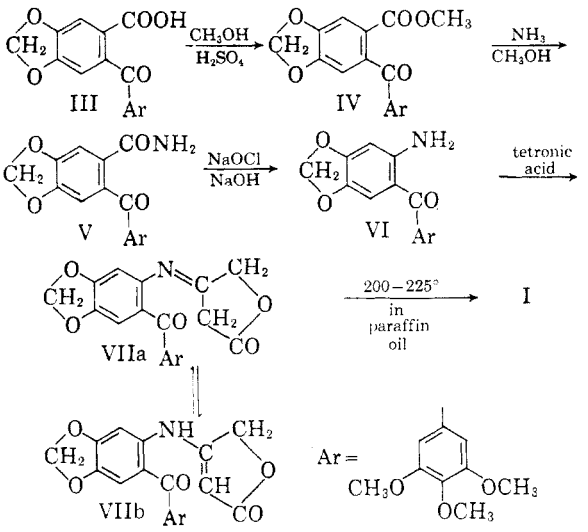
I



II

structural resemblance to the tumor-damaging lignan, podophyllotoxin, than do any of the quinoline derivatives previously described[2] and because it is a potential precursor of 2-hydroxymethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,-2,3,4-tetrahydro-3-quinolinecarboxylic acid lactone, one of the stereoisomers of which should be an exact quinoline analog of podophyllotoxin. We are now able to report that we have succeeded in synthesizing I by an adaptation of the general method described in the preceding paper in this series.[3]

The sequence of reactions leading to I is outlined in the accompanying diagram. 6-(3,4,5-



Trimethoxybenzoyl)piperonylic acid (III), prepared by the method of Gensler and Samour,[4] was esterified and the ester IV was ammonolyzed to give the amide V,[5] which underwent the Hofmann reaction on treatment with sodium hypochlorite to produce the corresponding amine VI. This *o*-aminoketone was condensed with tetronic acid and the resultant anil (VIIa or VIIb) was cyclized to the desired quinoline lactone I. The overall yield was about 10%, with most of the loss oc-

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(2) E. A. Fehnel, *J. Org. Chem.*, **23**, 432 (1958).

(3) E. A. Fehnel, J. A. Deyrup, and M. B. Davidson, *J. Org. Chem.*, **23**, 1996 (1958).

(4) W. J. Gensler and C. M. Samour, *J. Am. Chem. Soc.*, **73**, 5555 (1951).

(5) Attempts to prepare this amide by way of the corresponding acid chloride failed due to the readiness with which the acid III underwent ring-closure to a substituted anthraquinone in the presence of the usual halogenating agents.