Benzoylation of 2a.—A solution of **2a** (1 g, 0.00435 mol) and benzoyl chloride (1.4 g, 0.01 mol) in dry xylene (15 ml) was heated under reflux for 16 hr using a fiberglass heating mantle. The dark brown solution was diluted with benzene (10 ml), decolorized with charcoal, and concentrated to dryness in a rotating evaporator under reduced pressure. The residual yellow oil (1.8 g) partially crystallized. Trituration with cold dry ether and collection at the filter gave 0.47 g (32% yield) of product, mp 145–150°. Recrystallization from methanol gave pure **10** (0.35 g, mp 158–160°) identical with the material obtained from the pyrolysis of **2a**. From the ethereal filtrate there was obtained an oil (0.47 g) which gave a colorless fraction (0.17 g) soluble in warm pentane. This oil could not be crystallized despite indications of virtual homogeneity by tlc analysis. Although its infrared and mass spectra (M^+ = 333.0339; calcd for $C_{17}H_{13}Cl_2NO_2$: 333.0322) were nearly identical with the corresponding spectra of **10**, the CH_3 singlet in the nmr appeared at δ 2.13 ppm instead of at 2.28 ppm for compound **10**. Structure **12** for this oil was again ruled out by the following experiment.

Benzoylation of 3a.—Application of the foregoing procedure to 1.31 g (0.0057 mol) of **3a** gave a dark oil (1.8 g) that crystallized upon trituration with ether. Collection at the filter gave 1.05 g (mp 108–111°, 55% yield) of crude product. Several recrystallizations from methanol gave pure ***O*-benzoyl-*N*-(2,2-dichloroisopropenyl)benzimidate (12)**: mp 111–113°; ir ($CHCl_3$) 1700 cm^{-1} (C=O), and no NH; nmr ($CDCl_3$) δ 8.3–7.3 (m, 10, ArH), and 2.13 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.10; H, 3.92; Cl, 21.22; N, 4.19. Found: C, 61.36; H, 3.73; Cl, 21.43; N, 4.30.

Two solvent systems were used in tlc analyses to compare the three isomeric compounds **12**, **10**, and the oil obtained along with **10**: methylene chloride–nitrobenzene, 6:1, R_f 0.76, 0.86, and 0.86, respectively; and carbon tetrachloride–nitrobenzene, 6:1, R_f 0.47, 0.54, and 0.57, respectively. Tlc analysis of a crude reaction mixture from the benzoylation of the aziridine **2a** showed no more than a trace of material of R_f corresponding to that of **12**.

Registry No.—**2a**, 29431-38-7; **2b**, 29431-39-8; **2c**, 29431-40-1; **3a**, 29431-41-2; **3b**, 29431-42-3; **3d**, 29431-43-4; **7**, 29431-44-5; **8**, 29431-45-6; **10**, 29431-46-7; **11**, 29431-47-8; **12**, 29431-48-9.

Acknowledgment.—The authors are indebted to Mr. W. H. Washburn for the infrared spectra, to Mrs. Ruth Stanaszek and Mr. Richard Egan for the nmr spectra, to Mrs. Evelyn Baker for the chromatographic analyses, to Mr. Victor Rauschel for the microanalyses, to Dr. Milton Levenberg and Mrs. Sandra Mueller for the mass spectra, and to Dr. Peter Beak, University of Illinois, for helpful suggestions.

An Oxygen-18 Study of the Reaction of *N*-Phenylmaleamic Acid with Acetic Anhydride[1,2]

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N-Phenylmaleamic acid **1** labeled in the carboxyl group was prepared by basic hydrolysis of *N*-phenylmaleisoimide. The dehydration of **1** with *N*,*N*′-dicyclohexylcarbodiimide gave *N*-phenylmaleisoimide and *N*,*N*′-dicyclohexylurea; each contained 50% of the original label. Dehydration of the carboxyl-labeled **1** with an acetic anhydride–sodium acetate mixture produced an isoimide–imide product mixture which contained 34% of the original label. Treatment of carboxyl-labeled **1** with acetic anhydride alone was followed by isolation of maleic anhydride (as *endo-cis*-norbornene-5,6-dicarboxylic acid monomethyl ester) and acetanilide. These products contained 94 and 4% of the original label, respectively. The results rule out two mechanisms for this transacylation reaction: (1) a bicyclo [3.2.1] rearrangement of the mixed anhydride of **1** and acetic acid to give maleic anhydride and acetanilide, and (2) the reaction of acetic acid with the isoimide to produce these products. Other mechanisms for the transacylation and dehydration reactions of *N*-phenylmaleamic acid with acetic anhydride are discussed.

In a previous study[4] of the reaction of *N*-arylmaleamic acids **1** with acetic anhydride at 75°, maleic anhydride **2** and acetanilides **3** were found as products along with *N*-arylmaleisoimides **4** and *N*-arylmaleimides **5**. When sodium acetate was added to the reaction mixture, the same four products were observed, but the yields of maleic anhydride and the acetanilides decreased and the yields of the dehydration products **4** and **5** were increased. Furthermore, the production of **2** and **3** was more important when substituents attached to the position para to the amide nitrogen were electron donating than when the substituents were electron withdrawing. These reactions are outlined in Scheme I.

In earlier work Kretov and Kul'chitskaya[5] had isolated acetanilides from similar reactions run at the temperature of refluxing acetic anhydride, and Roderick and Bhatia[6] reported that heptafluorobutyranilide and *p*-methoxyheptafluorobutyranilide were obtained from the reaction of heptafluorobutyric anhydride with *N*-phenylsuccinamic acid and with *N*-*p*-anisylsuccinamic acid.

The previous study of the rearrangement of *N*-arylmaleisoimides to *N*-arylmaleimides in acetic anhydride with and without sodium acetate showed that the formation of the acetanilides and maleic anhydride did not occur as a result of the reaction of the isoimide with the solvent during kinetic runs.[4] We have now found that a small amount of acetanilide (and presumably maleic anhydride) is formed during a longer exposure of *N*-phenylmaleisoimide to acetic anhydride containing 2% acetic acid and that the acetanilides are unstable to the reaction conditions and react slowly with the solvent to form products which have been identified by mass spectra and nmr as *N*,*N*-diacylanilines. Previous

(1) A portion of this work was presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, Organic Division Abstracts No. 136.

(2) A preliminary account of part of this work has appeared: C. K. Sauers, *Tetrahedron Lett.*, 1149 (1970).

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(4) C. K. Sauers, *J. Org. Chem.*, **34**, 2275 (1969).

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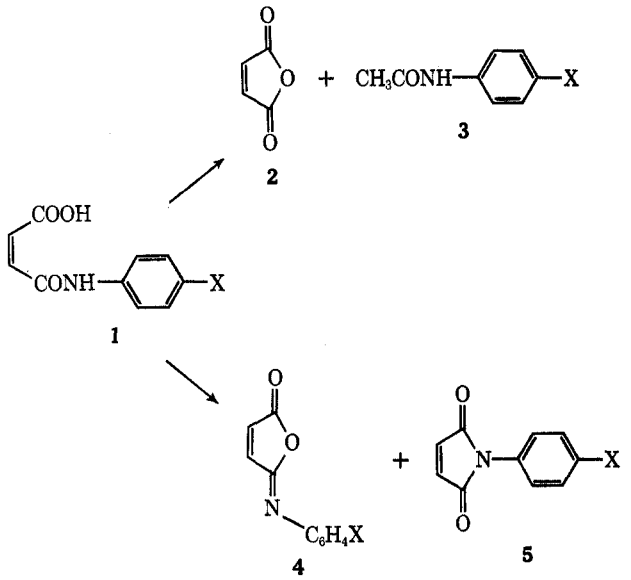
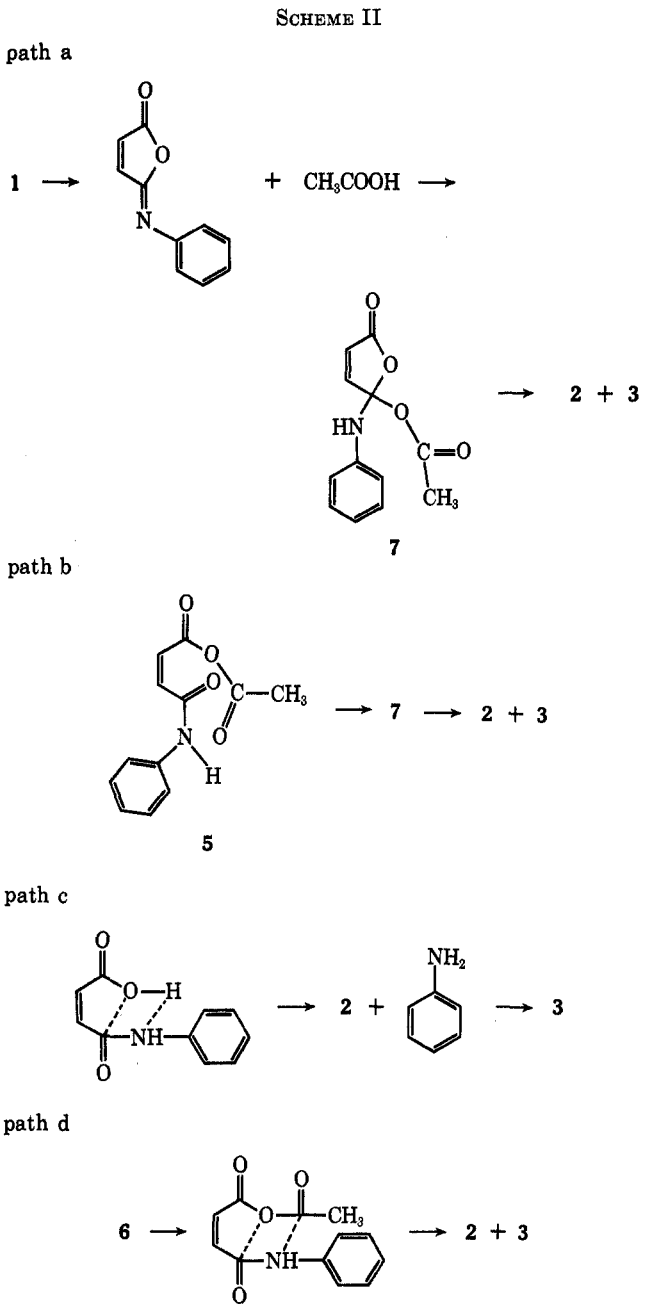
SCHEME I



SCHEME II



syntheses of these compounds involved more strenuous reaction conditions.[7-10]

A number of possible mechanisms may be suggested to account for the transacylation products, and these are outlined in Scheme II. The first process (path a) pictures the production of maleic anhydride and the acetanilides from a previously formed isoimide. The formation of the isoimides may occur by the loss of acetic acid from the mixed anhydride **6** formed by the reaction of acetic anhydride with the starting maleamic acid. Related mechanisms have been proposed for trifluoroacetic anhydride dehydration of amic acids,[6,11] and studies on the dehydration of amic acids with dicyclohexylcarbodiimide[12,13] support a similar mechanism for these reactions.

The addition of acetic acid to the carbon–nitrogen double bond to give a tetrahedral intermediate **7** which could collapse to anhydride and acetanilide is also analogous to reactions which have been previously reported. Thus, addition to the imino function of *N*-phenylphthalisoimide occurs with hydrazoic acid in chloroform[14] and during the acid-catalyzed hydrolysis of *N*-phenylmaleisoimide.[2] It is apparent from the very slow production of acetanilide from *N*-phenylmaleisoimide that this pathway cannot be a major one for this system.

Three additional mechanisms are possible to account for the transacylation reaction. Path b is analogous to the bicyclic mechanisms reported by Newman.[15] Path c is similar to the well-known catalysis of amide hydrolysis by neighboring carboxyl groups.[16] Other variations of path c are possible; *e.g.*, acylation at the nitrogen might take place before or during carboxyl participation. Path d combines features of path c with the suggestion by Roderick and Bhatia[6] that the transacylation reaction observed in the *N*-arylsuccinamic acid–heptafluorobutyric anhydride systems proceeds through a mixed anhydride intermediate.

Paths a and b may be differentiated from paths c and d by oxygen-18 labeling studies. In paths a and b one of the oxygens in the maleic anhydride product is derived from the acetic anhydride solvent. In contrast to this, paths c and d produce maleic anhydride composed of oxygens identical with those in the original maleamic acid. If the major source of the acetanilide

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and anhydride products were path a, then the anhydride would retain half the label and the acetanilide would be unlabeled. Furthermore, the collapse of **7** to acetanilide and maleic anhydride by a four-centered mechanism as in the third step of path b requires the carbonyl group of the acetanilide to have originated in the carboxyl group of the starting amic acid. In paths b and c the oxygen in the acetanilide carbonyl would be derived from the acetic anhydride.

These differences prompted us to synthesize *N*-phenylmaleamic acid labeled with oxygen-18. Labeled **1a** and **1b** (Scheme III) were prepared according to a procedure developed by Paul and Kende[13] for the synthesis of labeled *N*-*n*-butylmaleamic acid. *N*-Phenylmaleisoimide was treated with potassium hydroxide in water labeled with oxygen-18 and the location of the label in the *N*-phenylmaleamic acid product was determined by dehydrating this material with *N*,*N*′-dicyclohexylcarbodiimide. The oxygen-18 label was found to be equally distributed between the *N*,*N*′-dicyclohexylurea and the *N*-phenylmaleisoimide products. According to the mechanism of the carbodiimide dehydration reaction supported by the evidence of Kashelikar and Ressler[12] and Paul and Kende,[13] one of the carboxyl oxygen atoms would be removed during the reaction to become the carbonyl oxygen of the urea product. Therefore, the original maleamic acid produced by basic hydrolysis of the isoimide is labeled in the carboxyl group.

As we have previously reported,[2] hydrolysis of the *N*-phenylmaleisoimide under acidic conditions gives rise to a *N*-phenylmaleamic acid **1c** which is labeled primarily in the amide carbonyl oxygen. This conclusion arises from the observation that subsequent dehydration of **1c** with the carbodiimide reagent produces urea containing only 6% of the label and isoimide containing 94% of the label. These results were predicted by the kinetics of the hydrolysis of *N*-phenylphthalisoimide reported by Ernst and Schmir.[16e] Furthermore, it seems likely that hydrolysis of the isoimidium perchlorate salts derived from succinanilic acid[17] may proceed by attack of water at the immonium center.

A summary of the syntheses and dehydrations of the labeled *N*-phenylmaleamic acids is contained in Table I.

TABLE I

OXYGEN-18 ANALYSES[a] FOR THE SYNTHESIS OF *N*-PHENYLMALEAMIC ACID BY HYDROLYSIS OF *N*-PHENYLMALEISOIMIDE AND THE DEHYDRATION OF ACID BY *N*,*N*′-DICYCLOHEXYLCARBODIIMIDE

Hydrolysis conditions	Maleamic acid	Dehydration products: Isoimide	Dehydration products: Urea
Basic	**1a**, 8.3 ± 0.2	4.2 ± 0.1	4.3 ± 0.0
Basic	**1b**, 1.33 ± 0.02	0.65 ± 0.03	
Acidic	**1c**, 7.9 ± 0.1	7.4 ± 0.1	0.5 ± 0.1
Neutral[b]	**1d**, 8.2 ± 0.1	6.5 ± 0.0	1.6 ± 0.1
Neutral[b]	**1e**, 3.2 ± 0.1		0.6 ± 0.0

[a] Average atom per cent excess oxygen-18 ± average deviation for two or more analyses. [b] The hydrolysis conditions were not neutral except at the start because the products, *N*-phenylmaleamic acid and phthalic acid, are acidic. (See Experimental Section.)

Included are the results of the hydrolysis of *N*-phenylmaleisoimide in oxygen-18 containing water with no added acid or base. These reactions have been discussed previously.[2]

The labeled maleamic acid **1b** was treated with acetic anhydride containing sodium acetate at 65° for a length of time sufficient to complete the formation of the imide and isoimide products. These were isolated from an aqueous sodium bicarbonate solution used to hydrolyze the acetic anhydride, and the isoimide–imide mixture was purified by column chromatography and analyzed for excess oxygen-18. Formation of these products by the internal displacement by the oxygen or nitrogen of the amide group of the acetate group of the mixed anhydride would require 50% of the label from **1b** to be found in the imide–isoimide product mixture. This percentage would not be altered by the isoimide–imide rearrangement which is known to occur under the reaction conditions[4] and which may occur under the work-up conditions[16e] since the oxygens of the imide formed in this way would be identical with the oxygens of the isoimide which rearranges.

However, analysis of the isoimide–imide product mixture showed that these compounds contained 34% of the label originally contained in the carboxyl group. The possibility that some of the label may have been lost in the work-up procedure through a reversible addition of water to the isoimide to form a symmetrical tetrahedral intermediate was considered. When a sample of unlabeled isoimide was dissolved in acetic anhydride and then reisolated by treatment of the mixture with sodium bicarbonate solution prepared from labeled water, no label was incorporated into the isoimide. This result indicates that a symmetrical tetrahedral intermediate is not formed reversibly under these conditions.

It is possible that the label in the mixed anhydride is distributed to all positions of the anhydride *via* pathways analogous to those proposed by Denney and Greenbaum for the reaction of aromatic anhydrides with ammonia and amines.[18]

N-Phenylmaleamic acid **1a** (labeled in the carboxyl group) was treated with acetic anhydride at 100°. Addition of cyclopentadiene followed by methanol produced a mixture of compounds containing only one acidic component (aside from acetic acid). This compound, the methyl half-ester of *cis-endo*-5,6-norbornenedicarboxylic acid **8a** was isolated by extraction with base, and acetanilide **3a** was separated from the mixture of neutral materials by column chromatography. These reactions and the accompanying oxygen-18 analyses are summarized in Scheme III.

Oxygen-18 analysis of purified **8a** and **3a** demonstrated that 94% of the label originally present in the carboxyl group was located in **8a** whereas only 4% was found in the acetanilide. The oxygen-18 data eliminate pathways a and b as mechanisms for the formation of acetanilide and maleic anhydride.

The fact that the reaction is more important in the absence of acetate ion is in accord with path c by analogy to the pH-rate profiles for phthalamic, maleamic, and substituted maleamic acids.[16,19] The reaction proceeds faster when the amic acid is derived from amines of greater basicity and this again supports

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(18) Donald B. Denney and Michael A. Greenbaum, *J. Amer. Chem. Soc.*, **79**, 3701 (1957).

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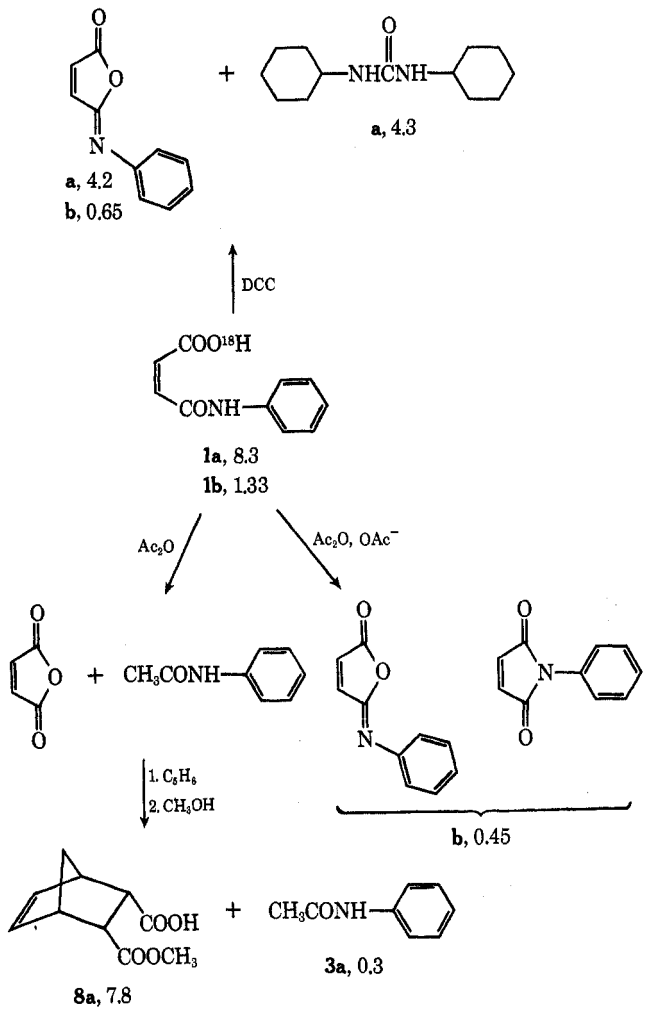
SCHEME III



path c by analogy to the observations of Dahlgren and Simmerman[16c] and Brown, Su, and Shafer[16d] on amic acid hydrolyses and Thanassi and Bruice on methyl hydrogen phthalate and chlorethyl hydrogen phthalate hydrolyses.[20] The high *isolated* yields of *N*-phenylphthalisoimmonium perchlorate obtained by Boyd[17] when the dehydrating reagent was acetic anhydride–perchloric acid suggest that the transacylation reaction is not taking place with this reagent. Since perchloric acid catalyzes a very rapid exchange reaction between acetic acid and acetic anhydride,[21] one would expect mixed anhydride formation to be very rapid with the acetic acid–perchloric acid reagent. For these reasons path c appears to be the most likely mechanism by which maleic anhydride and acetanilide are produced in these reactions, but path d or a combination of c and d cannot be unequivocally ruled out.

Experimental Section

Microanalyses were performed by George Robertson, Florham Park, N. J. Nuclear magnetic resonance spectra were run on a Varian A-60A spectrometer and infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. Melting points are uncorrected.

Oxygen-18 Analyses.[22]—The method of analysis for oxygen-18 content was that of Rittenberg and Ponticorvo[23] modified by the use of an apparatus similar to that described by Williams and Hager.[24] Sealed sample tubes containing mercuric chloride or mercuric cyanide were heated in a furnace at 500° for 2–24 hr. This procedure was always carried out in a hood since hydrogen cyanide is a product of the combustion when mercuric cyanide is the catalyst. The resulting carbon dioxide was collected and sublimed in a vacuum line and introduced into a mass spectrometer. Samples derived from acids prepared with 10 atom % excess oxygen-18 water were analyzed on a Hitachi Perkin-Elmer Model RMU mass spectrometer.[25] The peak heights of peaks 44, 45, and 46 were measured to the nearest tenth of a millimeter and the atom per cent oxygen-18 was calculated from the formula

$$\% \text{ O-18} = \frac{1/2(46 \times 100)}{44 + 45 + 46}$$

Correction for the natural abundance of oxygen-18 was made by subtracting 0.20 from the value for per cent oxygen-18. This quantity was multiplied by the number of oxygen atoms in the molecule to obtain the values reported in Table I. Samples derived from acids prepared with 1.5 atom % excess oxygen-18 water were analyzed on a Consolidated-Nier Model 201 isotope ratio mass spectrometer.[26] The per cent oxygen-18 in the molecule was calculated from a modification of the formula published by Denney and Greenbaum[27]

$$\frac{[0.00408]46/44(\text{sample})}{46/44(\text{tank})} = \frac{2(0.98892)[Z(0.00204) + X] + 2(Z)(0.01108)(0.00037)}{0.98892[Z(0.99759) - X]}$$

where Z is the number of oxygen atoms in the molecule of the original sample and X is the atom fraction excess oxygen-18 per molecule.

Synthesis of Oxygen-18 Compounds.—*N*-Phenylmaleisoimide was prepared and purified by the dehydration of *N*-phenylmaleamic acid with *N*,*N*′-dicyclohexylcarbodiimide followed by chromatography on Florisil.[28] After drying it was stored in a tightly stoppered bottle in the refrigerator and used within 1 week of its preparation. Tetrahydrofuran was purified by distillation from lithium aluminum hydride immediately prior to each use. The labeled water was 10 atom % and 1.5 atom % purchased from Bio-Rad Laboratories.

Hydrolysis of *N*-Phenylmaleisoimide in $K^{18}OH$–$H_2{}^{18}O$.[2] Preparation of 1a and 1b.—A solution of 1.7311 g of *N*-phenylmaleisoimide in 3.75 g of dry tetrahydrofuran was added in one portion to a solution of potassium hydroxide in labeled water prepared by the addition of 1.4043 g of potassium *tert*-butoxide (obtained from MSA Research Corporation) to 2.3032 g of water containing 10 atom % oxygen-18. The exothermic reaction mixture was stirred in an ice bath for 12 min. After evaporation under reduced pressure, 2 ml of $H_2{}^{16}O$ was added and the mixture was acidified with concentrated hydrochloric acid. The product was collected by filtration and washed with water. *N*-phenylmaleamic acid **1a**, an ivory powder having mp 197–199°, was isolated in 90% yield. Recrystallization from 80 ml of 95% ethanol yielded 70% purified **1a**, mp 201–202°. Analysis for oxygen-18: 8.40, 8.13 atom % excess. A second preparation of this compound was carried out with 2.6287 g of *N*-phenylmaleisoimide, 8.4176 g of water containing 1.5% oxygen-18, 2.7190 g of potassium *tert*-butoxide, and about 3 ml of dry tetrahydrofuran. The product **1b** was isolated as above except that concentrated sulfuric acid was used to precipitate the product. After recrystallization, 2.1886 g of *N*-phenylmaleamic acid **1b**, mp 200–201.5°, was obtained. Analysis for oxygen-18: 1.35, 1.32, atom % excess.

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(24) F. R. Williams and L. P. Hager, *Science*, **128**, 1434 (1958).
(25) We are indebted to Mrs. Van Es, School of Chemistry, Rutgers University, for obtaining these spectra.
(26) We are grateful to Professor Ernst Monse and Mr. Frank Torre, Rutgers University in Newark, for the use of this mass spectrometer.
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Hydrolysis of *N*-Phenylmaleisoimide in H_2SO_4–$H_2^{18}O$.[2] Preparation of 1c.—A solution of 0.7822 g of *N*-phenylmaleisoimide in 4.0 ml of dry tetrahydrofuran was added over 30 sec to a solution of 0.1114 g of concentrated sulfuric acid in 1.0464 g of water containing 10 atom % oxygen-18. After 10 min the slurry was evaporated under reduced pressure and $H_2^{16}O$ was added to the pasty residue. The product, *N*-phenylmaleamic acid, was collected by filtration and washed five times with distilled water and dried, 0.6849 g (79%), mp 198–200°. After recrystallization from 35 ml of 95% ethanol, 513 mg (59%) of purified *N*-phenylmaleamic acid **1c** was obtained, mp 201–202°. Oxygen-18 analysis: 7.96, 7.74, 8.04 atom % excess. A portion of this compound was subjected to the reaction conditions a second time in order to determine whether exchange of oxygen-18 in the molecule occurs during the reaction or work-up conditions. Thus 110 mg of **1c**, 105 mg of concentrated sulfuric acid, 4 ml of tetrahydrofuran, and 1 ml of $H_2^{16}O$ were stirred for 10 min and worked up as before. The *N*-phenylmaleamic acid thus recovered weighed 41 mg. Analysis for oxygen-18: 7.96, 8.11 atom % excess.

Hydrolysis of *N*-Phenylmaleisoimide in $H_2^{18}O$. Preparation of 1d and 1e.—A clear solution of 245 mg of *N*-phenylmaleisoimide in 5.6 ml of water containing 10 atom % excess oxygen-18 and 1.970 g of tetrahydrofuran was allowed to stand at room temperature for 24 hr. Large crystals of *N*-phenylmaleamic acid **1d** were deposited during this time. These were collected by filtration, the filtrate was evaporated under reduced pressure, and the residue was triturated with 95% ethanol and filtered. The combined precipitates were recrystallized from ethanol yielding 44 mg (16%) of a first crop and 25 mg (8%) of a second crop. Oxygen-18 analysis (first crop): 8.04, 8.28 excess atom %. Similarly a 213-mg sample of *N*-phenylmaleisoimide was added all at once to a mixture of 3.1071 g of $H_2^{16}O$ and 1.0307 g of $H_2^{18}O$ (containing 10 atom % oxygen-18). To this mixture was added 131 mg of Spectrograde acetonitrile. The pale yellow heterogeneous solution was stirred for 6 hr and then filtered, and the precipitate **1e** (90 mg, 38%) was analyzed after drying under vacuum for 12 hr. Analysis for oxygen-18: 3.21 atom % excess. The remainder of the maleamic acid, 64 mg, was recrystallized from *ca.* 4 ml of 95% ethanol, yielding 43 mg of **1e**. Analysis for oxygen-18: 3.27, 3.09 atom % excess. This reaction was repeated on a larger scale with unlabeled water. Thus 2 g of *N*-phenylmaleisoimide, 1.1 g of acetonitrile, and 40 ml of distilled water were stirred for 6 hr and the pH of the solution was monitored during this time. The pH fell rapidly to 4 and then slowly dropped to 2.8 at the end of the reaction. The product was isolated in the usual manner, 1.3 g (62%).

Dehydration of *N*-Phenylmaleamic Acid 1a–e with *N,N'*-Dicyclohexylcarbodiimide.—A slurry of 0.1493 g of *N*-phenylmaleamic acid **1a** and 0.1683 g of *N,N'*-dicyclohexylcarbodiimide in *ca.* 8 ml of dichloromethane contained in a dry flask was stirred for 24 hr. *N,N'*-Dicyclohexylurea (0.1322 g, 82%) was isolated by filtration and purified by repeated washings with boiling dichloromethane. Analysis for oxygen-18: 4.27, 4.27 atom % excess. Similarly, 154 mg of **1b** and 181 mg of the carbodiimide were stirred in dichloromethane and the urea and isoimide products were isolated and purified as above. The isoimide was analyzed. Oxygen-18: 0.63, 0.68 atom % excess. In a similar manner, 131 mg of **1c** was treated with 160 mg of the carbodiimide. *N*-phenylmaleisoimide (56 mg, 46%) was isolated. Analysis for oxygen-18: 7.35, 7.45 atom % excess. The urea (119 mg, 84%) was obtained. Analysis for oxygen-18: 0.58, 0.43 atom % excess. Similarly *N*-phenylmaleamic acid **1d** (32 mg) was treated with 33 mg of the carbodiimide, and the isoimide and urea products were isolated: isoimide, 11 mg (40%), analysis for oxygen-18, 6.52, 6.52 atom % excess; urea, 24 mg (69%), analysis for oxygen-18, 1.58, 1.45, 1.62 atom % excess. Similarly **1e** (30 mg) and 34 mg of the dehydrating agent yielded 15 mg (47%) of the urea and 6.2 mg of the isoimide which was lost during the subsequent analysis. The urea, analysis for oxygen-18: 0.58, 0.64 atom % excess.

Transacylation Reaction of *N*-Phenylmaleamic Acid–$CO^{18}OH$ with Acetic Anhydride.—*N*-Phenylmaleamic acid **1a** (0.3093 g, 0.00162 mol) was heated with 1.5 ml of freshly distilled acetic anhydride in a water bath at 100° for 10 min. The bright yellow reaction solution was cooled and treated with 1 ml of freshly distilled cyclopentadiene.[29] After the initial exothermic reaction had subsided, the reaction mixture was heated at 50° until the bright yellow color had faded. Methanol (50 ml) was added and the reaction mixture was heated at reflux for *ca.* 20 hr. The methanol was removed by distillation at atmospheric pressure. The residue, a deep red oil, was dissolved in about 60 ml of ether and this solution was washed twice with 50-ml portions of saturated sodium bicarbonate solution. The ether solution was used for the isolation of acetanilide. The bicarbonate solution was acidified with concentrated hydrochloric acid and was then extracted three times with ether. After drying (sodium sulfate) the ether was permitted to evaporate at atmospheric pressure. The clear red oil which resulted was triturated with pentane whereupon it slowly crystallized. Nmr indicated that the sample was contaminated with acetanilide (δ 2.17) and so it was redissolved in dichloromethane and extracted with three 30-ml portions of 0.1 *N* sodium hydroxide solution. The combined basic extracts were thoroughly washed with dichloromethane and then acidified with concentrated hydrochloric acid. The product was obtained by extraction with dichloromethane; the extract yielded 26 mg of *endo-cis*-norbornene-5,6-dicarboxylic acid monomethyl ester (**8a**). After recrystallization from ligroin (bp 65–85°) the sample (13 mg) was analyzed: 7.84 atom % excess oxygen-18. In an earlier reaction of acetic anhydride with **1a** in which the acetanilide was not entirely removed from the maleic anhydride derivative, the excess oxygen-18 was found to be 7.20, 7.24 atom % excess.[30]

The original ether extract which contained neutral compounds was dried, evaporated, and then chromatographed on a 0.75 × 14 in. column of Florisil with benzene and mixtures of ether–benzene. Sixty 10-ml fractions were taken and three products were isolated. The first fractions (21–24) had mp 142–143°; nmr δ 7.3 (m, 5 H), 6.29 (2 H), 3.44 (4 H), 1.69 (m, 2 H), consistent with *cis-endo*-norbornene-5,6-dicarboxylic acid *N*-phenylimide (lit.[31] mp 144°). The second product (49–51) was acetanilide, mp 110–112.5° (lit.[32] mp 114°) The third product was obtained upon washing the column with ether, mp 133–136°. The nmr was consistent with that expected for the anilide of the ester–acid contaminated with acetanilide. Analysis for oxygen-18 in the acetanilide: 0.27, 0.28 atom % excess.

Reactions of Acetanilides with Acetic Anhydride.—During the course of a study of the reactions of *N*-para-substituted phenylphthalamic acids and maleamic acids with acetic anhydride,[32] it was noticed that the yields of *p*-chloroacetanilide as determined by gpc decreased after a short period and that a new product with retention time slightly less than that of *p*-chloroacetanilide appeared in the chromatogram (column, 5.5-ft 3% SE-30 on Varaport 30, 143°). Treatment of *N*-*p*-chloroaniline with a large excess of acetic anhydride at 65° for 24 hr followed by an aqueous sodium bicarbonate work-up and distillation produced *N,N*-diacetyl-*p*-chloroaniline: mp 64–66.5° (lit.[7] mp 66–67°); nmr (CH_2Cl_2) δ 7.43 (db, 2 H), 7.14 (db, 2 H, J = 8.5 Hz), 2.13 (s, 6 H); mass spectrum, molecular ion peaks 211 and 213, 3:1 ratio. This material had the same retention time as the material produced during the transacylation reaction above. *Anal.* Calcd for $C_{10}H_{10}O_2NCl$: C, 56.75; H, 4.76; N, 6.62. Found: C, 57.08; H, 4.96; N, 6.97.

Similarly *N,N*-diacetylaniline was prepared from aniline and was purified by distillation, bp 95° (6 mm) [lit.[8] bp 145–146° (13 mm)], and crystallized to a white solid: mp 31.5–35.5° (lit.[8] mp 37–37.5°); nmr (CH_2Cl_2) (7.3) (δ) (m, 5 H), 2.15 (s, 6 H).

In the same manner, *N,N*-diacetyl-*p*-toluidine was prepared and purified: bp 113° (6 mm) [lit. bp 160–161° (15 mm);[8] mp 48°[9]]; nmr (CH_2Cl_2) δ 7.28 (db, 2 H), 7.05 (db, 2 H, J = 8.5 Hz), 2.37 (s, 3 H), 2.22 (s, 6 H).

When *p*-anisidine was treated with acetic anhydride at 65° for 48 hr followed by an aqueous sodium bicarbonate work-up,

(29) L. F. Fieser, "Organic Experiments," D. C. Heath, Boston, Mass., 1964, p 83.

(30) During earlier work,[4] we isolated a sample which had mp 78–82°. Reexamination of the spectra for this sample reveals a small amount of contamination by acetanilide. M. S. Morgan, R. S. Tipson, A. Lowry, and W. E. Baldwin, *J. Amer. Chem. Soc.*, **66**, 404 (1944), report mp 76–78.5° while L. M. Rice and E. E. Reid, *ibid.*, **74**, 3955 (1952), report mp 101–102°. We have prepared authentic **8** by a reaction between methanol and *cis-endo*-norbornene-5,6-dicarboxylic anhydride which had mp 98–100°. An nmr of this substance containing 15% acetanilide was found to be identical with that of the unpurified **8a**.

(31) J. R. A. Pollock and R. Stephens, Ed., "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965.

(32) C. K. Sauers, E. S. Ioannou, and C. L. Gould, unpublished work.

only *p*-methoxyacetanilide was obtained. The diacetyl derivative has previously been prepared by a similar reaction run at a higher temperature.[10]

Dehydration Reaction of *N*-Phenylmaleamic Acid $CO^{18}OH$ with Acetic Anhydride–Sodium Acetate.—*N*-Phenylmaleamic acid **1b** (0.4663 g, 0.00244 mol) was mixed with 0.5710 g of anhydrous sodium acetate and 10 ml of acetic anhydride. The mixture was heated at 65° for 90 min, then cooled, and slowly added to excess saturated sodium bicarbonate. The yellow precipitate which remained after the acetic anhydride had been hydrolyzed was filtered and dried. A benzene solution of this mixture was passed through a 2-in. column of Florisil in a Pasteur pipet and all of the yellow product was collected. After removal of the benzene at reduced pressure, the sample was dried *in vacuo* for 24 hr. An nmr ($CDCl_3$–TMS) indicated that the material was a mixture of imide and isoimide. Analysis for oxygen-18: 0.45, 0.45 atom % excess, 34% of the label found in **1b**.

Acetic anhydride (2 ml) was added to 0.157 g of *N*-phenylmaleisoimide; the resulting solution was poured into 18 ml of saturated sodium bicarbonate solution prepared from water containing 1.5 atom % oxygen-18. The mixture was stirred until the isoimide crystals could be isolated by filtration and purification was carried out as above. Analysis for oxygen-18: 0.00, 0.01 atom % excess.

Registry No.—*N*-Phenylmaleamic acid, 555-59-9; acetic anhydride, 108-24-7.

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Synthesis of D- and L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid *via* Resolution

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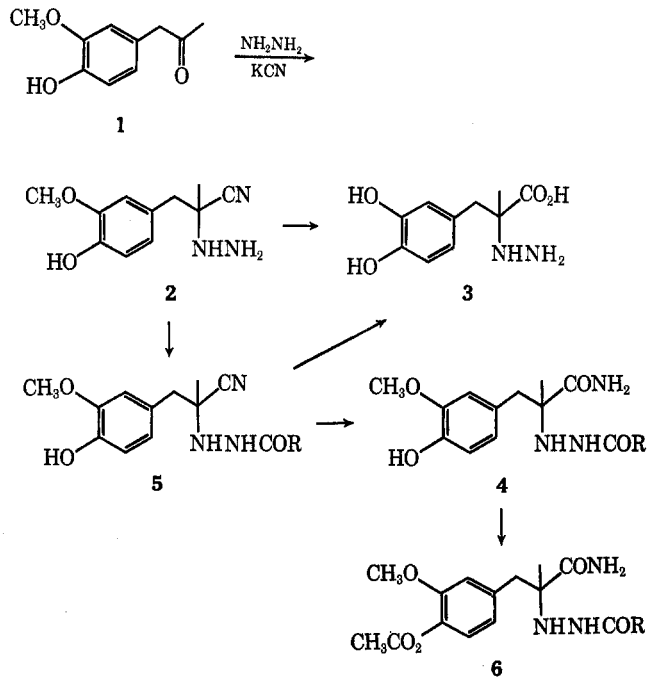
l-Menthoxyacetylation of *dl*-α-hydrazino-α-(4-hydroxy-3-methoxybenzyl)propionitrile (**2**) permits resolution and, after hydrolysis, the isolation of the two antipodes of α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**3**). The acylation is proven to have occurred on N^{β}.

In spite of seemingly increasing interest in the synthesis of α-hydrazinocarboxylic acids over the past decade,[1] only three methods are commonly used for their preparation. Two of these, the reduction of a hydrazone of an α-keto acid[1b] and the functionalization of a carbonyl compound in a Strecker-like synthesis,[2] are not particularly useful for the formation of optical isomers. The third, reaction of hydrazine with an α-halo acid, has so far proved to be the only useful route.[1a,b,3] Surprisingly, the resolution of racemic hydrazino acids by separation of diastereomers has yet to be reported.

The hydrazination reaction has severe limitations, especially in cases where the halogen to be replaced resides on a tertiary center and/or is ideally set up for base-promoted elimination as HX. Such a situation faced us in a projected preparation of the antipodes of α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**3**). Our interest in this work arose from the reported biological activity, both *in vitro*[4] and *in vivo*,[4,5] of the racemate[2] and the known "difference in biological activity associated with optical isomerism."[4b,6]

In this paper we report the first preparation of the antipodes of **3**[7] which was achieved by separation of diastereomeric hydrazides **5c** and by subsequent acid hydrolysis to the optically active hydrazino acids (**3**) (Scheme I). Inferences from the physical characteris-

SCHEME I



a, R = CH_3
b, R = C_6H_5
c, R = 1-menthoxymethyl

(1) For example, (a) A. Carmi, G. Pollak, and H. Yellin, *J. Org. Chem.*, **25**, 44 (1960); (b) E. J. Glamkowski, G. Gal, M. Sletzinger, C. C. Porter, and L. S. Watson, *J. Med. Chem.*, **10**, 852 (1967); (c) M. Sletzinger, R. A. Firestone, D. F. Reinhold, C. S. Rooney, and W. H. Nicholson, *ibid.*, **11**, 261 (1968), and references cited therein.

(2) M. Sletzinger, J. M. Chemerda, and F. W. Bollinger, *ibid.*, **6**, 101 (1963).

(3) A. Darapsky, *J. Prakt. Chem.*, **99**, 179 (1919); H. Niedrich and R. Grupe, *ibid.*, **27**, 108 (1965).

(4) (a) C. C. Porter, L. S. Watson, D. C. Titus, J. A. Totaro, and S. S. Byer, *Biochem. Pharmacol.*, **11**, 1067 (1962); (b) V. J. Lotti and C. C. Porter, *J. Pharmacol. Exp. Ther.*, **172**, 406 (1970).

(5) G. C. Cotzias, P. S. Papavasiliou, and R. Gellene, *New Engl. J. Med.*, **280**, 337 (1969), for example, report its usefulness in the treatment of Parkinsonism.

(6) A. H. Beckett, G. Kirk, and A. J. Sharpen, *Tetrahedron*, **21**, 1489 (1965).

(7) Attempts to resolve **2**, **3**, **4**, **5**, or **6** by separation of diastereomeric salts were thwarted by our inability to crystallize suitable salts with a variety of optically active acids.