The Dehydration of N-Arylmaleamic Acids with Acetic Anhydride

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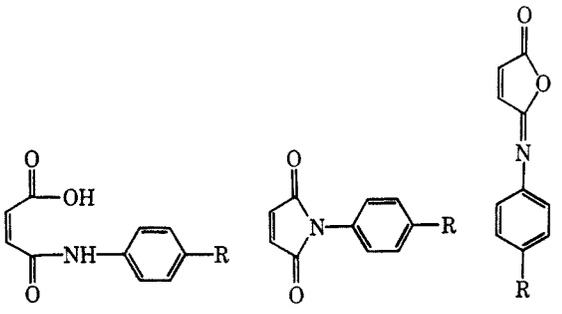
Dehydrations of N-arylmaleamic acids in acetic anhydride with and without sodium acetate were studied. N-Arylmaleimides, N-arylmaleisoimides, maleic anhydride, and substituted acetanilides were detected in these reactions. Mechanisms to account for these products were discussed. The kinetics of the acetate-catalyzed rearrangement of N-arylmaleisoimides to N-arylmaleimides were investigated. This reaction was shown to be a major source of maleimides in the dehydration reactions.

A standard synthesis[1,2] for N-arylmaleimides (**2**) is the dehydration of N-arylmaleamic acids (**1**) with acetic anhydride containing sodium acetate at temperatures below 100°. Under certain conditions acetic anhydride–sodium acetate mixtures also have been found to yield isoimides (**3**). For example, N-*p*-anisylmaleamic acid (**1a**) gave N-*p*-anisylmaleisoimide (**3a**) when treated with these reagents at low temperatures, but gave imide **2a** at higher temperatures.[3] Some N-*n*-butylmaleisoimide was detected in the dehydration of N-*n*-butylmaleamic acid to the imide in acetic anhydride containing sodium acetate.[4]

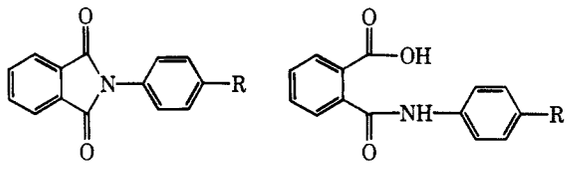


1 **2** **3**

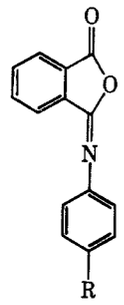
a, R = OCH_3
b, R = CH_3
c, R = H
d, R = Cl
e, R = $COCH_3$

Acetic anhydride without sodium acetate has been found to give isoimides in low yields.[5,6] Imides were also products of this reagent.[5] When this reaction was run at the temperature of refluxing acetic anhydride, acetanilide and substituted acetanilides were isolated.[2]

It has been suggested[4] that isoimides are the primary products of these dehydration reactions at moderate temperatures and that the imide products are formed by the rearrangement[3-9] of the isoimides. Roderick has shown that a major part of N-*p*-chlorophenylphthalimide (**4b**) formed in the acetic anhydride–sodium acetate dehydration of N-*p*-chlorophenylphthalamic acid (**5b**) must be formed directly.[5] Rearrangement of N-*p*-chlorophenylphthalisoimide (**6b**) under the conditions of the reaction was not sufficiently rapid to account for the yields of imide obtained.



4 **5**



6

a, R = H
b, R = Cl

We wished to study the dehydrations of N-arylmaleamic acids (**1**) to determine the effect of substituents on the benzene ring upon the products of the reactions. We also wished to study the effects of substituents upon the rate of the acetate-catalyzed rearrangement of N-arylmaleisoimides (**3**) to N-arylmaleimides (**2**). Results of such experiments would determine whether or not imide products were formed directly in the dehydrations or were formed by rearrangement of the initially formed isoimides.

Results

When the maleisoimides (**3a–e**) were treated with acetic anhydride containing sodium acetate at temperatures from 65 to 85°, rearrangement to the corresponding maleimides (**2a–e**) occurred. The rates of these reactions were measured by observing the disappearance of the upfield isoimide olefinic proton peaks and the appearance of the olefinic proton peaks assigned to the maleimides in the nuclear magnetic resonance spectra of the reaction mixtures. The nuclear magnetic resonance spectra are summarized in Table I.

First-order rate constants were calculated for individual rate runs by the method of least squares. The standard error was below 6%. Deviation of individual runs from the average of two or more duplicate

(1) N. E. Searle, U. S. Patent 2,444,536 (1948); *Chem. Abstr.*, **42**, 7340 (1948).

(2) A. E. Kretov and N. E. Kul'chitskaya, *Zh. Obshch. Khim.*, **26**, 208 (1956); *Chem. Abstr.*, **50**, 13771 (1956).

(3) A. E. Kretov, N. E. Kul'chitskaya, and A. F. Mal'nev, *J. Gen. Chem. USSR*, **31**, 2415 (1961).

(4) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).

(5) W. R. Roderick, *ibid.*, **29**, 745 (1964).

(6) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1311, 1317 (1966).

(7) For thermal rearrangements in the acyclic series see (a) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965); (b) D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967); (c) D. J. Hoy and E. J. Poziomek, *J. Org. Chem.*, **33**, 4050 (1968).

(8) M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).

(9) (a) A. Le Berre and B. Dumaitre, *C. R. Acad. Sci. Paris, Ser. C*, **266**, 334 (1968); (b) H. Feuer and J. P. Asunskis, *J. Org. Chem.*, **27**, 4684 (1962).

runs was less than ±10%. The kinetic data are summarized in Table II.

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR N-ARYLMALEISOIMIDES AND N-ARYLMALEIMIDES[a]

	Olefinic protons		Aromatic protons		
Compd	δ	J, cps	δ	J, cps	Substituent protons, δ
3a	7.47, 6.75	5.5	7.50, 6.98	9	3.82
2a	6.91		7.27, 7.03	9	3.83
3b	7.50, 6.79	5.5	7.28		2.34
2b	6.91		7.28		2.38
3c	7.54, 6.84	5.5	7.38		
2c	6.93		7.44		
3d	7.53, 6.86	5.5	7.40		
2d	6.95		7.51, 7.41	9.5	
3e	7.58, 6.92	5.5	8.05, 7.35	8.5	2.58
2e	7.00		8.11, 7.58	8.5	2.60

[a] Values for δ relative to internal tetramethylsilane in acetic anhydride.

TABLE II

RATE CONSTANTS FOR THE REARRANGEMENT OF N-ARYLMALEISOIMIDES TO N-ARYLMALEIMIDES IN ACETIC ANHYDRIDE

Expt	3, R	T, °C	M[a] of isoimide	M[b] of sodium acetate	10^4k,[c] sec^{-1}
1	OCH_3	65.0	0.383	0.024	2.7
2	OCH_3	75.0	0.329	0.024	5.2
3	OCH_3	75.0	0.413	0.039[d]	9.3
4	OCH_3	85.0	0.365	0.024	11
5	OCH_3	75.0	0.348	0	*e*
6	OCH_3	75.0	0.385	0[f]	*g*
7	CH_3	65.0	0.448	0.024	3.9
8	CH_3	75.0	0.395	0.024	7.8
9	CH_3	65.0	0.413	0.039[d]	15
10	CH_3	85.0	0.399	0.024	15
11	H	65.0	0.438	0.024	7.0
12	H	75.0	0.427	0.024	13
13	H	75.0	0.460	0.039[d]	27
14	H	85.0	0.422	0.024	31
15	Cl	65.0	0.346	0.024	19
16	Cl	75.0	0.314	0.024	38
17	Cl	75.0	0.346	0.039[d]	64
18	Cl	75.0	0.334	0	6.7
19	Cl	75.0	0.310	0.024[d]	55
20	Cl	75.0	0.345	0[f]	*h*
21	Cl	85.0	0.351	0.024	68
22	$COCH_3$	75.0	0.246	0.024	110
23	$COCH_3$	75.0	0.192	0[f]	*i*

[a] Average starting molarity of the isoimide. [b] Solutions contain 1% acetic acid except as noted otherwise. [c] Average value of the calculated first-order rate constants for two or more runs. [d] Contains 2% acetic acid. [e] 3% reaction after 100 min. [f] Freshly distilled acetic anhydride. [g] No reaction after 168 min. [h] 5% reaction after 185 min. [i] No reaction after 30 min.

The rate of the rearrangement reaction was increased in compounds with electron-deficient aromatic rings. The Hammett equation ρ value for expt 2, 8, 12, 16, and 22 is 1.7 ± 2.[10] The values for the activation energy, E_a, are 17 ± 3, 16 ± 1, 18 ± 2, and 16 ± 1 for **3a**, **3b**, **3c**, and **3d**, respectively. Sodium acetate appears to be a more potent catalyst than acetic acid (expt 2, 5, 16, and 18). Rearrangement in the solvent alone is small compared to the amount of rearrangement occurring in the presence of catalysts (expt 6, 20, and 23).

(10) Values for σ used are those listed in C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, **2**, 323 (1964).

The maleimides were obtained by complete isomerization (7–10 half-lives) of the maleisoimides. No products other than the imides were isolated or detected by nmr or vpc.

The dehydrations of the N-arylmaleamic acids (**1**) in acetic anhydride were more complex than the rearrangement reactions. The reactions appeared to occur as fast as the solution of the starting maleamic acid. Total solution at 75° was slow and so the reactions were heterogeneous. Maleic anhydride and the appropriately substituted acetanilides were detected by the appearance of the peaks corresponding to these materials in the nmr spectra of the reaction mixtures. The acetanilides were isolated from the reactions of **1a–d** with acetic anhydride alone. Maleic anhydride was isolated from the dehydration of **1b** in the presence of acetic anhydride alone. The reaction mixture was treated with cyclopentadiene followed by methanol at reflux and the methyl half-ester of *endo*-norbornene-*cis*-5,6-dicarboxylic acid was obtained as the only acidic product.

The reaction mixtures were analyzed by nmr; these data are summarized in Table III.

TABLE III

PRODUCTS OF THE DEHYDRATION OF N-ARYLMALEAMIC ACIDS IN ACETIC ANHYDRIDE AT 75°

	Conditions		Distribution of products, %		
Compd	M of sodium acetate[a]	Time,[b] min	Isoimide[c]	Isoimide + imide	Maleic anhydride[d]
1a	0.024	3 (10, 245)	88 (90, 43)	87	13
1b	0.024	3 (22, 60)	85 (90, 70)	81	19
1c	0.024	3 (8, 90)	77 (80, 29)	92	8
1d	0.024	3 (16, 45)	57 (48, 15)	95	5
1e	0.024	3 (8, 15)	35 (13, 8)	100	0
1a	0	5	100[e]	19	81
1b	0	5	100[e]	19	81
1c	0	5	100[e]	40	60
1d	0	5	95	72	36
1e	0	5	73	83	17

[a] Solutions containing sodium acetate also contain 1% acetic acid. Solutions without sodium acetate contain about 2% acetic acid. [b] The per cent isoimide was determined at three different times: 3 min (time of total solution of the maleamic acid, a later time). The analysis at 3 min were carried out on the soluble portion of the reaction mixtures. [c] The per cent isoimide in the isoimide–imide product. [d] The amount of acetanilide could not be easily determined from the spectra. [e] Maximum amount of imide as determined by vpc was 10%.

Discussion

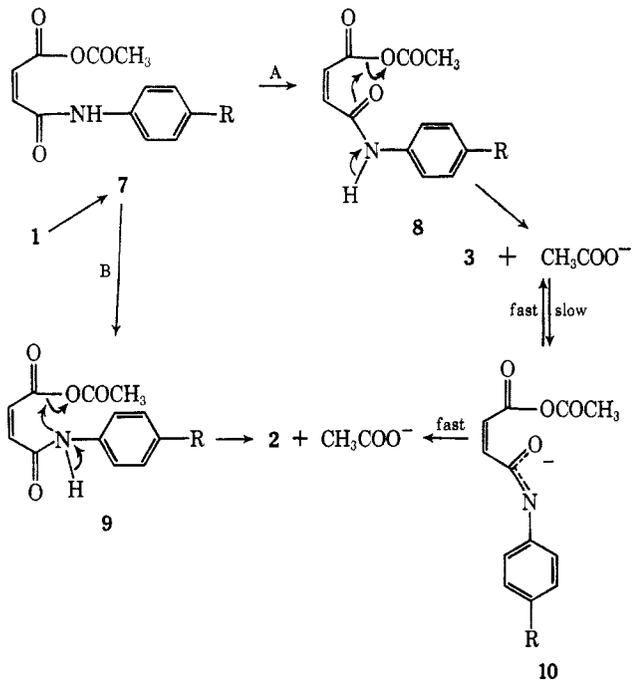
In contrast to the observations of Roderick on the dehydration of **5b**,[5] we have found that dehydrations of N-arylmaleamic acids (**1**) with acetic anhydride alone have given mixtures in which the maleisoimides predominate over the maleimides. In the presence of sodium acetate, more imide was formed initially and the ratio of maleimide to maleisoimide increased with decreasing electron density of the benzene ring. With the dehydration of **1e**, this ratio became greater than one. The rates of the rearrangement of the isoimides to the imides are not high enough to account for all of the imides produced in the presence of sodium acetate at 3 min. The acetic acid produced as the reaction proceeds would be expected to increase the rate of the rearrangement reaction and the possibility of catalysis by the other species present in the reaction cannot be

ruled out. In all the dehydrations reported here it is clear that the imides obtained when the reactions are run for longer periods[1,2] must be substantially derived from the isoimides by rearrangement.

The acetanilides isolated earlier by Kretov and Kul'chitskaya in the dehydrations of N-arylmaleamic acids at high temperatures with acetic anhydride were obtained along with maleic anhydride even at moderate temperatures. This "side reaction" is actually the main reaction in the dehydrations of **1a**, **1b**, and **1c** without sodium acetate.

The following reaction pathways may be suggested to account for these results. The first step in the dehydration reaction may be formation of the acetic acid–maleamic acid mixed anhydride **7**. This species could lose acetic acid in one of two ways (Scheme I). Path A

SCHEME I



involves participation by the neighboring amide carbonyl oxygen to eject acetate ion with simultaneous or subsequent loss of the proton on nitrogen to form the isoimide. Studies on the dehydration of amic acids with dicyclohexylcarbodiimide support a similar mechanism for these reactions,[11] and related mechanisms have been proposed for trifluoroacetic anhydride dehydrations.[5,6] The high ratio of isoimide to imide observed here may be the result of a large contribution to the structure of **7** from the amide dipolar resonance structure.[12] Hedaya, Hinman, and Theodoropulos have proposed that tautomerism of the amide may be involved in reactions leading to high isoimide yields.[6]

Path B involves loss of acetate ion assisted by the attack of nitrogen with simultaneous or subsequent loss of the proton on nitrogen to form the imide **2**.[13] Acetate ion probably hastens the formation of the mixed anhydride and it might aid in the loss of a proton from **8** and **9**.

The mechanism of the acetate-catalyzed isoimide–imide rearrangement reaction proposed previously[4,6] and supported by the kinetic studies of the rearrangement of **6a** to **4a**[8] is further supported by the results of the present work. That attack occurs at the carbonyl carbon seems probable because of the products obtained when isoimides are treated with other nucleophiles.[8,14] That ring closure to imide is not the slow step is supported by the increase in rate observed when R is an electron-withdrawing substituent. It is probable that some of the effect of substitution on the isoimides in the acetate-catalyzed rearrangement is due to stabilization of a transition state in which a considerable amount of negative charge has developed in that portion of the molecule which might be classified as the leaving group. The effect of substitution is similar to that observed in the nucleophile-catalyzed hydrolysis of phenyl esters.[15]

The effect of substitution in the ring attached to nitrogen for the acetate-catalyzed rearrangement of cyclic isoimides is opposite to the effect of substitution in the ring attached to nitrogen for the uncatalyzed rearrangement of acyclic isoimides.[7b] Curtin and Miller have proposed that this thermal reaction proceeds from isoimide to imide through a four-centered cyclic transition state, a route which is denied to the cyclic isoimides.

Maleic anhydride and the acetanilides may be formed directly from **7** by an internal attack of the nitrogen on the acetate carbonyl, but this process would involve a seven-membered ring transition state. It has been suggested that the heptafluorobutyranilide obtained from the reaction of heptafluorobutyric anhydride with N-phenylsuccinamic acid was formed by a similar mechanism.[14b] Alternatively, **7** could undergo a bicyclo[3.2.1] rearrangement analogous to those proposed by Newman and Courduvelis[16] with the formation of **10**. This intermediate could eliminate acetic acid to form isoimide **3** or collapse *via* a four-center mechanism to form acetanilide and maleic anhydride. In the absence of acetate ion, process C might become competitive with processs A and B (Scheme II).

Another possible route to the formation of maleic anhydride and the acetanilides is participation by neighboring carboxyl in loosening the amide carbon–nitrogen bond to the extent that the amine could be captured by acetic anhydride as shown in path D. A similar mechanism has been proposed for the hydrolysis of amides containing a neighboring carboxyl group.[8,17]

Mechanisms which involve starting with imides or isoimides are ruled out by the fact that no maleic anhydride or acetanilides are formed in the simple

(11) R. Paul and A. S. Kende, *J. Amer. Chem. Soc.*, **86**, 4162 (1964).

(12) J. D. Roberts and M. J. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, p 674.

(13) A related experiment on the succinamic–acetic acids mixed anhydride has been reported. The ring closure to imide has a Hammett ρ value of −1.649: R. C. Thamm, Ph.D. Thesis, University of Illinois, 1957; *Dissertation Abstr.*, **17**, 2428 (1957).

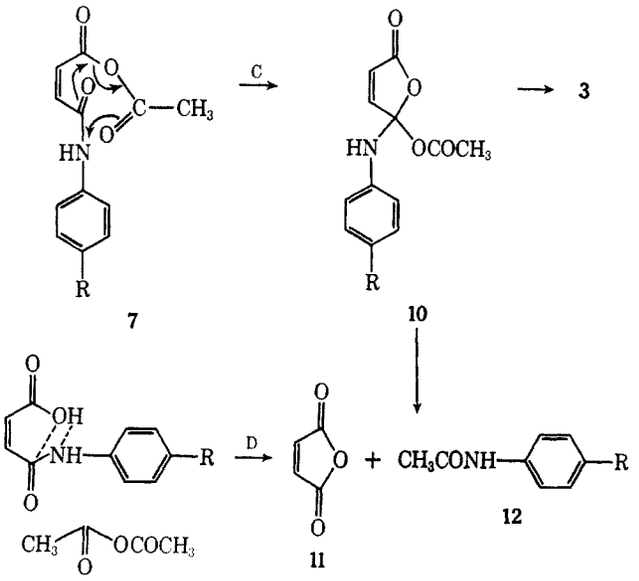
(14) (a) Y. L. Fan and D. F. Pollart, *J. Org. Chem.*, **33**, 4372 (1968); (b) W. R. Roderick and P. L. Bhatia, *ibid.*, **28**, 2018 (1963); (c) C. K. Sauers and R. J. Cotter, U. S. Patent 3,041,376 (1962); *Chem. Abstr.*, **58**, 4432(1963); (d) C. K. Sauers and R. J. Cotter, U. S. Patent 3,023,240 (1962); *Chem. Abstr.*, **57**, 11,100 (1962).

(15) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966, p 21.

(16) M. S. Newman and C. Courduvelis, *J. Amer. Chem. Soc.*, **88**, 781 (1966).

(17) (a) M. L. Bender, F. Chloupek, and M. C. Neveu, *ibid.*, **80**, 5380 (1958); (b) G. Dahlgren and N. L. Simmerman, *J. Phys. Chem.*, **69**, 3626 (1965); (c) H. Morawetz and J. Shafer, *J. Amer. Chem. Soc.*, **84**, 3783 (1962).

SCHEME II



rearrangement reactions. The present data do not permit a choice between paths C and D.[18]

Experimental Section

The microanalyses were performed by George Robertson, Florham Park, N. J. Melting points are uncorrected. Nuclear magnetic resonance spectra were obtained with a Varian A-60A spectrometer.

Maleisoimides.—The maleisoimides were prepared from the corresponding maleamic acids by dehydration with N,N′-dicyclohexylcarbodiimide.[4,19] Two maleisoimides were new compounds, **3d** and **3e**. N-*p*-Chlorophenylmaleisoimide (**3d**) was obtained in 90% yield by the dehydration of N-*p*-chlorophenylmaleamic acid with N,N′-dicyclohexylcarbodiimide. The product crystallized as yellow plates from ether, mp 96–98°. *Anal.* Calcd for $C_{10}H_6NO_2Cl$: C, 57.85; H, 2.91; N, 6.75. Found: C, 57.68; H, 2.88; N, 6.48. N-*p*-Acetylphenylmaleisoimide (**3e**) was obtained similarly in 75% yield. Pale yellow crystals isolated from ether–dichloromethane had mp 120.5–123°. *Anal.* Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.17. Found: C, 66.70; H, 4.34.

Rearrangement of N-Arylmaleisoimides to N-Arylmaleimides. Kinetic Studies.—Reagent grade acetic anhydride was distilled before use. A large forerun was discarded, then the fraction boiling at 136–138° was collected. Solutions of reagent grade fused sodium acetate and/or acetic acid were prepared from this material. The weighed maleisoimides were dissolved at room temperature in these solutions. The solutions were transferred to ten to twelve nuclear magnetic resonance tubes, capped with pressure caps, and placed in a constant-temperature bath. One tube was removed within 1 min and the time recorded as time zero. Subsequent tubes were removed until the reaction had proceeded to 70–90% conversion. After removal from the bath and before analysis the tubes were stored at 0°. Analysis was carried out by running the nuclear magnetic resonance spectra on an expanded scale (250–100-cps sweep width) followed by integration of the spectra. The value for the integral (average of two or more determinations of the integral) of the maleimide olefinic peaks was halved and the integral for the upfield maleisoimide olefinic peaks was recorded as read. The per cent isoimide was calculated from the following formula.

$$\% \text{ isoimide} = \frac{\text{isoimide upfield olefinic integral} \times 100}{\frac{1}{2}\text{ maleimide olefinic integral} + \text{isoimide upfield olefinic integral}}$$

This method gave good agreement (within 2%) in analyses of known N-*p*-tolylmaleisoimide-N-*p*-tolylmaleimide mixtures from 100 to 40% isoimide but was not so accurate below 40% isoimide or with the other isoimide–imide mixtures. It was possible to calibrate the method using solutions of known compositions for each isoimide–imide pair and thus to obtain a corrected per cent isoimide. When this was done the corrected per cent isoimide agreed with the weight per cent isoimide within 3%. First-order rate constants were calculated by computer using the integrated form of the rate equation and the method of least squares. The data presented in Table II are average values for k of two or more duplicate runs. Sodium acetate solutions made with acetic anhydride containing 1% acetic acid produced the same rate constants as those made from freshly distilled acetic anhydride with a prolonged reflux time to effect solution. Sodium acetate occasionally crystallized from the solutions on standing which indicates that the solutions are supersaturated at room temperature. It was necessary to warm the solutions, cool them to room temperature, and then remove the required amount of acetic anhydride containing the sodium acetate by pipet. Errors in concentration probably resulted from this procedure.

Product Studies.—The nuclear magnetic resonance tubes from a kinetic run were returned to the bath for 7–10 half-lives. The solutions were cooled, poured into saturated aqueous sodium bicarbonate solution, and stirred until the acetic anhydride had hydrolyzed. The maleimides were isolated by filtration, dried, and weighed. The yields were above 90% and the nuclear magnetic spectra of the acetic anhydride solutions corresponded to those of the authentic *para*-substituted N-phenylmaleimides.

Dehydrations of N-Arylmaleamic Acids. Composition of Products.—Samples of the maleamic acids (**1a–e**, 0.5 g) were added to 5 ml of prewarmed solutions of 0.024 *M* sodium acetate in acetic anhydride. These were placed in a bath at 75°. The yellow supernatant liquids were drawn off and analyzed by nmr at 3 min, at the time of total solution, and at later times. The relative amounts of the components of the mixture were estimated from the integrals of the olefinic peaks for maleic anhydride (at δ 7.19 relative to tetramethylsilane), the olefinic integrals for the maleimides, and the upfield maleisoimide olefinic peaks. The calibration used in the kinetic runs was used to calculate the isoimide–imide ratio. The reaction was repeated with acetic anhydride containing about 2% acetic acid. After 5 min the supernatant liquids were removed and analyzed. When freshly distilled acetic anhydride was used the reaction was very slow because of the low solubility of the acids, and the per cent of maleic anhydride formed from **1a**, **1b**, and **1c** was lower than when acetic acid was present. Some rearrangement of isoimide to imide occurred on vpc columns. This method was used to detect imide in the acetic anhydride alone dehydrations of **1a**, **1b**, and **1c**. The maximum amount of imide observed was 10%. The column used was 3% SE-30 on Aeropack 30 at 190°.

Isolation of Products. *p*-Methoxyacetanilide.—Maleamic acid **1a** (2 g) was added to 5 ml of acetic anhydride and the mixture contained in a test tube was heated in a boiling-water bath for 30 min. The nmr of the mixture indicated a large amount of maleic anhydride as well as the acetanilide and the isoimide. The reaction mixture was cooled and poured into saturated aqueous sodium bicarbonate solution to remove acetic anhydride. The crude product was recrystallized from water yielding 1.1 g (73%) of crystals, mp 124–126.5°. A mixture melting point with authentic[20] *p*-methoxyacetanilide was 126.5–128° (lit.[21] mp 127°).

***p*-Methylacetanilide and N-*p*-Tolylmaleisoimide.**—*p*-Methylacetanilide was isolated from the dehydration of **1b** at 100° followed by treatment of the reaction mixture with aqueous sodium

(18) Tracer studies would differentiate between paths C and the other mechanisms since only in C is one of the oxygens in the maleic anhydride derived from the solvent. We hope to do these experiments.

(19) Attempts to prepare N-*p*-nitrophenylmaleisoimide by the above method gave complex mixtures of products. The nuclear magnetic resonance spectrum of the mixture indicated some isoimide was present. Dehydration of the amic acid with ethyl chloroformate and triethylamine[4] produced the imide. Attempts to prepare the isoimide (which has been obtained previously by dehydration of the amic acid with trifluoroacetic anhydride[14b]) were discontinued when it became evident that its rearrangement rate would probably be too fast for convenient measurement.

(20) The authentic acetanilides were prepared following the directions in R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1964, p 259.

(21) M. Frankel and S. Patai, "Tables for Identification of Organic Compounds," 2nd ed, The Chemical Rubber Publishing Co., Cleveland, Ohio, 1964.

hydroxide solution. The yield after recrystallization from water was 76% crystals having mp 143–147°, mmp 144–147° (lit.[21] mp 147°). In another run the crude product was chromatographed in cyclohexane–benzene on Florisil. N-*p*-tolylmaleisoimide (5%) was isolated having mp 70–72° (lit.[14b] mp 74°).

N-Phenylmaleimide, N-Phenylmaleisoimide, and Acetanilide.—The dehydration reaction of **1c** was carried out as described above. The crude product was dissolved in benzene and the solution was dried with magnesium sulfate. The dried benzene solution was chromatographed on Florisil and 12% N-phenylmaleisoimide and 11% N-phenylmaleimide were isolated. Nmr indicated that each compound was contaminated with about 10% of the other. Later fractions gave 35% acetanilide, mp 112–114°, mmp 112–115° (lit.[21] mp 114°).

N-*p*-Chlorophenylmaleimide and *p*-Chloroacetanilide.—The reaction was run as above and the crude mixture was poured into saturated sodium bicarbonate solution. The precipitate formed was dried in air and chromatographed on Florisil with cyclohexane–benzene to yield 33% N-*p*-chlorophenylmaleimide [mp 107–109°, mmp 107–109° (lit.[2] mp 108–110°)] and in a later fraction 37% *p*-chloroacetanilide, mp 176–177° (lit.[21] mp 179°).

N-*p*-Acetylmaleimide.—In a similar manner 40% N-*p*-acetylmaleimide was obtained, mp 152–155° (lit.[22] mp 151°).

***endo*-Norbornene-*cis*-5,6-dicarboxylic Acid Monomethyl Ester.**—A third run of the dehydration reaction of **1b** in acetic anhydride alone was treated with excess cyclopentadiene.[23] After the exothermic reaction had subsided, an equal volume of methanol was added and the solution was heated at reflux for 2 hr. The solvents were removed by distillation and the residue was poured into water and extracted with ether. The ether extracts were combined and extracted with saturated sodium bicarbonate solution. The aqueous solution was acidified with concentrated hydrochloric acid to pH 3 and extracted with ether. After drying (magnesium sulfate) the ether was removed by evaporation. The residue, a clear colorless oil, solidified on standing to a white solid, mp 79–82° (lit.[24] mp for *endo*-norbornene-*cis*-5,6-dicarboxylic acid monomethyl ester, 76–78.5°). The nmr was identical with that of an authentic sample.

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Registry No.—**2a**, 1081-17-0; **2b**, 1631-28-3; **2c**, 941-69-5; **2d**, 1631-29-4; **2e**, 1082-85-5; **3a**, 19990-24-0; **3b**, 19990-25-1; **3c**, 19990-26-2; **3d**, 19990-27-3; **3e**, 19990-28-4; acetic anhydride, 108-24-7.

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Stereochemistry of Microbiological Hydroxylation. II. Oxygenation of 1-Benzoylalkylpiperidines

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The microorganism *Sporotrichum sulfurescens* has been found to oxygenate a series of 1-benzoylalkylpiperidines. Oxygenation of 1-benzoyl-4-*n*-propylpiperidine (**2**) gives 1-benzoyl-4-(2-oxo)propylpiperidine (**3**); of 1-benzoyl-4-methylpiperidine (**4**) gives 1-benzoyl-4-hydroxymethylpiperidine (**5**) and 1-benzoyl-4-methyl-4-piperidinol (**6**); of (±)-1-benzoyl-3-methylpiperidine (**7**) gives 1-benzoyl-3-methyl-3-piperidinol (**8**) and (−)-1-benzoyl-3-methyl-4-piperidinol (**9**); of (±)-1-benzoyl-2-methylpiperidine (**12**) gives (2*S*,3*S*)-1-benzoyl-2-methyl-3-piperidinol (**13**), (2*R*,4*S*)-1-benzoyl-2-methyl-4-piperidinol (**14**), and (2*R*-)1-benzoyl-2-methyl-4-piperidinone (**16**); and of 1-benzoyl-*cis*-2,6-dimethylpiperidine (**32**) gives 1-benzoyl-*cis*-2,6-dimethyl-3-piperidinol (**33**). The substrates, 1-benzoyl-2-ethylpiperidine (**19**) and 1-benzoyl-2-*n*-propylpiperidine (**25**), also are oxygenated.

The hydroxylation of organic compounds by microbial enzyme systems is a valuable reaction for the introduction of functionality into a saturated molecule. Of additional interest is the fact that enzymatic reactions, when performed upon the substrate specific to the enzyme, generally are highly stereoselective. Enzymatic reactions upon foreign substrates may also be stereoselective in which case they are particularly valuable in synthesis. Stereoselectivity may be of two types in the case of hydroxylation reactions. First, the introduction of a hydroxyl group in the place of a particular hydrogen atom in the substrate molecule may result in the formation of a single alcohol epimer. As examples, the hydroxylation of steroids usually gives either the α- or the β-hydroxy product rather than a mixture of the two.[1] The second potential result, which is a consequence of the first, is the formation of an optically active product, either through the introduction of asymmetry into the molecule or through resolution of a racemate.[2] Examples in which both hydroxylation and introduction of optical activity occur are few, largely because most substrates used for this reaction have been naturally occurring steroids. Two notable exceptions are the hydroxylation and resolution of a racemic intermediate by the mold *Ophiobolus herpotrichus* in the total synthesis of *d*-aldosterone[3] and of a series of synthetic gonanes by the microorganism *Aspergillus ochraceus*.[4]

We have recently described the microbial hydroxylation of molecules other than steroids by the microorganism *Sporotrichum sulfurescens* in which both the stereospecific introduction of hydroxyl[5] and the intro-

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(2) Resolution may be accomplished upon either the substrate or the product. Resolution of the latter requires further degradation of one enantiomer of the product.

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