Acid-Catalyzed Cyclodehydration of Hydroxyamides. I.[1] δ-Hydroxyamides

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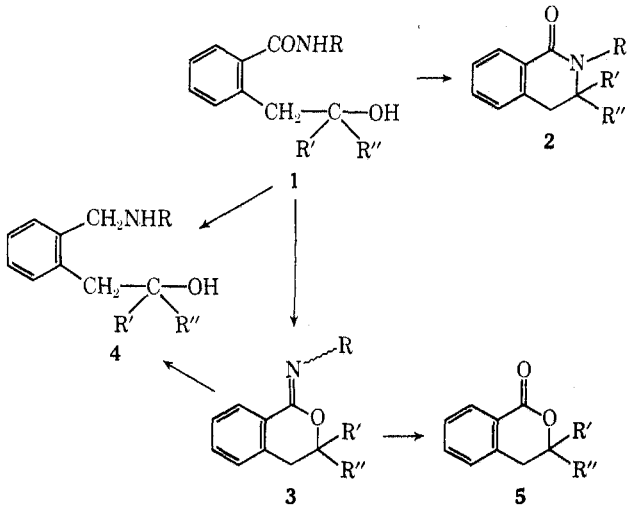
The H_2SO_4-catalyzed cyclodehydration of certain δ-hydroxyamides first described by Hauser, *et al.*,[2] has been reexamined. Most of the products previously described as 3,4-dihydroisocarbostyrils have been found instead to be the isomeric 3,4-dihydro-1*H*-benzopyran-1-imines. The course of the cyclization has been examined as a function of structure and a mechanistic proposal has been advanced.

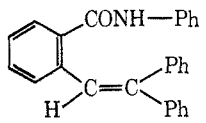
Hauser, *et al.*,[2] have examined the acid-catalyzed cyclization of a number of δ-hydroxyamides and have proposed δ-lactams as the products. The resistance to $LiAlH_4$ reduction[3] of the cyclization product from **1a** and the anomalous reduction product obtained with $LiAlH_4$–$AlCl_3$ led us to reformulate many of the products as imino ethers[1] (Scheme I).

SCHEME I



Compd	R	R′	R″
a	CH_2Ph	CH_3	CH_3
b	CH_3	C_2H_5	C_2H_5
c	CH_3	Ph	H
d	CH_3	Ph	C_2H_5
e	CH_3	Ph	Ph
f	Ph	Ph	H
g	Ph	Ph	Ph

We have repeated the acid-catalyzed cyclization of six of the ten hydroxyamides (**1b–g**) investigated by these workers. Careful examination of the product mixtures revealed that the course of the reaction depended strongly on the structure of the starting hydroxyamide **1**. Treatment of hydroxyamides **1b–e** with cold, concentrated H_2SO_4 led to the formation of the acid-soluble imino ethers as the exclusive **3b** or major **3c–e** products. In addition, **1c–e** gave varying amounts of the acid-insoluble δ-lactams **2c–e**. When **1e** was heated in acetic acid containing a catalytic amount of H_2SO_4 according to a modified procedure,[2] it gave the δ-lactam **2e** in high yield. The hydroxyanilides **1f** and **1g** afforded the corresponding *acid-insoluble* imino ethers **3f** and **3g** accompanied, respectively, by the lactone **5c** and the olefin–amide **6**. In



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the latter case, **6** was the predominant product of the reaction (58% by glc). Table I summarizes the results of these experiments.

TABLE I

CYCLODEHYDRATION OF δ-HYDROXYAMIDES WITH COLD, CONCENTRATED H_2SO_4

δ-Hydroxyamide	Product (% yield)	Mp or bp (mm), °C	Lit.[a] mp or bp (mm), °C
1a	**3a** (80)	160–161 (0.45)	
1b[b]	**3b** (82)	115–116 (0.75)	134 (2.5)
1c[c]	**2c** (8)	116–117	
	3c (92)	164–165 (0.7)	190–192 (?)
1d[b]	**2d** (7)	148–149	
	3d (93)	165–166 (0.85)	182 (1.5)
1e[c]	**2e** (43)	198–199	196–198
	3e (51)	92–93	
1e[c]	**2e** (87)[d]	198–199	196–198
1f[b]	**3f** (83)[e]	105.5–106.5[f]	106–107
	5c (17)[e]	86–87	88.5–89.5[g]
1g[b]	**3g** (35)[e]	130–131.5[f]	124–125
	6 (58)[e]	151–152[f]	
	Unknown (7)[e]		

[a] Unless otherwise noted, for products obtained in ref 2. [b] Prepared according to ref 2. [c] Prepared according to R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964). [d] Acetic acid–sulfuric acid at reflux, modified procedure of ref 2. [e] Glc analysis of product mixture. [f] % yield by chromatography: **3f**, 45; **3g**, 24; **6**, 21. [g] See footnote *c*.

Treatment of the imino ethers **3b–g** with refluxing 3 *N* HCl led, again depending on the structure of the starting material, to a variety of products (Table II).

It remained for us to demonstrate that the authentic δ-lactams **2a–g** were inert to refluxing, dilute HCl. In order to do this, we first synthesized the missing **2a** and **2b** by an unambiguous route. Additionally, to confirm our structural assignment, we prepared **2c** from the known[4] 3,4-dihydroisocarbostyril (**8c**). When the homologous isocyanates, **7a** and **7b**,[5] were stirred at 50° with polyphosphoric acid, the corresponding lactams were produced in poor yield, albeit sufficient for our

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(1) A preliminary report of these findings has been published: D. M. Bailey and C. G. De Grazia, *Tetrahedron Lett.*, **9**, 633 (1970).

(2) C. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 83 (1969).

(3) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960), observed similar results on the attempted lithium aluminum hydride reduction of *N*-benzylphthalanimines.

(4) T. C. Aschner, U. S. Patent 2,647,902 (1953).

(5) Les Laboratoires Français de Chimiotherapie, British Patent 613,111 (1948).

TABLE II

HYDROLYSIS OF IMINO ETHERS IN REFLUXING 3 *N* HCl

Imino ether	Reflux period, hr	Products	Isolated yield, % (glc analysis, %)
3a	24	**5a**[a]	80
3b	19	**5b**	76
3c	3[b]	**2c**	(13)
		5c[c]	57 (70)
		Unknown	(17)
3d	3	**2d**	44 (78)
		5d	5 (6)
		Unknown	(16)
3e	17	**2e**	100
3f	15	**5c**[c]	82 (100)
3g	4	**6**	78 (100)

[a] G. Berti, *Ann. Chim. (Rome)*, **50**, 669 (1960). [b] The HCl salt precipitates from the reaction mixture and slowly redissolves. [c] Table I, footnote *c*.

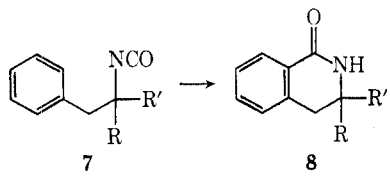
TABLE III

SPECTRAL PROPERTIES OF IMINO ETHERS AND δ-LACTAMS

Compd		Infrared[a]			Nmr[b]	
Imino ether	δ-Lactam	C=N	C=O	C-O-C		
	2a		1635		N-CH_2-	4.90
3a		1645		1118, 1090	N-CH_2-	4.76
	2b		1635		N-CH_3	3.05
3b		1650		1115, 1090	N-CH_3	3.08
	2c		1640		N-CH_3	3.07
3c		1660		1120, 1092	N-CH_3	3.16
	2d		1635		N-CH_3	3.00
3d		1655		1121, 1098	N-CH_3	3.25
	2e		1635		N-CH_3	2.83
3e		1666		1120, 1090	N-CH_3	3.37
3f		1650		1120, 1080		
3g		1647		1115, 1075		

[a] In cm^{-1} in $CHCl_3$. [b] In ppm from $(CH_3)_4Si$.

purposes. The use of the ethyl carbamates in this reaction resulted in even lower yields.[6] The preparation of **8c** was also attended with difficulty. When **7c** was treated with $AlCl_3$ in nitrobenzene,[4] the lactam was isolated in low yield only as a stable 1:1 molar complex with 1-(1,2-diphenylethyl)urea (derived from **7c**). The complex could be recrystallized from a variety of solvents to give material with a constant melting point. Selective hydrolysis with hot, dilute sulfuric acid gave, after column chromatography, **8c** in 64% yield. The



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a, R = R′ = CH_3
b, R = R′ = C_2H_5
c, R = H; R′ = Ph

lactam was accompanied by a 63% yield of *trans*-stilbene, derived from the acid-catalyzed decomposition of the complexed urea.[7] The same complex was produced by cooling an isopropyl acetate solution of equimolar quantities of **8c** and 1-(1,2-diphenylethyl)urea. Each of the lactams **8a–c** was converted to the sodium salt (NaH–DMF) and alkylated with the appropriate alkyl halide. The methylated product from **8c** was identical in all respects with **2c** obtained in the cyclodehydration experiments above.

Hauser, *et al.*,[2] cite infrared "carbonyl" absorptions and nmr data as support for their assigned structures. A comparison of the spectral properties of isomeric compounds (Table III) indicates that these values are not diagnostic while the C–O–C stretching frequencies are characteristic only of the imino ethers.

We have concluded from the relative positions of the *N*-methyl signals in the lactams and imino ethers that the latter compounds exist exclusively in the configuration in which the *N*-methyl group is anti to the fused ring. In the lactams, **2b** and **2c** show little difference in the position of the methyl signal while the upfield shift of this resonance in **2d** and **2e** is indicative of increased shielding. Traversing the same series of substituents in the imino ether series **3b–e** produces a continuously increasing downfield shift typical of deshielding. Of further interest is the comparison of series pairs, *i.e.*, **2b** and **3b**, **2c** and **3c**, etc; substituents which produce the greatest shielding in the lactams also produce the greatest deshielding in the imino ethers. An examination of Dreiding stereomodels shows little possibility for interaction of the 3-phenyl groups and the *N*-methyl in the syn configuration while in the anti configuration the methyl group is favorably oriented to experience the observed deshielding.[8]

Each of the δ-lactams, **2a–e**, was subjected to refluxing 3 *N* HCl for periods of time equal to those used to hydrolyze the isomeric imino ethers (Table II). In all cases, the recovery of the starting lactam was essentially quantitative. A comparison of these results with those shown in Table II clearly supports the imino ether structures for the major products of cyclodehydration in strong acid. In contrast to our initial reduction of imino ether **3b**, lactam **2b** was smoothly converted by $LiAlH_4$–$AlCl_3$ to 3,3-diethyl-1,2,3,4-tetrahydro-2-methylisoquinoline.

In a discussion of the mechanism of this type of cyclization, Hauser, *et al.*,[2] suggested the intermediacy of dications. What we consider to be the possible modes of decomposition of δ-hydroxyamides are outlined in Scheme II.

This mechanism can best be defined by contrasting reactions involving **1e** using different acid strengths. In weakly acidic medium (HOAc–H_2SO_4), this hydroxyamide gave exclusively lactam **2e** which can arise in this medium only from monocation **13**.[9] In concentrated sulfuric acid, however, comparable quantities of imino ether and lactam were realized.

It seems logical, based on the approximately equal basicities of the amide and alcohol functions,[10] that two monocations, **9** and **13**, can exist in solution. Proto-

(6) Mixed success had attended the cyclizations of phenethyl isocyanates and carbamates: see W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, Wiley, New York, N. Y., 1951, Chapter 2; G. Berti, *Gazz. Chim. Ital.*, **90**, 559 (1960); S. Karady, *J. Org. Chem.*, **27**, 3720 (1962); reference 4.

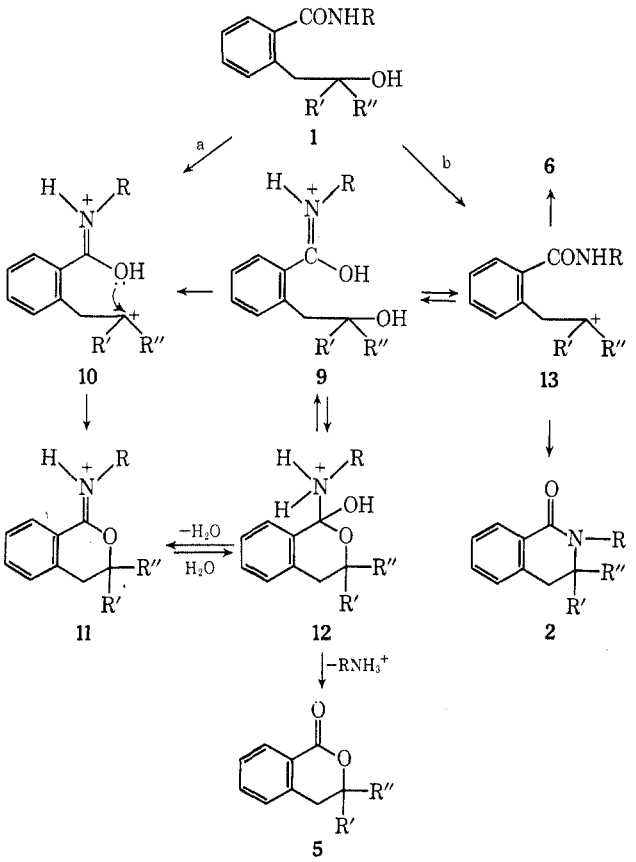
(7) (a) For an investigation of the acid-catalyzed *N*-alkyl cleavage of amides, see A. G. Mohan and R. T. Conley, *J. Org. Chem.*, **34**, 3259 (1969), and references cited therein. (b) Acid-catalyzed *N*-alkyl cleavage of certain thioureas has been reported: G. V. Nair, *Indian J. Chem.*, **4**, 516 (1966).

(8) For a discussion of shielding effects, see J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 74 ff.

(9) Compound **13** can also arise by heterolytic cleavage of **11**, *vide post*.

(10) For a comparative table, see J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 219 ff.

SCHEME II



nation of **9** to dication **10** or intramolecular cyclization to **12** can precede formation of the imino ether **11** while **13** can cyclize to **2** or lose a proton to give **6** (as in the case of **1g**).

The relative abundance of **9** and **13** depends on the stabilization afforded by the groups (R′, R″): (Ph, Ph) ≫ (Ph, C_2H_5) ∼ (Ph, H) > (C_2H_5, C_2H_5). Thus, as these groups are better able to stabilize the carbonium ion, the "apparent basicity" of the OH function increases with the concomitant increase in the concentration of the form **13**. Where R′ and R″ are alkyl, as in **1a** and **1b**, only products of route a are observed. In **1c** and **1d**, where some stabilization of the carbonium ion is afforded by the α-aryl group, small quantities of lactams are isolated (route b). The lactam **2** can reenter the equilibrium in sulfuric acid only when the resulting heterolysis product **13** is highly stabilized. Thus, when **2e** was subjected to the conditions of the cyclodehydration, a mixture resulted consisting of 52% recovered lactam and 10.6% imino ether **3e**. The 3,3-dialkyllactam **2b**, on the other hand, was quantitatively recovered from sulfuric acid. Since Mohan and Conley[7a] have shown that *N*-benzoyl-α-methyl-α-butylbenzylamine undergoes 97% *N*-alkyl cleavage when treated with polyphosphoric acid at room temperature for 1 hr, it seems likely that the results with **2b** are a consequence of rapid intramolecular C–N recombination of fragments rather than the absence of C–N heterolysis.

Support for the thesis that **13** should give rise to lactam is provided by Mohan and Conley[7a] who have demonstrated the C–N recombination of carbonium ion and amide fragments obtained in acid-catalyzed heterolysis reactions, by Schäfer[11] who intramolecularly trapped carbonium ions with the N atom of amides, and by Prajsner[12] whose work supports the reversibility of Ritter-type reactions.

An aspect of the present work not encountered in the above studies is the effect of the N substituent on the relative nucleophilicities of O and N in the amide moiety. Reduced nucleophilicity of nitrogen[13] in the *N*-phenyl cases **1f** and **1g** results in the total absence of lactams in the cyclodehydration reaction mixtures of these materials.[14] Instead, there is produced imino ether and lactone (route a) in the former case and imino ether (route a) and olefin–amide (route b) in the latter.

Further confirmation of the importance of charge stabilization is afforded by an examination of the dilute acid hydrolysis data in Table II. Heterolysis of **11** is competitive with hydrolysis (to lactone **5**) only where **13** is effectively stabilized by R′ and R″. In the *N*-methyl series this effect can be ranked for (R′, R″) as (Ph, Ph) > (Ph, C_2H_5) ≫ (Ph, H) ≫ (C_2H_5, C_2H_5). Again, the reduced nucleophilicity of nitrogen in the *N*-phenyl examples **3f** and **3g** is sufficient to completely obviate the formation of lactam in favor of **5c** and **6**, respectively.[15]

Conclusions

We have demonstrated that the treatment of δ-hydroxyamides with sulfuric acid produces products whose structures are intimately dependent on substituents present in the starting materials. Contrary to the original assumption,[2] the reaction appears to be more general for the production of imino ethers of the type **3** than for lactams.

Experimental Section

Boiling points are uncorrected. Melting points, uncorrected, were obtained with a Mel-Temp capillary apparatus. Infrared spectra were determined using a Perkin–Elmer Model 257 Grating spectrophotometer. Ultraviolet spectra were measured with a Cary Model 15 recording spectrophotometer. Nuclear magnetic resonance spectra were taken on Varian Associates A-60 and HA-100 spectrometers; spectra were recorded in $CDCl_3$ solution and chemical shifts are reported in δ (parts per million) relative to Me_4Si as internal standard. The mass spectra were obtained on a Jeolco JMS-01SC High Resolution double-focusing mass spectrometer. All gas chromatographic (glc) analyses were performed on a Hewlett–Packard research chromatograph, Model 5751 B, equipped with glass columns packed with 3% OV-17 on 100–120 mesh Gas-Chrom Q and with 3% OV-1 on 100–120 mesh Supelcoport. Purity of products was determined by thin layer chromatography (tlc) with silica gel F-254 precoated on glass plates. Components were located by short wave ultraviolet. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. and Instranal Laboratories, Inc., Rensselaer, N.Y.

2-(β,β-Dimethyl-β-hydroxy)ethyl-*N*-benzylamide (1a).—This δ-hydroxyamide was obtained by adopting the general conditions employed by Hauser.[2] To a stirred solution of 0.1 mol of

(11) H. Schäfer, *Justus Liebigs Ann. Chem.*, **729**, 234 (1969).

(12) B. Prajsner, *Zesz. Nauk. Politech. Slask. Chem.*, **24**, 241 (1964).

(13) *Cf.* R. Huisgen and H. Brade, *Chem. Ber.*, **90**, 1432 (1957), who report that N substituents have less effect on the basicities of amides than on those of the corresponding amines.

(14) Steric hindrance has been ruled out on the basis of the observation that *N* phenyllactams *are* produced in the lower homologous series (see following paper).

(15) With the lower homolog (see following paper) where increased carbonium ion stabilization can be afforded by an additional aryl group, small amounts of lactam are formed during cyclodehydration. Additionally, significant amounts of lactam are formed during hydrolysis of imino ether. These observations suggest that the present results are *not* a result of steric hindrance about the N atom.

N-benzyl-*o*-toluamide in THF (200 ml) cooled in an ice bath was added, under N_2, 0.2 mol of *n*-BuLi in hexane. After stirring for 30 min, the red solution was assumed to contain 0.1 mol of dilithioamide. To this solution was added Me_2CO (0.1 mol) in THF (80 ml). The reaction mixture was stirred for 30 min and then poured onto ice-cooled H_2O (1000 ml). The solid was removed by filtration and the two layers of the filtrate were separated. The organic layer was combined with two Et_2O extracts of the aqueous layer, and the solvent was removed. The residue was combined with the original solid and recrystallized from EtOH–Et_2O in 45% yield: mp 126–127°; ir ($CHCl_3$) 3610 (OH), 3450 (NH), 3290, and 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.18 (s, 6, CH_3), 2.87 (s, 2, $ArCH_2C$), 4.55 (d, 2, $ArCH_2N$, collapses with D_2O), 5.08 (s, 1, OH), and 7.41 (m, 10, ArH and NH).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.12; H, 7.47; N, 4.86.

Cyclodehydration of δ-Hydroxyamides with Concentrated H_2SO_4.—In Table I are the summarized results. The modified procedure of Hauser, *et al.*,[2] was employed.

The δ-hydroxyamide (**1a–e**) was dissolved during 1 hr in cold, concentrated H_2SO_4. After 1 hr, the reaction mixture was poured onto crushed ice and diluted with H_2O. Neutral product, if any, was removed by extraction with Et_2O, purified, and identified. The aqueous portion was made alkaline with 35% NaOH. The imino ether was taken up in Et_2O, isolated, and purified by distillation or by crystallization.

***N*-Benzyl-3,4-dihydro-3,3-dimethyl-1*H*-2-benzopyran-1-imine (3a)** was analyzed: uv λ_{max}^{EtOH} 246 mμ (ε 13,170) and 288 sh (1190); nmr ($CDCl_3$) δ 1.31 (s, 6, CH_3), 2.88 (s, 2, $ArCH_2C$), 4.76 (s, 2, $ArCH_2N$), and 7.41 (m, 9, ArH); mass spectrum *m/e* 265 (parent ion).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.48; H, 7.27; N, 5.14.

***N*-Methyl-3,3-diethyl-3,4-dihydro-1*H*-2-benzopyran-1-imine (3b)** was analyzed: uv λ_{max}^{EtOH} 245 mμ (ε 11,130) and 289 (797); nmr ($CDCl_3$) δ 0.85 (t, 6, CH_2CH_3), 1.62 (m, 4, CH_2CH_3), 2.78 (s, 2, $ArCH_2C$), 3.08 (s, 3, NCH_3), and 6.67–8.33 (m, 4, ArH); mass spectrum *m/e* 217 (parent ion).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.74; H, 8.87; N, 6.26.

3,4-Dihydro-2-methyl-3-phenylisocarbostyril (2c) was analyzed: uv λ_{max}^{EtOH} 227 mμ sh (ε 8745), 234 sh (8396), 250 sh (6661), 278 sh (1586), and 287 sh (1110); nmr ($CDCl_3$) δ 2.97, 3.60 (2 q, 2, J_{AB} = 15.5 Hz, $ArCH_2C$), 3.07 (s, 3, NCH_3), 4.73 (q, 1, J_{AC} = 3.2 Hz, J_{BC} = 6.5 Hz, ArCHN), and 6.70–8.20 (m, 9, ArH); mass spectrum *m/e* 237 (parent ion).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.08; H, 6.40; N, 5.85.

***N*-Methyl-3,4-dihydro-3-phenyl-1*H*-2-benzopyran-1-imine (3c)** was analyzed: uv λ_{max}^{EtOH} 245 mμ (ε 11,530) and 287 (861); nmr ($CDCl_3$) δ 2.70–3.40 (m, 2, J_{AB} = 16.0 Hz, $ArCH_2C$), 3.16 (s, 3, NCH_3), 5.15 (q, 1, J_{AC} = 6.0 Hz, J_{BC} = 9.0 Hz, ArCHO–), and 6.90–8.30 (m, 9, ArH); mass spectrum *m/e* 237 (parent ion).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.73; H, 6.59; N, 6.10.

3-Ethyl-3,4-dihydro-2-methyl-3-phenylisocarbostyril (2d) was analyzed: uv λ_{max}^{EtOH} 235 mμ sh (ε 8199), 251 sh (6611), 263 sh (4567), 280 sh (1555), and 288 sh (1109); nmr ($CDCl_3$) δ 1.03 (t, 3, CH_2CH_3), 1.70–2.50 (m, 2, CH_2CH_3), 3.00 (s, 3, NCH_3), 3.15, 3.36 (AB pattern, 2, J_{AB} = 16.5 Hz, $ArCH_2C$), and 6.70–8.20 (m, 9, ArH); mass spectrum *m/e* 265 (parent ion).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.21; H, 7.26; N, 5.08.

***N*-Methyl-3-ethyl-3,4-dihydro-3-phenyl-1*H*-2-benzopyran-1-imine (3d)** was analyzed: uv λ_{max}^{EtOH} 247 mμ (ε 11,160), 282 sh (1284), and 290 (8875); nmr ($CDCl_3$) δ 0.77 (t, 3, CH_2CH_3), 1.70–2.20 (m, 2, CH_2CH_3), 3.25 (s, 2, $ArCH_2C$), 3.30 (s, 3, NCH_3), and 6.85–8.20 (m, 9, ArH); mass spectrum *m/e* 265 (parent ion).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.49; H, 7.48; N, 5.43.

3,4-Dihydro-3,3-diphenyl-2-methylisocarbostyril[2] (2e) was analyzed: uv λ_{max}^{EtOH} 237 mμ sh (ε 8962), 252 (7415), 265 sh (4717), 280 sh (1717), and 290 sh (1018); nmr ($CDCl_3$) δ 2.83 (s, 3, NCH_3), 3.75 (s, 2, $ArCH_2C$), and 6.67–8.17 (m, 14, ArH); mass spectrum *m/e* 313 (parent ion).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.56; H, 6.07; N, 4.48.

***N*-Methyl-3,4-dihydro-3,3-diphenyl-1*H*-2-benzopyran-1-imine (3e)** was analyzed: uv λ_{max}^{EtOH} 247 mμ (ε 10,520), 282 sh (1421), and 290 (982); nmr ($CDCl_3$) δ 3.37 (s, 3, NCH_3), 3.63 (s, 2, $ArCH_2C$), and 6.92–8.08 (m, 14, ArH); mass spectrum *m/e* 313 (parent ion).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.28; H, 6.08; N, 4.29.

In the case of δ-hydroxyanilide **1f**, the H_2SO_4 reaction mixture when poured onto an ice–H_2O mixture gave a precipitate which was isolated by several extractions with $CHCl_3$. The product mixture was separated by column chromatography on silica gel using hexane–*i*-$PrNH_2$ (97:3) as eluent. Pure imino ether (**3f**) was obtained from 95% EtOH.

***N*-Phenyl-3,4-dihydro-3-phenyl-1*H*-2-benzopyran-1-imine (3f)** was analyzed: uv λ_{max}^{EtOH} 246 mμ (ε 13,980) and 293 (8270); nmr ($CDCl_3$) δ 3.08 (m, 2, $ArCH_2C$), 5.25 (m, 1, J_{AC} = 6.0 Hz, J_{BC} = 8.5 Hz, ArCHO–), and 6.67–8.50 (m, 14, ArH); mass spectrum *m/e* 299 (parent ion).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.12; H, 5.80; N, 4.53.

Similarly, δ-hydroxyanilide **1g** gave a wax like residue which was separated by column chromatography on silica gel using PhH as eluent. The pure components, **3g** and **6**, were crystallized from 95% EtOH.

***N*-Phenyl-3,4-dihydro-3,3-diphenyl-1*H*-2-benzopyran-1-imine (3g)** was analyzed: uv λ_{max}^{EtOH} 251 mμ (ε 10,800) and 293 (5217); nmr ($CDCl_3$) δ 3.70 (s, 2, $ArCH_2C$) and 6.67–8.33 (m, 19, ArH); mass spectrum *m/e* 375 (parent ion).

Anal. Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.13; H, 5.68; N, 3.60.

In a subsequent preparation, some of **3g** was isolated as the hydrogen sulfate salt, mp 123–125° dec.

Anal. Calcd for $C_{27}H_{23}NO_5S$: C, 68.48; H, 4.89; N, 2.96; S, 6.77. Found: C, 68.26; H, 4.78; N, 2.90; S, 6.89.

***o*-(2,2-Diphenylvinyl)-*N*-phenylbenzamide (6)** was analyzed: ir ($CHCl_3$) 3420 (NH) and 1675 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.90–7.80 (m, 21, NH, CH=C, ArH); mass spectrum *m/e* 375 (parent ion).

Anal. Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.08; H, 5.79; N, 3.57.

2-(Benzylaminomethyl)-α,α-dimethylphenethyl Alcohol (4a).

A. Reduction of 3a to 4a.—To a suspension of $LiAlH_4$ (1.52 g, 0.04 mol) in Et_2O (20 ml) was added dropwise a solution of $AlCl_3$ (5.32 g, 0.04 mol) in Et_2O (40 ml). After 15 min, a solution of **3a** (5.3 g, 0.02 mol) in THF (20 ml) was introduced at a rate such as to produce gentle reflux. The reaction mixture was stirred and refluxed for 4 hr. After cooling, H_2O (40 ml) and 10% NaOH (50 ml) were added. The mixture was transferred to a separatory funnel, and after removing the organic layer, the aqueous portion was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried, and removed (rotary evaporator) to give a semisolid (4.7 g). The crude residue was triturated with hexane to furnish a colorless solid which after two recrystallizations from hexane afforded 2.7 g (50%) of the amino alcohol (**4a**): mp 76–78°; ir ($CHCl_3$) 3300 (NH/OH) and 3160–3140 cm^{-1} (intramolecular hydrogen bonding); nmr ($CDCl_3$) δ 1.25 (s, 6, CH_3), 2.85 (s, 2, $ArCH_2C$), 3.70, 3.80 (2 s, 4, $ArCH_2N$), 4.07 (broad, 2, OH and NH, exchanged with D_2O), and 7.00–7.50 (m, 9, ArH); mass spectrum *m/e* 269 (parent ion).

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.16; H, 8.39; N, 5.20.

B. Reduction of 1a to 4a.—By the same procedure described above, **1a** (0.5 g, 1.8 mmol, mp 126–127°) was reduced to give 2-(benzylaminomethyl)-α,α-dimethylphenethyl alcohol (0.13 g, 27%), mp 75–77°. This substance was characterized by identical ir and mixture melting point with those of an authentic sample prepared above.

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.28; H, 8.39; N, 5.21.

α,α-Diethyl-2-(methylaminomethyl)phenethyl Alcohol (4b).—This reaction was effected by employing $LiAlH_4$–$AlCl_3$ as described above. Imino ether **3b** [2.17 g, 0.01 mol, bp 115–116° (0.75 mm)] was reduced in 17 hr to **4b** which was obtained as colorless crystals (0.95 g, 43%) from hexane: mp 76–77°; ir ($CHCl_3$) 3310 (NH–OH) and 3180–3100 cm^{-1} (intramolecular hydrogen bonding); nmr ($CDCl_3$) δ 0.67–1.25 (m, 6, CH_2CH_3), 1.25–1.75 (m, 4, CH_2CH_3), 2.43 (s, 3, NCH_3), 2.82 (s, 2, $ArCH_2C$), 3.67 (s, 2, $ArCH_2N$), and 7.17 (m, 4, ArH); mass spectrum *m/e* 221 (parent ion).

Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.31; H, 10.78; N, 6.25.

Hydrolysis of Imino Ethers in Refluxing 3 *N* HCl.—Hydrolysis products, refluxing period, and yields are given in Table II.

A. 3,3-Diethyl-3,4-dihydroisocumarin (5b) was analyzed: bp 125–126° (0.01 mm); ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.92 (t, 6, CH_2CH_3), 1.67 (m, 4, CH_2CH_3), 2.97 (s, 2, $ArCH_2C$), and 7.00–8.33 (m, 4, ArH).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.34; H, 7.95.

B. 3-Ethyl-3,4-dihydro-3-phenylisocumarin (5d) was recrystallized from EtOAc–hexane: mp 94–95°; ir ($CHCl_3$) 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.85 (t, 3, CH_2CH_3), 1.98 (q, 2, CH_2CH_3), 3.45 (s, 2, $ArCH_2C$), and 6.83–8.17 (m, 9, ArH).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.10; H, 6.43.

C. When imino ether **3c** was treated with 3 *N* HCl prior to refluxing, a precipitate identified as the HCl salt was obtained. Crystallization from EtOH–Et_2O gave colorless fluffy needles, mp 157–158°.

Anal. Calcd for $C_{16}H_{16}NOCl$: C, 70.20; H, 5.89; N, 5.12; Cl, 12.95. Found: C, 70.16; H, 5.89; N, 5.23; Cl, 13.19.

D. The product mixture obtained from **3d** was separated by column chromatography over silica gel using PhH–EtOAc (19:1).

Treatment of 3e with Glacial HOAc–H_2SO_4.—Imino ether **3e** (0.1 g, 0.32 mmol, mp 93–94°) was dissolved in glacial HOAc containing a trace of concentrated H_2SO_4; the solution was refluxed for 20 min. After cooling, the solution was diluted with H_2O (25 ml) and the resulting white precipitate was collected. Crystallization from MeCN gave 3,4-dihydro-3,3-diphenyl-2-methylisocarbostyril (**2e**), mp 197–199°, characterized by indentical ir, melting point, and mixture melting point with those of an authentic sample prepared previously.

3,3-Diethyl-3,4-dihydroisocarbostyril (8b).—In a 1-l., three-necked flask provided with a mechanical stirrer, water condenser topped with a $CaCl_2$ drying tube, and thermometer to measure the internal temperature was placed polyphosphoric acid (PPA) (350 g) and crude isocyanate[5] **7b** (21 g). The mixture was stirred at room temperature whereupon a brown viscous mass formed. During 1 hr, the temperature of the reaction mixture rose to 50° due to mechanical heating. After cooling, the mixture was poured into crushed ice (1500 g), stirred, and extracted three times with $CHCl_3$. The combined extracts were washed with H_2O, dried, and removed under reduced pressure to give a semisolid (10.3 g). Trituration of the residue with $CHCl_3$–Et_2O furnished a pale yellow solid, which after one recrystallization from $CHCl_3$–Et_2O afforded off-white crystals (6.7 g, 33%), characterized as **8b**: mp 162–163°; ir ($CHCl_3$) 3400 (NH) and 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.67–1.17 (m, 6, CH_2CH_3), 1.33–1.92 (m, 4, CH_2CH_3), 2.90 (s, 2, $ArCH_2C$), 6.85 (broad, 1, NH), 7.00–7.58 (m, 3, ArH), and 8.00 (m, 1, ArH); mass spectrum *m/e* 203 (parent ion) and abundant ion at *m/e* 174.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.80; H, 8.57; N, 6.81.

3,4-Dihydro-3,3-dimethylisocarbostyril (8a).—The above procedure was employed on crude isocyanate[5] **7a** (6.0 g) to yield 0.61 g (10%) of **8a**, obtained as pale yellow crystals from Et_2O: mp 146–147°; ir ($CHCl_3$) 3395 (NH) and 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.30 (s, 6, CH_3), 2.88 (s, 2, $ArCH_2C$), and 7.00–8.17 (m, 5, ArH and NH).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.36; H, 7.42; N, 7.94.

2-Benzyl-3,4-dihydro-3,3-dimethylisocarbostyril (2a).—To a suspension of NaH (0.68 g, 0.028 mol) in DMF (10 ml) was introduced dropwise a solution of **8a** (0.25 g, 1.4 mmol, mp 146–147°) in DMF (10 ml). After 2 hr at 60°, the Na salt suspension was treated during 10 min with a solution of benzyl bromide (0.5 ml) in DMF (10 ml). The mixture was stirred and heated at 70° for 2 hr. Upon cooling, the excess NaH was destroyed with H_2O and the mixture poured into ice H_2O (200 ml). The resultant cloudy suspension was extracted thrice with $CHCl_3$ which was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed over silica gel using Et_2O–C_6H_{14} (1:1) to yield a solid which, after recrystallization from hexane, afforded colorless plates (0.12 g, 32.5%), identified as **2a**: mp 132–133°; uv λ_{max}^{EtOH} 232 mμ (ϵ 10,120), 253 (7325), 263 sh (5445), 280 sh (2011), and 289 sh (1416); nmr ($CDCl_3$) δ 1.30 (s, 6, CH_3), 3.00 (s, 2, $ArCH_2C$), 4.90 (s, 2, $ArCH_2N$), and 7.00–8.30 (m, 9, ArH); mass spectrum *m/e* 265 (parent ion).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.19; H, 7.26; N, 5.13.

3,3-Diethyl-3,4-dihydro-2-methylisocarbostyril (2b).—The general procedure employed above was followed. The Na salt obtained from **8b** (3.6 g, 0.018 mol, mp 162–163°) was treated with a solution of MeI (5 ml) in DMF (15 ml). After 2 hr at 40°, the mixture, after work-up, gave a semisolid. Crystallization of the crude product from Et_2O–C_6H_{14} afforded off-white crystals (2.2 g, 55%) characterized as **2b**: mp 53–54°; uv λ_{max}^{EtOH} 230 mμ (ϵ 8143), 235 sh (7945), 253 (6058), 263 sh (4498), 281 sh (1718), and 290 sh (1291); nmr ($CDCl_3$) δ 0.85 (m, 6, CH_2CH_3), 1.67 (m, 4, CH_2CH_3), 2.95 (s, 2, $ArCH_2C$), 3.05 (s, 3, NCH_3), and 7.33–8.08 (m, 4, ArH); mass spectrum *m/e* 217 (parent ion).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.32; H, 8.97; N, 6.32.

3,4-Dihydro-3-phenylisocarbostyril (8c).—Following the published procedure,[4] the isocyanate **7c** (18.8 g, 0.0845 mol) was added dropwise to a stirred mixture of $PhNO_2$ (150 ml) and $AlCl_3$ (28 g), and the resulting mixture was stirred at 75 ± 2° for 2.5 hr. The mixture was cooled, poured onto ice, and extracted with $CHCl_3$. The organic solution was washed with H_2O and 5% NaOH and the $CHCl_3$ and $PhNO_2$ were distilled off under reduced pressure. Trituration of the residual black gum (17.4 g) with PhH gave 3.5 g of crude complex. Recrystallization from 35 ml of PhH gave 3.3 g (17%) of the pure complex as fine needles: mp 141–143°; recrystallized from MeCN (87% recovery), mp 143–145°; recrystallized from *i*-PrOAc (90% recovery), mp 143–145°; ir ($CHCl_3$) 3510, 3400 (NH) and 1670 cm^{-1} (broad C=O).

Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 77.72; H, 6.31; N, 9.07. Found: C, 77.82, 78.07, 77.64; H, 6.33, 6.43, 6.32; N, 9.02, 8.93, 8.92.

A 1.66-g (3.6 mmol) sample of the complex was dissolved in 20 ml of 50% aqueous HOAc containing 4 ml of H_2SO_4 and the mixture was stirred and refluxed for 5 hr. The cooled mixture was diluted with PhH and H_2O and the organic phase was washed with H_2O and dried ($MgSO_4$). The residue (1.0 g) on evaporation of the solvent was chromatographed on 20 g of silica gel. *trans*-stilbene (0.41 g, 63%) was eluted with 75 ml of PhH. The lactam **8c** (0.51 g, 64%) was eluted with EtOAc: mp 127–129° (recrystallized from MeCN, mp 128.5–129.5°); ir (Nujol) 3460 (sharp, NH), 3320, 3160 (broad, bonded NH), and 1660 cm^{-1} (broad, C=O).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.56; H, 5.99; N, 6.05.

Preparation of the Urea–Lactam Complex.—1-(1,2-Diphenylethyl)urea was prepared from **7c** and dry NH_3 in PhH: mp 104–106° (*i*-PrOAc–C_6H_{14}); ir ($CHCl_3$) 3510, 3410 (NH), and 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.14; H, 6.66; N, 11.74.

A solution of 9.6 mg (0.04 mmol) of the above and 8.9 mg (0.04 mmol) of **8c** in 0.20 ml of boiling *i*-PrOAc was cooled in ice to precipitate the complex. The supernatant liquid was drawn off with a capillary and the residue was dried. It amounted to 15.4 mg (83.2%), mp and mmp (with material obtained above) 143–145°. The ir spectra of the two materials were identical.

3,4-Dihydro-2-methyl-3-phenylisocarbostyril (2c).—A solution of **8c** (0.51 g, 2.3 mmol) in 3.0 ml of DMF was treated portionwise with a large excess (0.175 g, 4 mmol) of 57% NaH in oil and the resulting mixture of Na salt was stirred for 15 min. Methyl iodide (0.25 ml, 0.56 g, 4 mmol) was added followed, after 30 min, by H_2O to precipitate the product as a fine solid. The material was filtered off, washed with H_2O and pentane and crystallized from *i*-PrOAc–C_6H_{14}. The product thus obtained (0.28 g, 52%) had mp 115–116°. A mixture melting point with material from the cyclodehydration of **1c** (mp 116–117°) gave mmp 115–117°. Solution ir spectra of the two materials were superimposable.

Reduction of 2b to 3,3-diethyl-1,2,3,4-tetrahydro-2-methylisoquinoline.—By the same procedure described previously, the δ-lactam **2b** (1.08 g, 5.0 mmol, mp 53–54°) was reduced using excess reagent (0.01 mol of $LiAlH_4$ and 0.01 mol of $AlCl_3$ in 35 ml Et_2O). After 2 hr at gentle reflux, work-up afforded 0.68 g (68%) of 3,3-diethyl-1,2,3,4-tetrahydro-2-methylisoquinoline:

nmr ($CDCl_3$) δ 0.88 (m, 6, CH_2CH_3), 1.50 (m, 4, CH_2CH_3), 2.33 (s, 3, NCH_3), 2.63 (broad s, 2, $ArCH_2C$), 3.85 (broad s, 2, $ArCH_2N$), and 7.07 (m, 4, ArH); mass spectrum *m/e* 203 (parent ion).

The cyclohexanesulfamate salt of 3,3-diethyl-1,2,3,4-tetrahydro-2-methylisoquinoline was prepared and recrystallized from Me_2CO–*i*-PrOAc, mp 132–133°.

Anal. Calcd for $C_{20}H_{34}N_2O_3S$: C, 62.79; H, 8.96; N, 7.32; S, 8.38. Found: C, 62.69; H, 8.93; N, 7.20; S, 8.52.

Registry No.—**1a**, 26322-39-4; **2a**, 26278-47-7; **2b**, 21868-91-7; **2c**, 21868-89-3; **2d**, 21868-90-6; **2e**, 20141-85-9; **3a**, 26278-52-4; **3b**, 26278-53-5; **3c**, 26278-54-6; **3c** HCl, 26278-55-7; **3d**, 26278-56-8; **3e**, 26278-57-9; **3f**, 26278-58-0; **3g**, 26278-59-1; **4a**, 26278-60-4; **4b**, 26278-61-5; **5b**, 26278-62-6; **5d**, 26278-63-7; **6**, 24097-54-9; **8a**, 26278-65-9; **8b**, 26278-66-0; **8c**, 26278-74-0; 1-(1,2-diphenylethyl)-urea, 26278-75-1; 3,3-diethyl-1,2,3,4-tetrahydro-2-methylisoquinoline, 26278-76-2; 3,3-diethyl-1,2,3,4-tetrahydro-2-methylisoquinoline cyclohexanesulfamate salt, 26278-77-3.

Acid-Catalyzed Cyclodehydration of Hydroxyamides. II.[1] γ-Hydroxyamides

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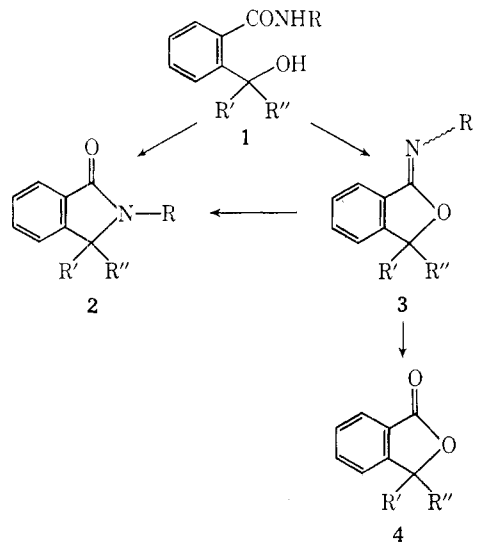
The H_2SO_4-catalyzed cyclodehydration of certain γ-hydroxyamides first described by Hauser, *et al.*,[2a] has been reexamined. The primary products have been found to be N-substituted phthalanimines instead of the isomeric phthalimidines. The course of the cyclization has been examined as a function of structure.

Following an earlier report[2b] on the acid-catalyzed cyclization of δ-hydroxyamides, Hauser, *et al.*,[2a] presented evidence for the formation of phthalimidines by cyclodehydration of γ-hydroxyamides. However, when we repeated the acid-catalyzed cyclizations of **1a–d** (Scheme I), the products were imino ethers which,

SCHEME I



Compd	R	R′	R″
a	CH_3	C_6H_5	H
b	CH_3	C_6H_5	C_6H_5
c	CH_3	$-(CH_2)_5-$	
d	C_6H_5	C_6H_5	C_6H_5

with the exception of **3d**, had physical properties in essential agreement with the "γ-lactams" of Hauser (Table I). The lability of **3d** (giving **2d**, see below) may account for **2d** being the only material isolated by these investigators.

TABLE I

CYCLODEHYDRATION OF γ-HYDROXYAMIDES[a]

γ-Hydroxy-amide	Acid	Product (% yield)	Mp, °C	Lit. mp or bp, °C (mm)[b]
1a	H_2SO_4	**3a** (59)	141.5–143.5	145.5–146.5
1b	H_2SO_4	**3b** (89)[c]	149–150[d]	153–153.5
		2b (11)[c]		
1b	H_2SO_4	**3b**·H_2SO_4 (86)	142–143[e]	128–129
1c	$HClO_4$	**3c**·$HClO_4$ (27)	226–227	
		4c (58)	80–81	81.5–82.5[f]
		3c (91)[g]	61.5–63.0	145 (3)
1d	H_2SO_4	**3d** (89)[c]	131–132[h]	
		2d (10)[c]	187–188[h]	189–190
		4b (1)[c]	118–119[i]	116–117[f]

[a] All reactions were carried out at 0–5°. [b] For products obtained in ref 2a. [c] Glc analysis of total reaction product. [d] Isolated in 53% yield by crystallization. [e] Sealed tube, strongly dependent on rate of heating. [f] W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964). [g] From **3c**·$HClO_4$. [h] Isolated by column chromatography: **3d**, 62%; **2d**, 7%. [i] Prepared for identification according to reference in footnote *f*.

Before we attempted hydrolysis of the imino ethers, we turned to the syntheses of the anticipated products, the phthalimidines **2a–d** and the phthalides **4a–c**. All of the phthalides were known materials, and the products obtained here had physical properties in accord with published values as well as compatible elemental analyses and parent ions in the mass spectra. Of the phthalimidines, **2a**[3] and **2d**[4] had been prepared before. To provide an additional synthesis for **2a**, we subjected the known[5] 3-hydroxy-2-methyl-3-phenylphthalimidine to hydrogenolysis over palladium.[6] The melting point of the product (101.0–102.5°) was in agreement with that of material obtained by heating 3-phenylphthalide with methylamine at 190–200° (105°).[3] The 3,3-di-

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(1) Part I: D. M. Bailey and C. G. De Grazia, *J. Org. Chem.*, **70**, 4088 (1970).

(2) (a) C. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 475 (1969); (b) *ibid.*, **6**, 83 (1969).

(3) W. Theilacker and W. Schmidt, *Justus Liebigs Ann. Chem.*, **597**, 95 (1955).

(4) O. Fischer and E. Hepp, *Chem. Ber.*, **27**, 2790 (1894).

(5) G. Wittig, G. Closs, and F. Mindermann, *Justus Liebigs Ann. Chem.*, **594**, 89 (1955).

(6) *Cf.* N. Sperber and F. E. Roth, *J. Med. Chem.*, **7**, 453 (1964).