Synthesis of Phthalimidines.
Acid-Catalyzed Cyclodehydration versus Cyclodeamination of
γ-Hydroxyamides Obtained from Dilithio-N-substituted Benzamides and Ketones.

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An earlier method of preparation of γ-hydroxyamides from N-substituted benzamides and ketones or aldehydes by means of n-butyllithium was improved and extended. The γ-hydroxyamides were found to undergo cyclodehydration to form γ-lactams with relatively strong acids, but cyclodeamination formed γ-lactones with relatively weak acids; the γ-lactams are substituted phthalimidines. The predominant course of cyclization was dependent also on the structure of the γ-hydroxyamide. Certain γ-hydroxyamides afforded phthalimidines with cold, concentrated sulfuric acid whereas certain others yielded γ-lactones with this acid. The latter γ-hydroxyamides, however, produced phthalimidines with the stronger acid, perchloric acid. The cyclodehydration reaction furnished a convenient and, apparently, quite general method for the synthesis of 2,3,3-trisubstituted or 2,3-disubstituted phthalimidines. Mechanisms are considered.

Condensation at the *ortho*-position of N-methylbenzamide (1a) with ketones or aldehydes have recently been effected by means of n-butyllithium in tetrahydrofuran (THF)-hexane to form γ-hydroxyamides, which readily underwent cyclodeamination to form γ-lactones (1). For example, the intermediate dilithioamide (2a) was condensed with benzophenone to give the γ-hydroxyamide (3a), which was cyclized thermally to afford the γ-lactone (4). We have similarly condensed benzanilide (1b) with benzophenone to yield the γ-hydroxyamide (3b), which was cyclized thermally to produce the γ-lactone (4) (Scheme I).

SCHEME I

1a, R = CH₃
b, R = C₆H₅

2a, R = CH₃
b, R = C₆H₅

1) (C₆H₅)₂CO
2) H₂O

4

3a, R = CH₃
b, R = C₆H₅

More significantly, we have found that such γ-hydroxyamides undergo cyclodehydration with strong acids to form γ-lactams, which are substituted phthalimidines; relatively weak acids produced γ-lactones. Before this new cyclodehydration could be generalized, however, the method of preparation of the γ-hydroxyamides had to be improved, since, of the six such compounds formed previously, only three of them were isolated; the other three γ-hydroxyamides were converted during the reaction or work-up period to corresponding γ-lactones (1).

Preparation of γ-Hydroxyamides. Improved Method.

In the development of a general method, a study was made of the factors that may facilitate lactone formation during preparation of a γ-hydroxyamide; to this end, preparations of γ-hydroxyamides (3a-b) were investigated under various conditions. The dilithiation and condensation steps leading to 3a (see Scheme I) have previously been effected in refluxing THF-hexane (1). These two steps have now been accomplished equally well, and the corresponding two steps leading to 3b much better, at 0° than at the reflux temperature, as reflected in the yields of these products. Therefore, the lower temperature was adopted generally. The manner of neutralization of the reaction mixture and temperature maintained during the subsequent work-up were found to be especially critical, as evidenced by the experiments listed in Table 1. Thus, pure 3a or 3b was obtained when the reaction mixture was added
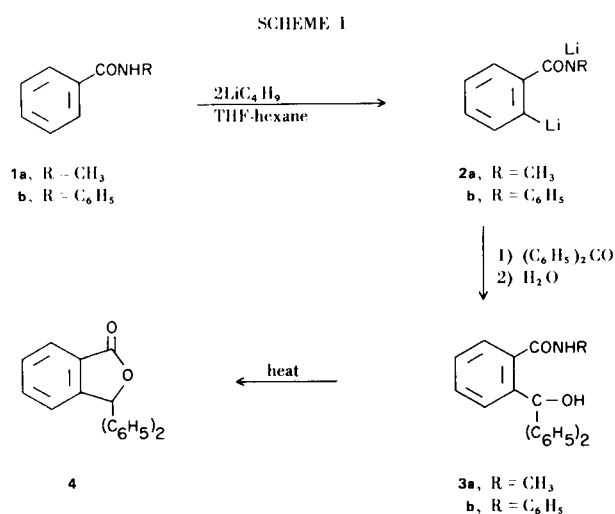
TABLE I

Yields of γ-Hydroxyamides 3a and 3b and Lactone 4 on Neutralization
and Work-up of Appropriate Reaction Mixture Under Various Conditions (a)

| Experiment No.	Mode of Neutralization (b)	Work-up Temperature °C	γ-Hydroxyamide	Yield % (c)	Lactone 4 yield % (d)
1	Inverse (H$_2$O)	0-10	3a	73	0 (e)
2	Inverse (HCl)	0-10	3a	64	0 (e)
3	Inverse (H$_2$O)	0-10	3b	75	0 (e)
4	Inverse (HCl)	0-10	3b	73	0 (e)
5	Direct (H$_2$O) (dropwise)	0-20	3a	30	26
6	Direct (H$_2$O) (dropwise)	0-20	3b	41	31
7	Direct (HCl) (dropwise)	0-20	3a	50	30
8	Direct (HCl) (dropwise)	0-20	3b	65	20
9	Inverse (H$_2$O)	92 (f)	3a	0	77
10	Inverse (HCl)	80-90 (f)	3a	0	66
11	Direct (H$_2$O) (all at once)	0-10	3a	73	0 (e)
12	Direct (H$_2$O) (all at once)	0-10	3b	72	0 (e)

(a) The dilithiation and condensation steps were effected at 0° (see improved procedure in Experimental). (b) Cold water or dilute hydrochloric acid was used. (c) The melting point of the γ-hydroxyamide was the same as that recorded in Table II. (d) The lactone melted at 116-117° (lit. (1) m.p. 116-117°). (e) No lactone was detected by IR in the crude product. (f) Steam bath temperature.

to cold water or dilute hydrochloric acid (inverse neutralization) and the subsequent work-up was performed at 0-10° (Table I, Experiments 1-4), whereas much lactone (4) was produced when cold water or acid was added dropwise to the reaction mixture (direct neutralization) even though the subsequent work-up was performed at low temperature (Experiments 5-8). Moreover, lactone (4) was the sole product isolated when the reaction mixture was neutralized inversely but then heated on the steam bath to remove solvent (Experiments 9, 10). Nevertheless, pure γ-hydroxyamide (3a or 3b) was isolated when cold water was added all at once to the reaction mixture (Experiments 11, 12), as was apparently done in the previous preparation of 3a (1); this procedure, however, might not be satisfactory for much larger scale runs.

The lactone 4 produced by dropwise addition of water or acid presumably arose through preferential protonation at the amido anion of the dilithio salt (5) in the reaction

mixture to form the monolithio salt (6), since the amido anion should be more basic than the oxide anion (2); the salt (6) may undergo cyclization eliminating LiNHR or, more likely, the cyclic salt (7) may be formed as an intermediate, from which the neutral amine is eliminated after neutralization.
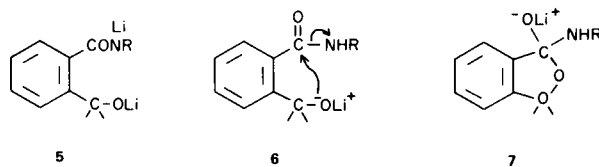
That the cyclodeamination of the γ-hydroxyamide (3a) is base-catalyzed was supported by treatment of a solution of 3a in dimethylformamide (DMF) at 0° with one-half molar equivalent of n-butyllithium in hexane for thirty minutes, after which almost half of the 3a had been

TABLE II

Condensations of N-Substituted Benzamides With Ketones and Benzaldehyde

Amide	Carbonyl Compound	Condensation Temperature, °C	Neutralization Medium (a)	Product	M.p., °C (b)	Yield %
1a	Benzophenone	0	H_2O or HCl	3a	164-165 (dec) (c,d)	73
1b	Benzophenone	0	H_2O or HCl	3b	145-147 (dec) (d,e)	75
1a	Acetophenone	0	H_2O or HCl	8a	158-160 (dec) (d,f)	40
1a	Benzaldehyde	0	H_2O or HCl	8c	128.5-129 (dec) (g)	28 (h)
1a	Propiophenone	-78 (i)	HCl	8b	140-142 (dec) (d)	70
1b	Propiophenone	-78 (i)	HCl	8d	129-133 (dec) (d)	80
1a	Cyclohexanone	0	H_2O	9a	141-144 (dec) (d)	40
1b	Cyclohexanone	0	H_2O	9b	132-134 (dec) (d)	56
1a	Fluorenone	0	H_2O	10a		47 (j)
1b	Fluorenone	0	H_2O	10b		55 (j)

(a) Cold water or dilute hydrochloric acid was used. (b) These melting (decomposition) points were taken with gradual elevation of temperature in the usual manner; higher m.p. (dec.) values may be obtained by raising the temperature more rapidly (see note e). (c) Lit. (1) m.p. 162-163.5°. (d) Recrystallized from acetonitrile. (e) When the temperature was raised rapidly, the sample melted with decomposition at 180-190°. (f) Lit. (1) m.p. 157-159°. (g) Recrystallized from benzene. (h) Some lactone was also obtained. (i) Dry ice-acetone bath temperature. (j) Crude product.

TABLE III

Infrared Spectra and Analyses for γ-Hydroxyamides

γ-Hydroxyamide	Infrared Data (cm^{-1}) OH and/or NH	C=O	Empirical Formula	Calcd. C	H	N	Found C	H	N
3b	3300, 3190	1635	$C_{26}H_{21}NO_2$	82.29	5.58	3.69	82.61	5.58	3.43
8b	3300, 3200	1635	$C_{17}H_{19}NO_2$	75.81	7.11	5.20	76.06	7.26	4.95
8c	3310, 3210	1635	$C_{15}H_{15}NO_2$	74.66	6.27	5.81	74.86	6.18	5.73
8d	3350, 3230	1630	$C_{22}H_{21}NO_2$	79.73	6.39	4.23	79.97	6.50	4.11
9a	3310, 3130	1620	$C_{14}H_{19}NO_2$	72.07	8.21	6.00	72.24	7.94	5.93
9b	3310, 3230	1650	$C_{19}H_{21}NO_2$	77.26	7.17	4.74	77.22	6.76	4.94

converted to the lactone (4); the mono-anion (6) was presumably formed as an intermediate. In contrast, none of the γ-hydroxyamide (3a) underwent cyclodeamination in the absence of the base even at room temperature (see Experimental).

The lactone (4) produced when the reaction mixture was heated on the steam bath, after inverse neutralization with water (Table I, Experiment 9), may have arisen either thermally or by the base-catalyzed mechanism (6 or 7), since lithium hydroxide would then have been present in

equilibrium. The lactone (4) produced in the corresponding experiment with acid may have arisen thermally or by an acid-catalyzed mechanism (see next section).

On the basis of these results, an improved general procedure was adopted in which both the reaction and the work-up periods were carried out at low temperature and the inverse neutralization procedure was employed. Also, the liberated γ-hydroxyamide was removed as soon as feasible from the neutralized reaction mixture; this minimized possible cyclodeamination by the basic and
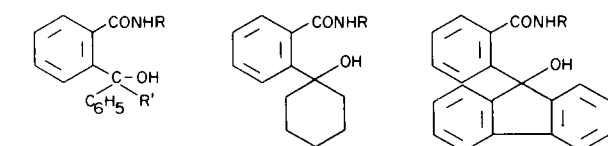
TABLE IV

Acid-Catalyzed Cyclization of γ-Hydroxyamides 3a-b to Form
γ-Lactams and γ-Lactone 4 Under Various Conditions

γ-Hydroxyamide	Acidic Reagent	Reaction Temperature, °C	Reaction Time, hours	γ-Lactam (a)	Yield %	γ-Lactone 4a, Yield %
3a	H_2SO_4	0	2.0	12a	73 (b)	0
3a	H_2SO_4	10-20	1.5	12a	72 (b)	0
3a	H_2SO_4	20-30	1.5	12a	67 (b)	6
3b	H_2SO_4	0	2.0	12b	60	Trace
3a	$HClO_4(c)/DMF(d)$	0	2.0	12a	83	0
3a	BTDA (e)	0	4.0	12a	74	0
3a	CH_3COOH	20-30	3.0	12a	0	86
3b	CH_3COOH	20-30	3.0	12b	0	96
3a	HCl/CH_3COOH	0-20	3.0	12a	0	89
3a	HCl/DMF (d,f)	0-20	1.0	12a	0	88

(a) The product was identified by m.m.p. and IR. (b) Isolated as hydrogen sulfate salt. (see experimental). (c) 70% Perchloric acid was used. (d) Dimethylformamide. (e) Boron trifluoride diacetic acid complex. (f) γ-Hydroxyamide 3a (95-96%) was recovered after standing in DMF solution at 20-30° for 1.5 or 12 hours.

acidic media produced when the neutralization was effected with water and acid, respectively (see above).

The improved method was employed for preparations, not only of γ-hydroxyamides, 3a-b, but also of γ-hydroxyamides 8a-d, 9a-b and 10a-b, which were obtained from condensations of dilithioamide 2a or 2b with the appropriate ketones or benzaldehyde. Although satisfactory analyses for 10a-b were not obtained, these compounds were prepared sufficiently pure for cyclodehydration to give phthalimidines (see next section). γ-Hydroxyamides 8a, 8c, 9a and 10a have previously been formed, but only 8c was then isolated (1).

8a, R = R' = CH₃
b, R = CH₃, R' = C₂H₅
c, R = CH₃, R' = H
d, R = C₆H₅, R' = C₂H₅

9a, R = CH₃
b, R = C₆H₅

10a, R = CH₃
b, R = C₆H₅

The data for the γ-hydroxyamides are summarized in Tables II and III. Table II shows that these products were generally obtained in good yield. They were recrystallized satisfactorily from hot acetonitrile or benzene (see notes d and g. Table II), but not from hot ethanol which

promoted cyclodeamination. Since the melting (decomposition) points were dependent on the rate of elevation of the temperature (see note b, Table II), they are not necessarily reproducible. The structures of the new γ-hydroxyamides were supported by infrared spectra and analyses (see Table III). These spectra showed peaks at 3100 to 3350 cm⁻¹ for the OH and NH functional groups and at 1620 to 1650 cm⁻¹ for carbonyl absorptions.

Acid Catalyzed Cyclodehydration versus Cyclodeamination of γ-Hydroxyamides. Synthesis of Phthalimidines.

Interestingly, the γ-hydroxyamides (3a-b) underwent cyclodehydration with cold, concentrated sulfuric acid to form the γ-lactam salts (11a-b, X = HSO₄) which, on
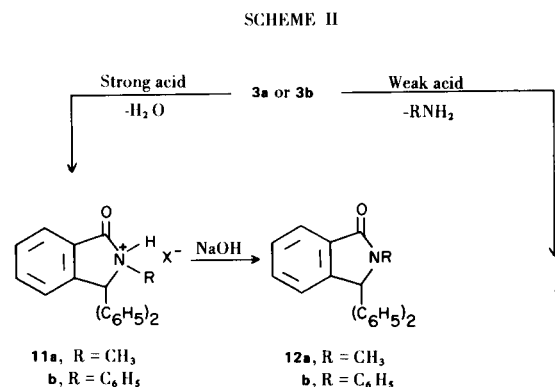
SCHEME II

11a, R = CH₃
b, R = C₆H₅

12a, R = CH₃
b, R = C₆H₅

TABLE V

Cyclodehydration of γ-Hydroxyamides to Form Phthalimidines

γ-Hydroxyamide	Acid Employed	Cyclodehydration Product	Yield %	M.p. or B.p. (mm) °C	Recrystallization Solvent
3a	H_2SO_4	2-Methyl-3,3-diphenyl-phthalimidine (12a)	68	153-153.5	Ethanol
3b	H_2SO_4	2,3,3-Triphenylphthalimidine (12b)	60(a)	189-190(b)	Acetonitrile
8a	H_2SO_4	2,3-Dimethyl-3-phenyl-phthalimidine (19a)	75(a)	165-167(2.5)	
8b	H_2SO_4	2-Methyl-3-ethyl-3-phenyl-phthalimidine (19b)	75(a)	67-69	Hexane
8c	H_2SO_4	2-Methyl-3-phenylphthalimidine (19c)	75(a)	145.5-146.5(c)	Acetonitrile
8d	$HClO_4$	2,3-Diphenyl-3-ethylphthalimidine (19d)	63	225(2)	
9a	$HClO_4$	Spiro[2-Methylphthalimidine-3,1'-Cyclohexane] (21a)	76	145(3)	
9b	$HClO_4$	Spiro[2-Phenylphthalimidine-3,1'-Cyclohexane] (21b)	77	95-97	Aqueous ethanol
10a(d)	$HClO_4$	Spiro[2-Methylphthalimidine-3,9'-fluorene] (23a)	26(e)	141.5-143.5	Ethanol
10b(a)	$HClO_4$	Spiro[2-phenylphthalimidine-3,9'-fluorene] (23b)	37(f)	196-197	Ethanol

(a) Crude product contained a trace of lactone (by IR). (b) Lit. (5) m.p. $190°$. (c) Lit. (6) m.p. $105°$. (d) Crude γ-hydroxyamide was used. (e) Overall yield from amide 1a and fluorenone. (f) Overall yield from amide 1b and fluorenone.

TABLE VI

Infrared Spectra and Analyses for Phthalimidines

Phthalimidine	IR (C=O) cm^{-1}	Empirical Formula	Calcd. C H N			Found C H N		
12a	1700	$C_{21}H_{17}NO$	84.25	5.72	4.68	84.12	5.69	4.47
19a	1710	$C_{16}H_{15}NO$	80.98	6.37	5.90	81.02	6.25	6.01
19b	1705	$C_{17}H_{17}NO$	81.24	6.81	5.56	81.38	6.70	5.26
19c	1710	$C_{15}H_{13}NO$	80.69	5.87	6.27	80.41	5.76	6.32
19d	1690	$C_{22}H_{19}NO$	84.30	6.11	4.47	84.46	6.11	4.23
21a	1700	$C_{14}H_{17}NO$	78.10	7.96	6.51	78.13	7.93	6.24
21b	1680	$C_{19}H_{19}NO$	82.28	6.91	5.05	82.18	6.84	4.84
23a	1700	$C_{21}H_{15}NO$	84.82	5.09	4.71	84.56	5.01	4.46
23b	1680	$C_{26}H_{17}NO$	86.88	4.77	3.90	87.04	4.67	3.73

neutralization, afforded the γ-lactams (12a-b), respectively; however, 3a-b underwent cyclodeamination with acetic acid to give the γ-lactone (4, scheme II) (3). Also, the γ-hydroxyamide (3a) was converted to the γ-lactam (12a) and the lactone (4) by certain other relatively strong and weak acids, respectively (see Table IV).

Of the acids listed in Table IV, sulfuric acid was probably the weakest acid to effect cyclodehydration, and hydrogen chloride in acetic acid or dimethylformamide the strongest acid to effect cyclodeamination; in the two latter cases, the acid would presumably be $CH_3COOH_2^+$ and $HCON(CH_3)_2H^+$, respectively. The BF_3 in the boron trifluo-

ride diacetic acid complex (BTDA) evidently effected the cyclodehydration, not $CH_3COOH_2^+$ which, presumably, was also present (see above).

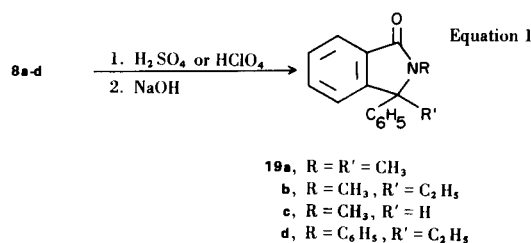That the cyclodeamination of the γ-hydroxyamide (3a) was acid-catalyzed, not merely a thermal reaction was shown by recovery of 3a from dimethylformamide even after standing at higher temperature than that employed in the experimental which produced lactone (4) in the presence of an acid catalyst (see note f, Table IV). Actually, the γ-hydroxyamides were found to be relatively stable in aprotic solvents.

The mechanism of the acid-catalyzed cyclodeamination probably involves protonation of the amide group, either at the amide nitrogen to produce 13 or at the carbonyl oxygen to give 14, followed by cyclization. Since there is evidence for preferential protonation at the carbonyl oxygen of certain other carboxamides (4), 14 may be more likely. In either event, a cyclic intermediate (15) or a protonated form of 15 may be produced which eliminates amine to give the lactone. Also, the mechanism of the thermal cyclodeamination of γ-hydroxyamides may involve intermediate 15 formed through ring-chain tautomerism. The catalytic effect of the acid-catalysis might then be ascribed to promotion of formation of 15 through 14 and/or protonation of the amine nitrogen of 15.

The mechanism of the cyclodehydration would presumably involve protonation of the hydroxy oxygen but, since this hydroxyl group should be less basic than the amide group (2), the mono-cation (16) may be present in only low concentration; cyclization of 16 might involve the indicated concerted process or an intermediate carbonium ion. Another possible mechanism would involve protonation of the hydroxyl oxygen, as well as the amide group, to form the di-cation (17), the cyclization of which might involve the indicated concerted process or the intermediate carbonium ion (18). Indeed, such a mechanism is suggested by the fact that cyclodehydration has been observed only with relatively strong acids (see Table IV). Perhaps cyclodeamination needs to be retarded before cyclodehydration can occur and this may be accomplished through formation of the di-cation, in which the hydroxyl oxygen is no longer a suitable nucleophile. Although the nucleophilicity of the amide nitrogen is also lowered, it may still be sufficient to permit cyclization especially through the carbonium ion (18).
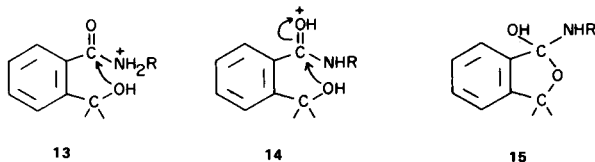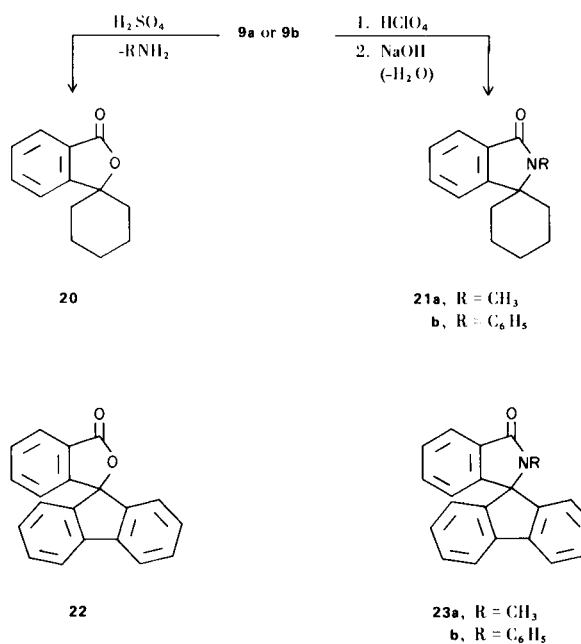

16   17   18
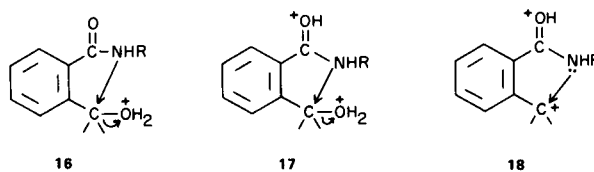
The cyclodehydration type of reaction was extended to other γ-lactams, which are substituted phthalimidines. Thus, besides 12a-b, phthalimidines 19a-c were obtained from γ-hydroxyamides 8a-c by treatment with sulfuric acid, followed by sodium hydroxide; in these cases, the intermediate γ-lactam salt was not isolated (see Equation 1). Although γ-hydroxyamide 8d afforded a mixture of phthalimidine 19d and the corresponding lactone, the phthalimidine 19d was obtained exclusively with the stronger acid, perchloric acid (Equation 1).

8a-d   1. H_2SO_4 or $HClO_4$
          2. NaOH

Equation 1

19a, R = R' = CH$_3$
b, R = CH$_3$, R' = C$_2$H$_5$
c, R = CH$_3$, R' = H
d, R = C$_6$H$_5$, R' = C$_2$H$_5$

Interestingly, the predominant course of cyclization was found to be dependent, not only on the strength of the acid, but also on the structure of the γ-hydroxyamide. This was indicated by the last result mentioned above and

SCHEME III

H_2SO_4
-RNH$_2$ 9a or 9b   1. HClO$_4$
                                          2. NaOH
                                          (-H$_2$O)

20   21a, R = CH$_3$
                                     b, R = C$_6$H$_5$

22   23a, R = CH$_3$
                                     b, R = C$_6$H$_5$

13   14   15

confirmed by reactions of the γ-hydroxyamides **9a-b**, which afforded exclusively the lactone **20** with sulfuric acid, but exclusively phthalimidines **21a-b** with perchloric acid (Scheme III).

Similarly, the crude γ-hydroxyamides **10a-b** yielded the lactone **22** with sulfuric acid but the phthalimidines **23a-b** with perchloric acid. The crude γ-hydroxyamides **10a-b** were employed in these reactions since attempts to purify them resulted in much cyclodeamination to give the lactone **22**.

All of the γ-lactams described above are 2,3,3-trisubstituted phthalimidines except **19c**, which is a 2,3-disubstituted phthalimidine. The 2,3,3-trisubstituted phthalimidines (**21a-b** and **23a-b**) are also spiro type compounds. The data for these products are summarized in Tables V and VI. Table V shows that the yields were generally good. The overall yields from amides **1a** or **1b** with fluorenone are given for phthalimidines **23a-b**, since the intermediate γ-hydroxyamides **10a-b** were not purified. Possibly the overall yields for certain of the other phthalimidines could be improved by employing the crude intermediate γ-hydroxyamide. The structures of the new phthalimidines were supported by infrared spectra and analyses (see Table VI). These spectra showed carbonyl absorptions at 1680 to 1710 cm^{-1}.

Phthalimidine **12b** has previously been prepared in unreported yield by heating the lactone **4** with aniline and hydrochloride at 180° (5). This reaction was apparently effected under pressure, since we observed that heating the γ-hydroxyamide **3b** in aniline at 165-170° afforded the lactone **4** without appreciable further reaction of **4** with the aniline. Phthalimidine **19c** has been previously reported (6) to be formed on heating the corresponding lactone and methylamine at 190-200° in a bomb, but the melting point quoted was 40° lower than that obtained by us.

The present method of synthesis of 2,3,3-trisubstituted or 2,3-disubstituted phthalimidines appears more convenient than, and superior to this earlier method employing a lactone and an amine. Also, the present method seems preferable to another previous process involving a Schiff base and water gas under pressure with cobalt tetracarbonyl dimer as catalyst, which has been employed for synthesis of certain 2,3-disubstituted phthalimidines (7).

EXPERIMENTAL

Melting points and boiling points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium and M-H-W Laboratories, Garden City, Michigan. IR spectra were produced on a Perkin-Elmer Infracord Model 137 and 237. Tetrahydrofuran (THF) was used as freshly distilled from lithium aluminum hydride. n-Butyllithium was obtained from Foote Mineral Company, Exton, Pennsylvania.

Improved Method of Preparation of γ-Hydroxyamides.

This method is a modification and extension of an earlier one that involved condensation of amide **1** with certain ketones (1). The improved, general procedure is described below and the new results are summarized in Tables II and III.

To a stirred solution of 0.025 mole of N-methylbenzamide (**1a**) or benzanilide (**1b**) in 100 ml. of tetrahydrofuran (THF) cooled in an ice bath and kept under nitrogen, was added, over a period of 30 minutes, 0.052 mole of n-butyllithium in hexane. The resulting dark red solution of dilithioamide (**2a** or **2b**) was stirred at 0° or at -78° (dry ice-acetone bath) for 30 minutes longer, and a solution of 0.025 mole of an appropriate ketone or benzaldehyde in 20 ml. of THF was then added. The reaction mixture was stirred for 30 minutes, and then poured into stirred cold water (300 ml.) or cold hydrochloric acid (150 ml., about 3N). The solid was collected by filtration, washed with water and then a small amount ether, and was recrystallized from acetonitrile to give essentially pure γ-hydroxyamide.

In the experiment with benzaldehyde, no precipitate was produced on pouring the reaction mixture into water. The layers of the resulting mixture were separated. The organic layer was combined with an ethereal extract of the aqueous layer, and the solution was dried (magnesium sulfate). The solvent was removed to give 4.2 g. of solid, which was indicated by an infrared spectrum to consist of a mixture of the γ-hydroxyamide **8c** and the corresponding lactone. This mixture was triturated with 10 ml. of benzene. Evaporation of the benzene solution afforded 1.19 g. (23%) of 3-phenylphthalide, m.p. 116-117° (lit. (1) m.p. 114.5-116.5°); IR (potassium bromide) 1750 cm^{-1} (C=O). The remaining solid was recrystallized from benzene to give 1.67 g. (28%) of γ-hydroxyamide **8c**.

Thermal Cyclodeamination of γ-Hydroxyamide (**3b**).

A 1.0 g. sample of γ-hydroxyamide **3b** was heated at 165-170° for 2 hours; then the resulting colorless oil was allowed to cool. The resulting tar was triturated with 10 ml. of ether to produce a white solid; evaporation of the ether solution afforded a somewhat discolored solid. Crystallization of the combined solid (0.69 g.) from hexane-ethanol gave 0.56 g. (74%) of lactone **4** as colorless plates, m.p. and m.m.p. 116-117° (lit. (1) m.p. 116-117°).

A similar reaction was conducted in aniline. The resulting, cooled, reddish brown solution was poured into stirred ice and 2N hydrochloric acid to provide crude lactone **4** (0.75 g.). Crystallization from hexane-ethanol gave 0.59 g. (78%) of lactone **4**, m.m.p. 116-117°.

Cyclodeamination of γ-Hydroxyamide (**3a**) With n-Butyllithium.

To a solution of 3.17 g. (0.01 mole) of γ-hydroxyamide **3a** in 40 ml. of dimethylformamide (DMF) cooled in an ice bath was added 0.005 mole of n-butyllithium in hexane. After 30 minutes, the reaction mixture was poured onto 200 ml. of ice water. The resulting precipitate was collected and washed with water. This crude product (indicated by IR to consist of starting amide **3a** and lactone **4**) was triturated with 50 ml. of benzene. Evaporation of the benzene solution gave 1.0 g. (38%) of lactone **4**, m.m.p. 116-117°. The residue from the trituration was recrystallized from acetonitrile to give 1.8 g. (57%) of γ-hydroxyamide **3a**.

When a solution of 0.01 mole of γ-hydroxyamide **3a** in 50 ml. of DMF was allowed to stand at room temperature (20-30°) for 1.5 or even 12 hours and then poured onto 200 ml. of water, there was recovered 3.0-3.05 g. (95-96%) of **3a**. No lactone **4** was detected (by IR) in the crude product.

Cyclization of γ-Hydroxyamides (**3a-b**) With Various Acids.

In Table IV are summarized the yields of lactone **4** and phthalimidines **12a-b** or hydrogen sulfate salts **11a-b** (X = HSO₄). obtained in these experiments. Procedures with the various acids are described below.

A. With Acetic Acid.

A solution of 1.0 g. of γ-hydroxyamide **3a** or **3b** in 60 ml. of commercial, glacial acetic acid was stirred at room temperature for 3 hours, and then poured onto 200 ml. of cold water. The resulting precipitate was collected, washed with water, and recrystallized from hexane-ethanol to give lactone **4**, m.p. and m.m.p. 116-117°

B. With Hydrogen Chloride in Acetic Acid.

A solution of 1.0 g. of γ-hydroxyamide **3a** in 60 ml. of commercial, glacial acetic acid was cooled in an ice-water bath and saturated with hydrogen chloride gas over a period of 30 minutes. The yellow solution was stirred at 0-20° for 2.5 hours, then worked up as described under A to give lactone **4**. The result was similar when acetic acid was first saturated with hydrogen chloride, and **3a** then dissolved in the acidified medium.

C. With Hydrogen Chloride in Dimethylformamide (DMF).

A solution of 0.5 g. of **3a** in 20 ml. of DMF was cooled in an ice-water bath and then saturated with hydrogen chloride gas over a period of 0.5 hours. The solution was stirred at 0-20° for another 0.5 hour, then worked up as described under A to give lactone **4**. In the absence of hydrochloric acid, **3a** was recovered (see experiment with n-butyllithium).

D. With Sulfuric Acid.

A 1.0 g. sample of **3a** was dissolved in 15 g. of concentrated sulfuric acid at the temperatures indicated in Table IV. After 1.5-2.0 hours, the solution was poured onto 200 g. of crushed ice. The resulting precipitate was collected, washed with benzene, and recrystallized from ethanol-ether to give the hydrogen sulfate salt **11a** (X = HSO₄), m.p. 128-129° (sealed capillary tube); IR (Nujol) 3460 (OH) and 1725 cm⁻¹ (C=O).

Anal. Calcd. for C₂₁H₁₉NO₅S: C, 63.46; H, 4.82; N, 3.53; S, 8.07. Found: C, 62.99; H, 4.80; N, 3.19; S, 7.96.

Similarly, γ-hydroxyamide **3b** was treated with sulfuric acid at 0° to give the hydrogen sulfate salt **11b** (X = HSO₄) contaminated with a little lactone **4** (by IR); IR (Nujol) 3420 (OH) and 1670 cm⁻¹ (C=O).

E. With Perchloric Acid.

A 1.0 g. sample of **3a** was stirred with a mixture of 10 ml. of 70% perchloric acid and 10 ml. of dimethylformamide cooled in an ice bath for 2 hours. The mixture was poured onto 200 g. of crushed ice, and 50 ml. of water was then added. The resulting precipitate was collected, washed with water, and stirred with 100 ml. of 6N sodium hydroxide solution for 1 hour. The solid was collected, washed with water, and recrystallized from acetonitrile to give phthalimidine **12a**, m.p., m.m.p. 152-154°.

F. With Boron Trifluoride Diacetic Acid Complex (BTDA).

A 1.0 g. sample of **3a** was stirred with 10 ml. of BTDA cooled in an ice bath. The solution was stirred at 0° for 4 hours, then poured onto 200 ml. of cold water. The resulting precipitate was collected and stirred with 100 ml. of 6N sodium hydroxide solution to give phthalimidine **12a** (recrystallized from acetonitrile), m.p., m.m.p. 152-154°.

Cyclization of Various γ-Hydroxyamides With Sulfuric and Perchloric Acids.

The results for the phthalimidines are summarized in Tables V and VI; the results for the lactones obtained with sulfuric acid are included under the general procedure for this acid (see below).

A. With Sulfuric Acid.

A 1.0-3.0 g. sample of the γ-hydroxyamide was dissolved, during about 1 hour, in 10-30 ml. of concentrated sulfuric acid cooled in an ice bath. The solution was allowed to stand at this temperature for another 2 hours and then poured onto 200-300 g. of crushed ice and water. The resulting precipitate of the phthalimidine hydrogen sulfate salt was either collected by filtration and then stirred with 6 N sodium hydroxide solution, or directly neutralized with sodium hydroxide solution. The liberated phthalimidine was either collected by filtration and recrystallized or taken up in ether; the ethereal solution was evaporated and the product recrystallized or distilled.

Certain γ-hydroxyamides afforded partly or entirely the corresponding lactones by this procedure. γ-Hydroxyamide **8d** appeared to form a mixture of phthalimidine **19d** and the corresponding lactone was indicated by IR. γ-Hydroxyamides **9a-b** and **10a-b** afforded exclusively lactones **20** and **22**, respectively, in good yield; these lactones were identified by m.m.p. and IR employing authentic samples of the compounds.

B. With Perchloric Acid.

A 1.0-3.0 g. sample of γ-hydroxyamide was treated for 3-4 hours with 30-50 ml. of 70% perchloric acid cooled in an ice bath. The resulting mixture was poured onto 100-200 g. of crushed ice, and 100 ml. of water was then added. The resulting phthalimidine perchlorate salt was collected by filtration and washed thoroughly with water, and then with benzene. The salt was stirred with 100 ml. of 6N sodium hydroxide solution for 30-50 minutes, and the free phthalimidine was either collected by filtration or by extraction with ether, and purified by recrystallization from an appropriate solvent or by distillation.

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