5,6-Dihydro-4*H*-1,3,4-oxadiazines. II. Structural Requirements for Effective Hydrazido–Hydroxyl Interaction[1]

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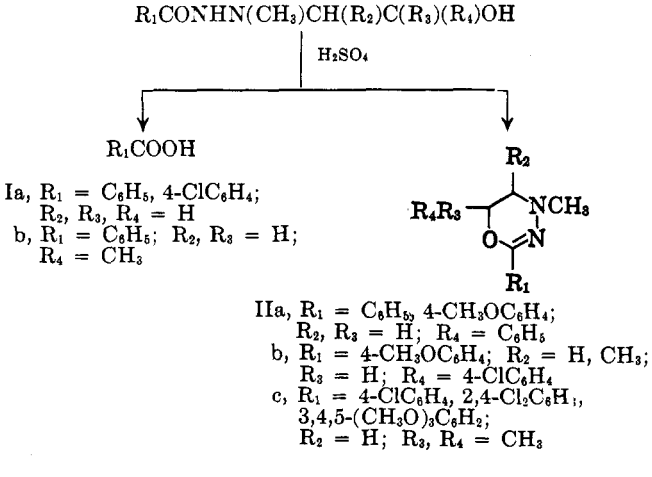
The scope of the sulfuric acid cyclodehydration of 2-(β-hydroxyalkyl) acid hydrazides to 5,6-dihydro-4*H*-1,3,4-oxadiazines has been investigated. The type of acyl and hydroxyl groups necessary for effective neighboring group participation has been determined. A mechanism for the reaction is proposed.

The observation[2] that the sulfuric acid dehydration of certain 2-(β-hydroxyalkyl) acid hydrazides proceeds *via* neighboring group participation with concomitant formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine prompted us to investigate the structural requirements for effective participation of the hydroxyl group and the acyl group. The criterion for an effective neighboring group participation was the formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine.

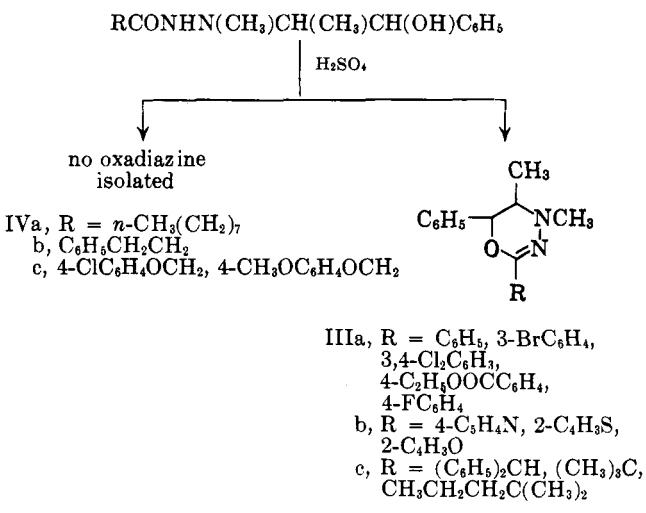
2-(β-Hydroxyalkyl) acid hydrazides, all having the same type of acyl moiety (benzoyl or substituted benzoyl) and differing types of hydroxyl groups, were treated with concentrated sulfuric acid to determine the effect of the hydroxyl type on the course of the reaction. The hydroxyl types selected were primary (Ia), secondary aliphatic (Ib), secondary benzyl (IIa), secondary substituted benzyl (IIb), and tertiary (IIc). When the hydroxyl group is primary or secondary, except the benzyl or substituted benzyl types, hydrolysis of the hydrazide linkage occurs exclusively, and a quantitative yield of the corresponding carboxylic acid is obtained. When the hydroxyl group is secondary benzyl, secondary substituted benzyl, or tertiary, a substituted 5,6-dihydro-4*H*-1,3,4-oxadiazine is obtained. Thus, for effective participation the hydroxyl group of the 2-(β-hydroxyalkyl) acid hydrazide must be the type which yields a relatively stable carbonium ion when treated with concentrated sulfuric acid. (See Scheme I.)

SCHEME I



In order to determine the type of acyl group necessary for effective neighboring group participation, certain 2-(β-hydroxyalkyl) acid hydrazides, all with benzyl type hydroxyl and a variety of different types of acyl moiety, were treated with concentrated sulfuric acid. The acyl types selected were aromatic (IIIa), heterocyclic (IIIb), bulky aliphatic (IIIc), simple aliphatic (IVa), aralkyl (IVb), and aryloxyalkyl (IVc). When the acyl group is aromatic (benzoyl or substituted benzoyl), heterocyclic (2-furoyl, 2-thienoyl, or isonicotinoyl), or bulky aliphatic (benzhydryl or *t*-butyl), concentrated sulfuric acid dehydration yields a substituted 5,6-dihydro-4*H*-1,3,4-oxadiazine. However, when the acyl moiety is simple aliphatic, aralkyl, or aryloxyalkyl, no 5,6-dihydro-4*H*-1,3,4-oxadiazine is obtained. (See Scheme II.)

SCHEME II



Thus, the acyl moiety must be of the type which either renders the hydrazide linkage less susceptible to acid hydrolysis or increases the stability of the 5,6-dihydro-4*H*-1,3,4-oxadiazine in acid solution, or both. An investigation by van Alphen[3] of the stability of substituted 5,6-dihydro-4*H*-1,3,4-oxadiazin-5-ones in hot 0% sulfuric acid indicates that C_6H_5 or $C_6HCH{=}CH$ in the 2-position will prevent acid hydrolysis from occurring, whereas the CH_3–, CH_3CH_2–, $(CH_3)_2CH$–, or $C_6H_5CH_2CH_2$– group in the 2-position allows hydrolysis to occur readily.

We propose that the two main competing reactions in the sulfuric acid treatment of a 2-(β-hydroxyalkyl) acid hydrazide are the acid hydrolysis of the hydrazide linkage (reaction I) and the acid-catalyzed dehydration accompanied by ring closure (reaction II). (See Scheme III).

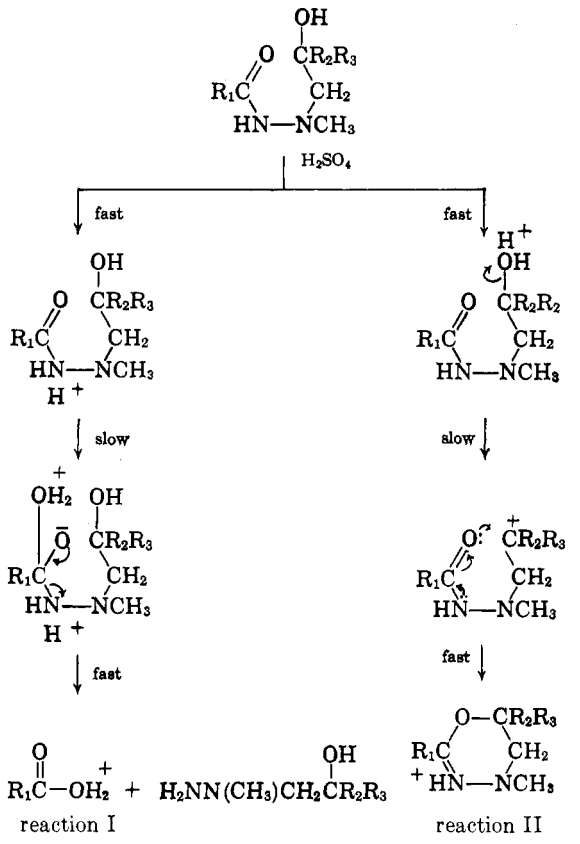
The rate-determining step in the acid hydrolysis of the hydrazide linkage is the slow attack of a water mole-

(1) Presented in part before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(2) D. L. Trepanier, V. Sprancmanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668 (1964).

(3) J. van Alphen, *Rec. trav. chim.*, **48**, 163 (1929); **48**, 417 (1929).

SCHEME III



cule on the carbonyl carbon of the N-protonated hydrazide. By analogy with amides, substituents exert only weak polar effects, but strong steric effects.[4] Thus, bulky R_1 groups would greatly retard acid hydrolysis of the hydrazide linkage.

The rate-determining step in the cyclodehydration reaction is the dissociation of the protonated alcohol into a neutral water molecule and a carbonium ion. The rate depends upon the stability of the carbonium ion formed. The more stable carbonium ions, such as tertiary and benzyl, form faster because electron releasing groups tend to disperse the partial positive charge which develops on carbon, and in this way lower the activation energy and accelerate the formation of those ions.[5]

Our experimental results indicate that reaction II predominates and a 5,6-dihydro-4*H*-1,3,4-oxadiazine is obtained whenever both the acyl moiety and the hydroxyl group are of a favorable type; that is, the acyl moiety is bulky and retards significantly the rate of hydrolysis of the hydrazide linkage, and the hydroxyl group is the type (either tertiary or benzyl) that accelerates the rate of carbonium ion formation. Although both the type of acyl moiety and the type of hydroxyl group influence the course of the reaction, the influence of the different types of hydroxyl groups is more pronounced, for either the 5,6-dihydro-4*H*-1,3,4-oxadiazine or a quantitative yield of the corresponding carboxylic acid is isolated.

The influence of the acyl group on the course of the reaction is not so clearly defined as is the influence of the hydroxyl group. This is probably true because the difference in bulkiness and consequential steric retardation of reaction I of the acyl groups examined is not markedly different but rather is a difference of degree only. If a 5,6-dihydro-4*H*-1,3,4-oxadiazine was obtained, the acyl moiety was designated as the type that participated; if a 5,6-dihydro-4*H*-1,3,4-oxadiazine was not obtained, the acyl moiety was classified as the type that does not effectively participate in this neighboring group reaction.

The identity of the reaction products in the cases where neither a 5,6-dihydro-4*H*-1,3,4-oxadiazine nor a carboxylic acid was obtained was not established; however, the experimental data indicated the probable course of the reaction. For example, the treatment of N-(*p*-methoxyphenoxyacetylamino)-*l*-ephedrine hydrochloride with concentrated sulfuric acid (see Experimental section) gave only an insignificant amount of product, indicating that hydrolysis of the hydrazide linkage had occurred.

The necessary 2-(β-hydroxyalkyl) acid hydrazides, listed in Table I, were prepared by N-acylation of appropriate hydrazino alcohols with acid chlorides. The hydrazino alcohols were synthesized either by N-nitrosation of amino alcohols followed by reduction, or by the opening of epoxides with methylhydrazine.

Acylation of hydrazino alcohols containing a primary hydroxyl group yielded, as the major product, the O,N-diacyl compound.

$$H_2NN(CH_3)CH_2CH_2OH + RCOCl \longrightarrow RCONHN(CH_3)CH_2CH_2OOCR$$

However, the O-acyl moiety could be preferentially removed by mild alkaline hydrolysis.

The sulfuric acid treatment of the 2-(β-hydroxyalkyl) acid hydrazides consisted of their portionwise addition to stirred concentrated sulfuric acid, followed by a standing period of 18 hr. The mixture was poured onto crushed ice and the 5,6-dihydro-4*H*-1,3,4-oxadiazine was removed by chloroform extraction. The 5,6-dihydro-4*H*-1,3,4-oxadiazines synthesized are listed in Table II.

Experimental[6]

The synthesis of N-nitroso-*l*-ephedrine, N-amino-*l*-ephedrine, and 1-methyl-1-(β-hydroxy-β-phenethyl)hydrazine has been reported.[2] The acid chlorides were either purchased or prepared from the appropriate acid by refluxing of the latter with excess thionyl chloride.

2-(β-Hydroxyalkyl) Acid Hydrazides Listed in Table I. General Procedure.—To a stirred solution of 0.5 mole of hydrazino alcohol either in benzene in the absence of a hydrogen chloride acceptor or in methylene chloride in the presence of 0.5 mole of pyridine or triethylamine was added, dropwise, 0.5 mole of acid chloride. The mixture was stirred and refluxed for 6 hr. In the instances in which no hydrogen chloride acceptor was used (compounds 12, 20, 21, 22, and 23), the solid was suction filtered from the cooled mixture and recrystallized. When pyridine or triethylamine was used, the cooled mixture was washed (water, hydrochloric acid, sodium hydroxide, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was either crystallized from an appropriate solvent or, if not readily crystallizable, converted to its hydrochloride using ethereal hydrogen chloride.

5,6-Dihydro-4*H*-1,3,4-oxadiazines Listed in Table II. General Procedure.—The 2-(β-hydroxyalkyl) acid hydrazide (10 g.)

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 786.

(5) R. T. Morrison and R. N. Boyd, "Organic Chemistry," Allyn and Bacon, Inc., Boston, Mass., 1959, p. 120.

(6) The melting points were obtained in a capillary tube with a Thomas–Hoover Uni-Melt apparatus and are corrected. The elemental analyses were done by Midwest Microlab., Inc., Indianapolis, Ind.

TABLE I

2-(β-HYDROXYALKYL) ACID HYDRAZIDES[a]

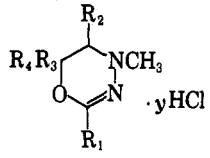
$R_1CONHN(CH_3)CH(R_2)C(R_3)(R_4)OH \cdot yHCl$

No.	R_1	R_2	R_3	R_4	y	M.p., °C.[b]	Yield, %	Recrystn. solvent	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	H	H	C_6H_5	0	145–147	65	EtOH–H_2O	70.83	7.06		71.19	6.82	
2	4-$CH_3OC_6H_4$	H	H	C_6H_5	0	121–123	39	EtOAc	67.98	6.71		68.70	7.06	
3	4-ClC_6H_4	H	CH_3	CH_3	0	118–120	33	*i*-PrOH	56.13	6.68	10.91	56.09	7.04	10.76
4	2,4-$(Cl)_2C_6H_3$	H	CH_3	CH_3	0	104–106	55	EtOAc	49.50	5.54		49.62	5.58	
5	3,4,5-$(CH_3O)_3C_6H_2$	H	CH_3	CH_3	0	148–149	61	EtOAc	57.67	7.74	8.97	57.66	7.80	9.20
6	$(CH_3)_3C$	CH_3	H	C_6H_5	1	195–196 dec.	39	*i*-PrOH	59.88	8.38		60.24	9.42	
7	$CH_3CH_2CH_2C(CH_3)_2$	CH_3	H	C_6H_5	1	179–181 dec.	51	*i*-PrOH	62.09	8.89		62.53	8.97	
8	C_6H_5	CH_3	H	C_6H_5	0	169–170.5	59	*n*-BuOH	72.11	7.10	9.87	71.92	7.37	10.03
9	3-BrC_6H_4	CH_3	H	C_6H_5	1	198–199 dec.	56	*i*-PrOH	51.08	5.04		51.10	5.40	
10	4-$C_2H_5OOCC_6H_4$	CH_3	H	C_6H_5	1	205–207 dec.	29	EtOH	61.14	6.41	7.13	61.33	6.65	7.36
11	4-FC_6H_4	CH_3	H	C_6H_5	0	139–140	54	*i*-PrOH	67.53	6.33		67.72	6.52	
12	4-C_5H_4N	CH_3	H	C_6H_5	0	141–142	23	EtOAc	67.35	6.71		67.48	6.89	
13	2-C_4H_3S	CH_3	H	C_6H_5	0	149–151	56	*i*-PrOH	62.04	6.25		61.94	6.34	
14	2-C_4H_3O	CH_3	H	C_6H_5	1	184–185 dec.	34	EtOH	57.97	6.16		58.55	5.19	
15	$(C_6H_5)_2CH$	CH_3	H	C_6H_5	0	173–174	37	*i*-PrOH	76.97	7.00	7.48	76.97	6.90	7.39
16	n-$CH_3(CH_2)_7$	CH_3	H	C_6H_5	0	138–140	36	EtOAc	59.30	8.45		59.74	8.02	
17	$C_6H_5CH_2CH_2$	CH_3	H	C_6H_5	1	172–173 dec.	48	EtOH	65.40	7.23	8.03	65.46	7.24	7.95
18	4-$ClC_6H_4OCH_2$	CH_3	H	C_6H_5	1	163–164 dec.	29	*i*-PrOH	56.11	5.75		56.07	5.90	
19	4-$CH_3OC_6H_4OCH_2$	CH_3	H	C_6H_5	1	167–168 dec.	41	*i*-PrOH	59.91	6.62		59.71	6.79	

[a] Compounds 1, 8, 13, 14, and 15 reported in ref. 2. [b] See ref. 6.

TABLE II

SUBSTITUTED 5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES[a,b]



No.	R_1	R_2	R_3	R_4	y	M.p., °C.[c]	Yield, %	Recrystn. solvent	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	H	H	C_6H_5	0	73–74	51	*i*-PrOH	76.15	6.39		76.15	6.59	
2	4-$CH_3OC_6H_4$	H	H	C_6H_5	1	163–164 dec.	19	*i*-PrOH	64.05	6.01		64.27	6.18	
3	4-ClC_6H_4	H	CH_3	CH_3	1	185–187	21	*i*-PrOH	52.37	5.86	10.18	52.76	6.12	10.14
4	4-$CH_3OC_6H_4$	CH_3	H	4-ClC_6H_4	0	108–110	61	*i*-PrOH	65.35	5.79		65.35	5.82	
5	2,4-$Cl_2C_6H_4$	H	CH_3	CH_3	1	166–168	53	CH_3OH–ether	46.55	4.88		45.90	5.01	
6	4-$CH_3OC_6H_4$	H	H	4-ClC_6H_4	0	120–122	56	EtOAc	57.80	5.14	7.93	58.89	5.63	7.39
7	3,4,5-$(CH_3O)_3C_6H_2$	H	CH_3	CH_3	0	119–121	27	*i*-PrOH	61.20	7.54	9.52	61.09	6.99	9.81
8	$(CH_3)_3C$	CH_3	H	C_6H_5	1	202–205 dec.	36	EtOAc	63.70	8.20		63.94	8.34	
9	$CH_3CH_2CH_2C(CH_3)_2$	CH_3	H	C_6H_5	1	125–127 dec.	27	CH_3OH–ether	65.68	8.75		65.89	9.23	
10	C_6H_5	CH_3	C_6H_5	H	0	142–143	32	*i*-PrOH	76.66	6.81	10.52	76.41	7.02	10.10
11	3-BrC_6H_4	CH_3	C_6H_5	H	1	224–226 dec.	27	CH_3OH	53.49	4.75		53.31	4.79	
12	4-$C_2H_5OOCC_6H_4$	CH_3	C_6H_5	H	0	127–128	37	*i*-PrOH	70.98	6.55		71.16	6.79	
13	4-FC_6H_4	CH_3	C_6H_5	H	0	57–60	45	*i*-PrOH	71.81	6.03		72.43	6.39	
14	4-C_5H_4N	CH_3	C_6H_5	H	1	240–242 dec.	37	*i*-PrOH	63.26	5.97	13.83	63.22	6.13	13.44
15	2-C_4H_3S	CH_3	C_6H_5	H	0	133–135	70	*i*-PrOH	66.14	5.92	10.29	65.93	6.09	10.38
16	2-C_4H_3O	CH_3	C_6H_5	H	0	141–142	61	*i*-PrOH	70.29	6.29	10.93	70.29	6.51	11.01
17	$(C_6H_5)_2CH$	CH_3	C_6H_5	H	0	133–134	55	*i*-PrOH	80.86	6.79	7.83	80.00	6.70	8.10

[a] Compounds 1, 2, 3, 5, 6, and 7 do not exhibit *cis–trans* isomerism; all other compounds are *trans* isomers. [b] Compounds 1, 10, 16, 17, and 18 reported in ref. 2. [c] See ref. 6.

was added, portionwise, to stirred concentrated sulfuric acid (75 ml.). After standing for 18 hr. at room temperature, the mixture was poured onto crushed ice and extracted with chloroform. The chloroform solution was washed (sodium hydroxide, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was crystallized from an appropriate solvent.

1-Methylhydrazino-*t*-butyl Alcohol.—To 322 g. (7.0 moles) of methylhydrazine and 5 drops of 1 *N* sodium hydroxide solution was added, over a period of 2 hr., 504 g. (7.0 moles) of isobutylene oxide. The mixture was refluxed for 18 hr. and then distilled to yield 734 g. (89%) of product, b.p. 80–84° (13 mm.).

Anal. Calcd. for $C_5H_{13}N_2O$: C, 51.25; H, 11.18; N, 23.91. Found: C, 50.53; H, 11.92; N, 23.44.

β-Methylnitrosaminoethanol.—To a stirred mixture of 375 g. (5.0 moles) of β-methylaminoethanol and 800 g. of crushed ice was added, portionwise, 420 ml. of concentrated hydrochloric acid. To the stirred, slightly acidic mixture (pH 5) was added, portionwise, 450 g. (6.5 moles) of sodium nitrite and simultaneously, dropwise, 110 ml. of concentrated hydrochloric acid. The mixture was stirred at room temperature overnight, saturated with sodium carbonate, and extracted with 2-butanone. The 2-butanone extract was dried (sodium sulfate) and distilled to yield 510 g. (92%), b.p. 149–151° (17 mm.).

Anal. Calcd. for $C_3H_8N_2O_2$: C, 34.61; H, 7.75; N, 26.91. Found: C, 35.15; H, 7.91; N, 26.05.

β-(1-Methylhydrazino)ethanol.—To a stirred suspension of 72 g. (1.9 moles) of lithium aluminum hydride in 800 ml. of tetrahydrofuran was added, dropwise, a solution of 162 g. (1.5 moles) of β-methylnitrosaminoethanol in 500 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 18 hr. The cooled, stirred mixture was treated with 150 ml. of water, dropwise. The mixture was stirred for 1 hr., then suction filtered and washed with isopropyl alcohol. The combined filtrate and washings were distilled under diminished pressure to yield 98 g. (70%), b.p. 87–95° (14 mm.), lit.[7] b.p. 110° (43 mm.).

Anal. Calcd. for $C_3H_{10}N_2O$: C, 39.98; H, 11.18; N, 31.09. Found: C, 40.30; H, 11.05; N, 30.95.

1-(1-Methylhydrazino)-2-propanol.—To refluxing methylhydrazine (320 g.) and 2 drops of 25% sodium hydroxide solution was added, over a period of 3 hr., 378 g. of propylene oxide. The mixture was refluxed for 18 hr. and then distilled to yield 532 g. (78%), b.p. 86–95° (15 mm.).

Anal. Calcd. for $C_4H_{12}N_2O$: C, 46.12; H, 11.62; N, 26.90. Found: C, 46.47; H, 12.00; N, 27.25.

2-Methyl-2-(β-hydroxypropyl)benzoic Acid Hydrazide.—To a stirred mixture of 104 g. (1.0 mole) of 1-(1-methylhydrazino)-2-propanol, 142 ml. (1.0 mole) of triethylamine, and 400 ml. of methylene chloride was added, dropwise, a solution of 141 g. (1.0 mole) of benzoyl chloride in 150 ml. of methylene chloride. The mixture was stirred and refluxed for 18 hr. The cooled mixture was washed (water, sodium carbonate) and evaporated to dryness *in vacuo*. The residual oil was dissolved in 300 ml. of hot ethanol, treated with a solution of 40 g. of sodium hydroxide in 250 ml. of water, and refluxed for 2 hr. Most of the ethanol was evaporated *in vacuo*. The cooled mixture was diluted with 300 ml. of water and extracted with methylene chloride. The methylene chloride extract was washed (water), dried (magnesium sulfate), and evaporated under diminished pressure. The solid residue was recrystallized from ethyl acetate to yield 35 g. (17%), m.p. 111–113°.

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.43; H, 7.74. Found: C, 63.65; H, 8.10.

2-Methyl-2-[β-hydroxy-β-(*p*-chlorophenyl)ethyl]anisic Acid Hydrazide.—A mixture of 55 g. of methyl *p*-chloromandelate[8] and 250 g. of 40% aqueous methylamine solution was refluxed for 18 hr. The cooled mixture solidified. The white solid was removed by suction filtration, washed (water), and air-dried, to yield 42 g. (76%), m.p. 142–144°. The white solid (41 g.) was dissolved in 500 ml. of tetrahydrofuran and added, dropwise, to a stirred suspension of 9.9 g. (0.26 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 18 hr. The cooled, stirred mixture was treated, dropwise, with a solution of 20 ml. of water in 200 ml. of tetrahydrofuran. The mixture was suction filtered and the filtrate was evaporated *in vacuo* leaving 34 g. (89%) of tan oil. The tan oil was dissolved in ether and treated with an ether solution of oxalic acid until the precipitation of the oxalic acid addition salt was complete, giving 24 g. (48%) of white solid, m.p. 160–164°. The oxalic acid addition salt was dissolved in 200 ml. of water, concentrated hydrochloric acid (3.0 ml.) was added, the mixture was stirred, and a solution of 5.0 g. (0.07 mole) of sodium nitrite in 75 ml. of water was added. The mixture was stirred at room temperature for 1 hr. and then was extracted with ethyl acetate. The ethyl acetate extract was washed (potassium carbonate), dried (magnesium sulfate), and evaporated *in vacuo*. The residual solid was recrystallized from ether–ligroine (b.p. 66–75°), giving 8.2 g. (59%) of white solid, m.p. 63–65°. A solution of 8.0 g. of the white solid in 90 ml. of glacial acetic acid was added, over a period of 1 hr., to a stirred suspension of 10.4 g. (0.2 mole) of powdered zinc in 20 ml. of water. The mixture was stirred and heated at 50° for 1 hr. The cooled mixture was suction filtered and the filtrate was concentrated *in vacuo*. The cooled concentrate was treated with a cold sodium hydroxide solution and extracted with ether. The dried (magnesium sulfate) ether extract was evaporated *in vacuo* leaving 6.5 g. (82%) of tan solid melting at 78–82°. A stirred mixture of 6.0 g. of the tan solid, 40 ml. of pyridine, and 40 ml. of benzene was treated, dropwise, with a solution of 6.8 g. of anisoyl chloride in 50 ml. of benzene. The mixture was stirred and heated on a steam bath for 3 hr. The cooled mixture was treated with sodium hydroxide solution and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*. The residual oil was dissolved in 30 ml. of hot ethanol, 30 ml. of 2 *N* sodium hydroxide solution was added, and the mixture was heated at 75° for 1.5 hr. The mixture was concentrated *in vacuo*, cooled, diluted with 100 ml. of water, and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residual viscous oil solidified by rubbing with ether to yield 5.1 g. (46%), m.p. 152–153°. The solid was recrystallized from isopropyl alcohol, m.p. 153–154°.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_3$: C, 60.98; H, 5.72; N, 8.37. Found: C, 61.20; H, 5.65; N, 8.04.

2-Methyl-2-[α-methyl-β-hydroxy-β-(*p*-chlorophenyl)ethyl]anisic Acid Hydrazide.—To a stirred mixture of 212 g. (0.86 mole) of α-bromo-*p*-chloropropiophenone and 50 ml. of benzene was added, over a period of 1 hr., 133 g. (1.72 moles) of 40% aqueous methylamine solution. The solution was stirred at room temperature for 2 hr. The benzene layer was removed, dried (magnesium sulfate), and treated with ethereal hydrogen chloride, giving 51 g. of white solid, m.p. 205–207°. The white solid (50 g.) which melted at 205–207° was dissolved in water, treated with sodium hydroxide solution, and extracted with ether. The dried (magnesium sulfate) ether extract was added, dropwise, to a stirred suspension of 8.7 g. of lithium aluminum hydride in 300 ml. of ether. The mixture was stirred and refluxed for 3 hr. The stirred, cooled mixture was treated, dropwise, with a solution of 18 ml. of water in 200 ml. of tetrahydrofuran. The mixture was suction filtered and the solid was washed thoroughly with tetrahydrofuran. The combined filtrate and washings were evaporated *in vacuo* leaving 28.5 g. of a gray solid, m.p. 59–68°. A mixture of 28 g. of the gray solid, 14 ml. of concentrated hydrochloric acid, 60 ml. of ethanol, and 400 ml. of water was treated, dropwise, with a solution of 14 g. (0.20 mole) of sodium nitrite in 100 ml. of water. During the dropwise addition of the sodium nitrite solution, there were added at 10-min. intervals four 1-ml. portions of concentrated hydrochloric acid. The mixture was stirred for 1 hr. and then extracted with ether. The ether extract was washed (sodium bicarbonate), dried (magnesium sulfate), and evaporated leaving 28 g. of brown oil. The brown oil (27.8 g.) was dissolved in glacial acetic acid, and the solution was added, dropwise, to a stirred suspension of 32 g. of zinc powder in 50 ml. of water. After the addition was completed, the mixture was stirred for 1 hr. and then was suction filtered. The filtrate was concentrated *in vacuo*, cooled, treated with a cold sodium hydroxide solution, and extracted with ether. The dried (magnesium sulfate) ether extract was evaporated, leaving 11.4 g. of a yellow oil. The yellow oil (11.0 g.) was dissolved in 50 ml. of benzene, pyridine (8.4 g.) was added, and the mixture was stirred and treated, dropwise, with a solution of 18.1 g. of anisoyl chloride in 50 ml. of benzene. The mixture was stirred and refluxed for 4 hr. The cooled mixture was treated with sodium hydroxide solution and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*, the residual tan oil was dissolved in 100 ml. of hot ethanol, 200 ml. of 2 *N* sodium hydroxide was added, and the

(7) G. Benoit, *Bull. soc. chim. France*, 242 (1947).

(8) *p*-Chloromandelic acid was esterified according to the procedure of S. S. Jenkins [*J. Chem. Soc.*, 2341 (1931)].

mixture was heated at 80° for 2 hr. The mixture was concentrated *in vacuo*, cooled, treated with 200 ml. of water, and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*, and the residual oil solidified by trituration with ether to yield 14.0 g., m.p. 145–148°. The material was recrystallized twice from isopropyl alcohol to yield 8.7 g., m.p. 151–153°.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_3$: C, 61.98; H, 6.07; Cl, 10.16. Found: C, 62.30; H, 6.23; Cl, 10.24.

2-(2-Benzoyl-1-methylhydrazino)ethyl Benzoate.—To a stirred mixture of 40 g. (0.44 mole) of β-(1-methylhydrazino)-ethanol, 72 g. (0.90 mole) of pyridine, and 200 ml. of toluene was added, dropwise, a solution of 126 g. (0.90 mole) of benzoyl chloride in 100 ml. of toluene. The mixture was stirred and refluxed for 5 hr. The cooled mixture was treated with a cold solution of 126 g. of sodium carbonate in 400 ml. of water. The toluene layer was removed, and the alkaline aqueous phase was extracted with chloroform. The combined toluene solution and chloroform extracts were dried (magnesium sulfate) and evaporated *in vacuo*. The oily residue was solidified by triturating with ether. The solid was recrystallized from 2-butanone to yield 68 g. (52%), m.p. 112–113°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.03; H, 5.96; N, 9.39.

2-Methyl-2-(β-hydroxyethyl)benzoic Acid Hydrazide.—A mixture of 8.0 g. of 2-(2-benzoyl-1-methylhydrazino)ethyl benzoate, 100 ml. of ethanol, and 400 ml. of 0.1 *N* aqueous sodium hydroxide solution was heated at 70° for 3 hr. The ethanol was removed by distillation *in vacuo*. The aqueous alkaline mixture was saturated with sodium sulfate and extracted with chloroform. The dried (sodium sulfate) chloroform solution was evaporated *in vacuo* and the solid residue recrystallized from benzene to yield 5.0 g. (93%), m.p. 120–121°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.43. Found: C, 61.62; H, 7.16; N, 15.17.

2-[2-(*p*-Chlorobenzoyl)-1-methylhydrazino]ethyl *p*-Chlorobenzoate.—To a stirred mixture of 18 g. (0.2 mole) of β-(1-methylhydrazino)ethanol, 32 g. (0.41 mole) of pyridine, and 100 ml. of toluene was added, dropwise, a solution of 70 g. (0.41 mole) of *p*-chlorobenzoyl chloride in 100 ml. of toluene. The mixture was stirred at room temperature for 18 hr. The cooled mixture was treated with a solution of 30 g. of sodium carbonate in 150 ml. of water. The toluene layer was removed and the alkaline aqueous phase was extracted with chloroform. The combined toluene solution and chloroform extracts were dried (magnesium sulfate) and evaporated *in vacuo*. The viscous oily residue was solidified by rubbing with ether. The solid was removed by suction filtration and was recrystallized from isopropyl alcohol to yield 40 g. (54%), m.p. 121–122°.

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_3$: C, 55.60; H, 4.39; N, 7.63. Found: C, 55.98; H, 4.51; N, 7.37.

2-Methyl-2-(β-hydroxyethyl)-*p*-chlorobenzoic Acid Hydrazide.—A mixture of 20 g. of 2-[2-(*p*-chlorobenzoyl)-1-methylhydrazino]ethyl *p*-chlorobenzoate, 250 ml. of ethanol, and 600 ml. of 0.1 *N* aqueous sodium hydroxide solution was kept at 70° for 3 hr. The ethanol was removed by distillation under diminished pressure. The alkaline aqueous mixture was saturated with sodium sulfate and extracted with chloroform. The dried (magnesium sulfate) chloroform solution was evaporated under diminished pressure and the residual solid recrystallized from 2-butanone to yield 10.9 g. (87%), m.p. 128–129°.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_2$: C, 52.52; H, 5.73; N, 12.25. Found: C, 51.96; H, 5.59; N, 12.20.

Treatment of 2-Methyl-2-(β-hydroxyethyl)benzoic Acid Hydrazide with Sulfuric Acid.—2-Methyl-2-(β-hydroxyethyl)benzoic acid hydrazide (2.0 g.) was added, portionwise, to stirred concentrated sulfuric acid (40 ml.). The mixture was allowed to stand at room temperature for 18 hr.[9] and then was poured onto crushed ice. The precipitate was removed by suction filtration, washed with water, and allowed to air-dry to yield 1.2 g. of benzoic acid (100%), m.p. 120–121°. The melting point of a mixture of this material and benzoic acid was 121–122°.

Treatment of 2-Methyl-2-(β-hydroxyethyl)-*p*-chlorobenzoic Acid Hydrazide.—2-Methyl-2-(β-hydroxyethyl)-*p*-chlorobenzoic acid hydrazide (2.0 g.) was added, portionwise, to stirred concentrated sulfuric acid (40 ml.). The mixture was allowed to stand at room temperature for 18 hr. and then was poured onto crushed ice. The precipitate was removed by suction filtration, washed with water, and allowed to air-dry to yield 1.6 g. of *p*-chlorobenzoic acid (102%), m.p. 240–242°. The material was recrystallized from isopropyl alcohol to yield 1.4 g. (100%), m.p. 241–242°. A mixture of this material and *p*-chlorobenzoic acid melted at 241–242°.

Treatment of 2-Methyl-2-(β-hydroxypropyl)benzoic Acid Hydrazide.—2-Methyl-2-(β-hydroxypropyl)benzoic acid hydrazide (5.0 g.) was added, portionwise, to stirred concentrated sulfuric acid (50 ml.). The mixture was allowed to stand at room temperature for 18 hr. The mixture was poured onto crushed ice and extracted with chloroform. The chloroform extract was washed (water), dried (magnesium sulfate), and evaporated to dryness *in vacuo*. The residue was crystallized by rubbing with *n*-hexane. The solid was removed by suction filtration, to yield 2.9 g., m.p. 117–119°. The solid was recrystallized from water, to yield 2.1 g. of benzoic acid (70%), m.p. 121–122°. A mixture of this material and benzoic acid melted at 121–122°.

Treatment of N-(*p*-Methoxyphenoxyacetylamino)-*l*-ephedrine Hydrochloride with Sulfuric Acid.—N-(*p*-Methoxyphenoxyacetylamino)-*l*-ephedrine hydrochloride (5.0 g.) was added, portionwise, to 20 ml. of concentrated sulfuric acid. After 18 hr. the mixture was poured onto crushed ice and extracted with methylene chloride. The washed (sodium carbonate, water) and dried (magnesium sulfate) methylene chloride extract was evaporated *in vacuo* leaving 0.2 g. of a tan liquid with a benzaldehyde-like odor. The insignificant amount of product indicated that hydrolysis of the hydrazide linkage had occurred.

Treatment of N-(Hydrocinnamoylamino)-*l*-ephedrine Hydrochloride with Sulfuric Acid.—N-(Hydrocinnamoylamino)-*l*-ephedrine hydrochloride (5.0 g.) was added, portionwise, to 20 ml. of concentrated sulfuric acid. After 18 hr. the mixture was poured onto crushed ice and extracted with chloroform. The chloroform extract was washed (sodium carbonate, water), dried (magnesium sulfate), and evaporated *in vacuo* leaving 0.2 g. of oil. The sulfuric acid–water mixture was treated with sodium carbonate and extracted with methylene chloride. Evaporation of the methylene chloride extract gave only 0.2 g. of oil. The insignificant amount of product indicated that hydrolysis of the hydrazide linkage had occurred.

Treatment of N-(*n*-Nonanoylamino)-*l*-ephedrine Hydrochloride with Sulfuric Acid.—To 50 ml. of stirred concentrated sulfuric acid was added, portionwise, 12 g. of N-(*n*-nonanoylamino)-*l*-ephedrine. After 18 hr. the mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated under diminished pressure leaving 9.5 g. of tan oil, which according to infrared analysis [$\lambda_{max}^{CHCl_3}$ 3.11 (broad and medium), 5.81 (w), 6.05 (vs) μ] was impure N-(*n*-nonanoylamino)-*l*-ephedrine.

Treatment of N-(*p*-Chlorophenoxyacetylamino)-*l*-ephedrine Hydrochloride with Sulfuric Acid.—N-(*p*-Chlorophenoxyacetylamino)-*l*-ephedrine (28 g.) was added, portionwise, to 100 ml. of concentrated sulfuric acid. After 18 hr. the mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium bicarbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated under diminished pressure leaving 2.3 g. of tan oil which could not be purified. The small amount of product indicated that hydrolysis of the hydrazide linkage had occurred.

(9) Benzoic acid was obtained in nearly quantitative yield when reaction time was reduced to 1 hr.