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5,6-Dihydro-4*H*,1,3,4-Oxadiazines. IV. Further Studies

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The scope of the acid-catalyzed cyclodehydration of 2-(β-hydroxyalkyl)carboxylic acid hydrazides into 5,6-dihydro-4*H*-1,3,4-oxadiazines has been extended through the use of acidic reagents other than concentrated sulfuric and polyphosphoric acids. Additional data are presented which corroborate previously proposed mechanisms of this reaction.

We have reported (2) on the scope of the concentrated sulfuric acid cyclodehydration of certain 2-(β-hydroxyalkyl)carboxylic acid hydrazides into 5,6-dihydro-4*H*-1,3,4-oxadiazines and proposed two alternative mechanisms for the formation of *trans* isomers in concentrated sulfuric acid and a mechanism for the formation of *cis* isomers in polyphosphoric acid. This paper describes the use of other reagents to extend the scope of this reaction. It presents data which allow us to select the preferred mechanism of the two alternatives proposed for the concentrated sulfuric acid formation of *trans* isomers. These data also corroborate the mechanism proposed for the formation of *cis* isomers in polyphosphoric acid.

Concentrated sulfuric acid cyclodehydrated *erythro*-(-)- and *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazides (I and II) into *trans*-(+)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III) (2c).

Polyphosphoric acid, at ambient temperature, cyclodehydrated I into mainly *cis*-(-)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (IV) contaminated with a small amount of III. At 60-70° a mixture of III and IV was obtained which was much richer in III, so much so that it was the predominant isomer in the mixture (2c). Another difference in the behavior of concentrated sulfuric and polyphosphoric acids was that the former cyclodehydrated 2-methyl-2-(β-hydroxyisobutyl)-2,4-dichlorobenzoic acid hydrazide into 4,6,6-trimethyl-2-(2,4-dichlorophenyl)-5,6-dihydro-4*H*-1,3,4-oxadiazine in 55% yield, and the latter, under the same reaction conditions (25°, 16 hours), had no effect.

Phosphorus pentoxide, in refluxing toluene, converted I into IV in 44% yield.

Hydrogen bromide in glacial acetic acid cyclodehydrated I into IV in significantly higher yield (87%) than was obtained with any other dehydrating agent. Interestingly, whereas concentrated sulfuric acid converted I into III, sulfuric acid in glacial acetic acid (18% solution) converted I into IV (53% yield).

Hydrogen chloride in chloroform cyclodehydrated I into IV and II into III.

An example of the greater ease of cyclodehydration of II than I is that, in one instance, during an attempted synthesis of II by treating *N*-amino-D(+)-*pseudo*-ephedrine with benzoyl chloride in refluxing benzene in the presence of pyridine, III was obtained. The greater ease of cyclodehydration of II than I is probably due to the fact that in II when the hydroxyl and hydrazido moieties are in close proximity the methyl and phenyl groups are *anti*, whereas in I, in the transition state for hydroxyl-hydrazido interaction, the phenyl and methyl must be crowded together in gauche positions (3).

Treatment of I with thionyl chloride did not cause cyclodehydration but rather brought about replacement of the hydroxyl group by a chlorine to give 2-methyl-2-(α-methyl-β-chlorophenethyl)benzoic acid hydrazide hydrochloride. Repeated attempts to obtain a pure product from the treatment of II with thionyl chloride were unsuccessful.

Treatment of I with acetic anhydride produced *O*-acetylation to give *erythro*-(-)-2-methyl-2-(α-methyl-β-acetoxyphenethyl)benzoic acid hydrazide.

Treatment of I with either Dowex-50A resin in refluxing chlorobenzene or *p*-toluenesulfonic acid in refluxing toluene produced no cyclodehydration and I was recovered unchanged in both experiments.

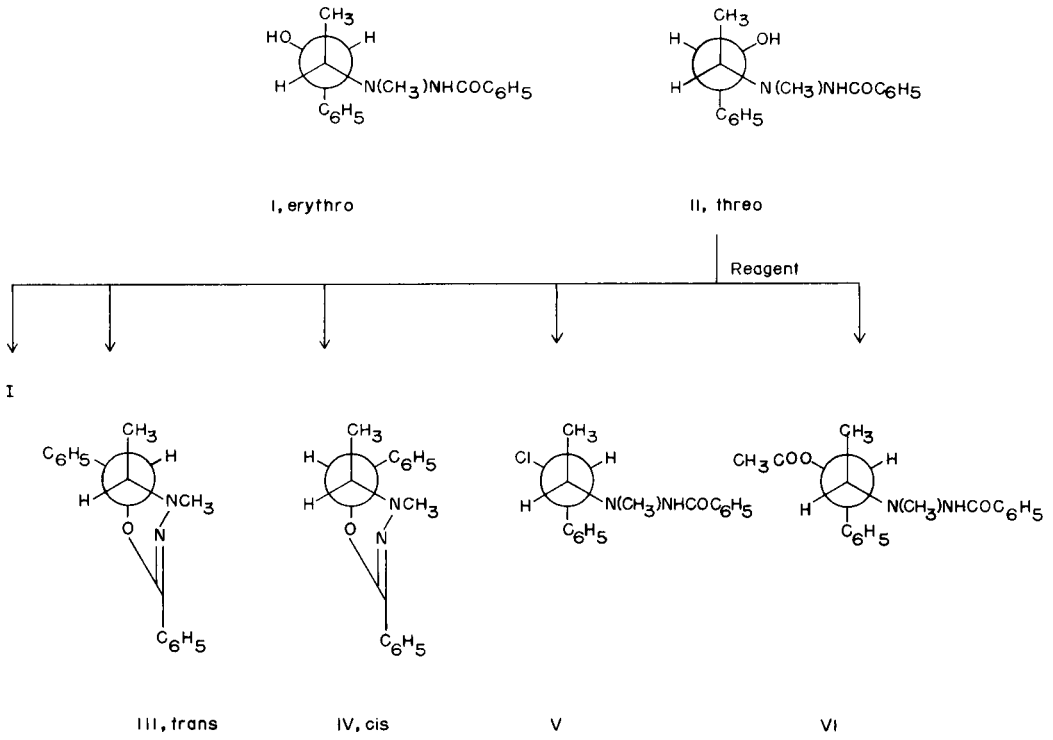
The compounds in a series of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazides (VII) were cyclodehydrated into *trans*-(+)-2-substituted phenyl 4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (VIII) by treatment with concentrated sulfuric acid at ambient temperature. Under these conditions the reaction is too fast to be amenable to a rate study. However, we were able to determine the effect of various substituents on the benzoyl group upon the yield of oxadiazine. R, % yield; 2-CH_3O, 67; 2-C_2H_5O, 67; 4-CH_3, 65; 3-CH_3, 62; 4-C_2H_5O, 60; 4-CH_3O, 57; H, 46; 4-Cl, 42; 2-Cl, 39; 4-C_2H_5OOC, 37; 3-Br, 27, 3,4-Cl_2; 4-O_2N, 6. These data indicate that substituents exert electronic and not steric influence, and that electronegative substituents decrease the yields.

In contrast, hydrogen bromide-acetic acid cyclodehydration of VII into *cis*-(2)-2-substituted phenyl-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (IX) was influenced by steric effects and not electronic effects. R, % yield; H, 87; 3-CH_3, 55;

3,5-$(CH_3)_2$, 57; 4-O_2N, 46; 2-CH_3, 17; 2-CH_3O, 0; 2-C_2H_5S, 0.

Concentrated sulfuric acid cyclodehydration of I to III proceeds much faster than does concentrated sulfuric acid isomerization of IV to III as evidenced by the fact that treatment of I with concentrated sulfuric acid for 1 minute yielded III, exclusively, and treatment of IV with concentrated sulfuric acid for 15 minutes yielded a 43:57 mixture of IV and III. Product mixtures were easily analyzed with n. m. r. because of the different chemical shifts exhibited by the 6-H and 5-CH_3 protons in the *cis* and *trans* oxadiazines.

Because of the significantly higher yield of IV obtained by cyclodehydrating I with hydrogen bromide-glacial acetic acid and because of the ease with which this procedure can be performed, we decided to determine whether or not this reagent would extend the scope of the reaction beyond that attained with concentrated sulfuric acid. In order to do this a variety of 2-(β-hydroxyalkyl)carboxylic acid hydrazides having differing types of hydroxyl and acyl groups were dissolved in glacial acetic acid and treated with gaseous hydrogen bromide to determine the effect of the hydroxyl type and acyl type of the course of the reaction.



Starting Material	Reagent	Reaction Conditions	Product	(Yield, %)
I	concentrated H_2SO_4	Neat, Ambient, 18 hours	III	(46)
II	concentrated H_2SO_4	Neat, Ambient, 18 hours	III	(65)
I	8% H_2SO_4-HOAc	Neat, Ambient	I	(100)
I	20% H_2SO_4-HOAc	Neat, Ambient	IV	(53)
I	PPA	Neat, Ambient, 24 hours	IV	(67)
I	PPA	Neat, 60°, 1 hour	III	(49)
II	PPA	Neat, Ambient, 18 hours	III	(64)
I	P_2O_5	Toluene, Reflux, 18 hours	IV	(44)
I	HCl	$CHCl_3$, Ambient, 48 hours	IV	(55)
II	HCl	$CHCl_3$, Ambient, 48 hours	III	(77)
I	HBr	HOAc, Ambient	IV	(87)
II	HBr	HOAc, Ambient, 18 hours	III	(73)
I	$SOCl_2$	Neat, Ambient, 2 hours	V	(54)
I	Ac_2O	Ac_2O, Reflux, 6 hours	VI	(100)
I	Dowex-50A	Chlorobenzene, Reflux, 24 hours	I	(85)
I	*p*-TSA	Toluene, Reflux, 6 hours	I	(55)

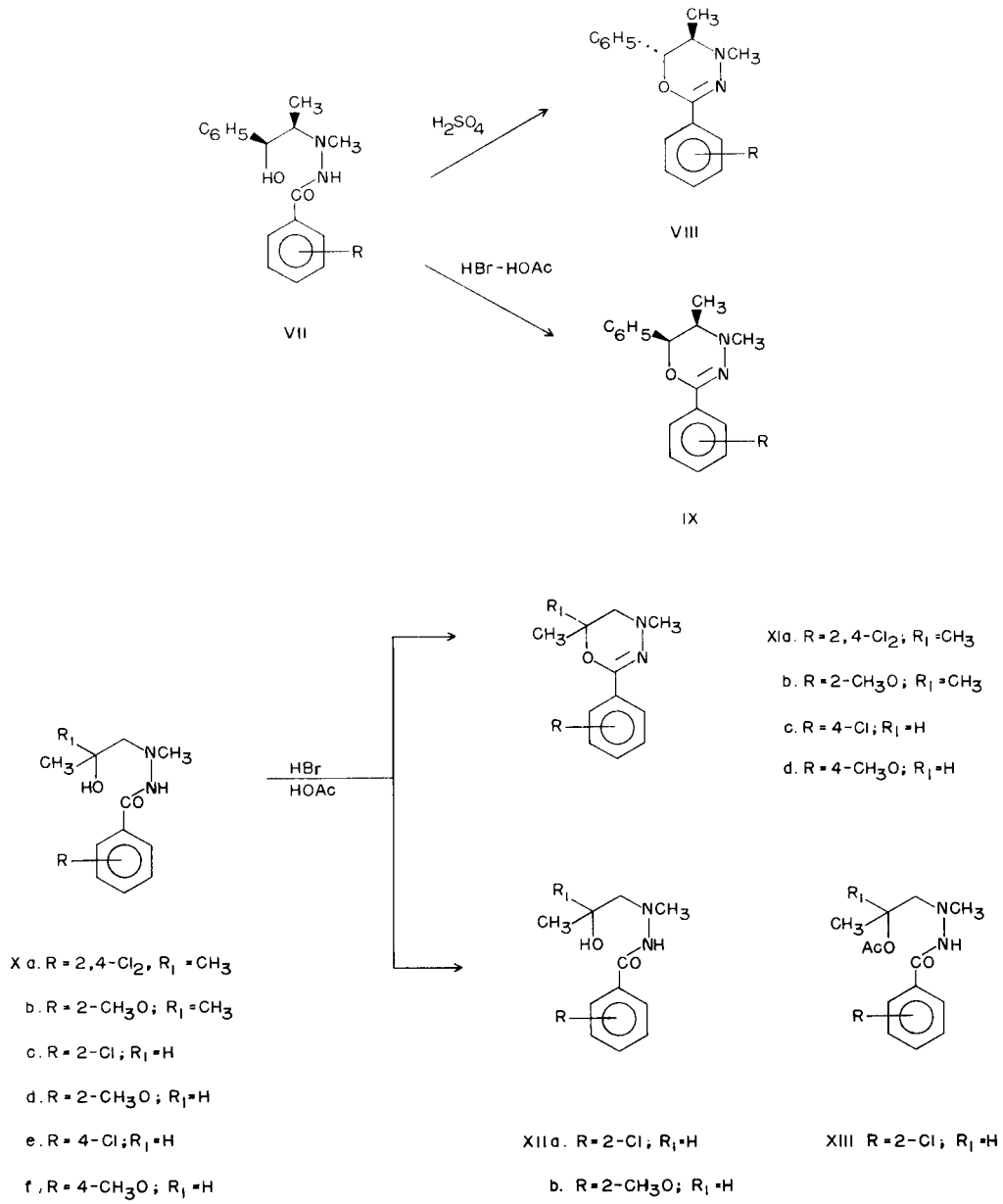


TABLE I

2-(β-Hydroxyalkyl)Carboxylic Acid Hydrazides (a)

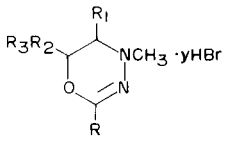
$RCONHN(CH_3)CHR_1CR_2R_3OH \cdot yHBr$

No.	R	R_1	R_2	R_3	y	M.p. °C	Yield %	Recrystn. Solvent	Calcd., % C	H	N	Found, % C	H	N
1	cyclo-C_6H_{11} (b)	CH_3	H	C_6H_5	0	127-128	45	EtOAc	70.31	9.02	9.65	70.35	9.20	9.56
2	$C_6H_5CH_2$	H	H	CH_3	0	94-95	53	EtOAc	64.84	8.16		64.89	8.55	
3	2-ClC_6H_4	H	H	CH_3	1	165-166 (dec.)	65	MeOH-Et_2O	40.82	4.98	24.69 (c)	40.92	5.17	24.85 (c)
4	2-$CH_3OC_6H_4$	H	H	CH_3	1	162-164 (dec.)	60	MeOH-Et_2O	45.15	6.00	25.04 (c)	45.24	6.20	25.45 (c)
5	4-ClC_6H_4	H	H	CH_3	0	92-94	61	Toluene	54.43	6.23	11.54	54.11	6.18	11.33
6	4-$CH_3OC_6H_4$	H	H	CH_3	0	126-128	76	EtOAc	60.49	7.61		60.41	8.02	
7	$C_6H_5OCH_2$	H	CH_3	CH_3	0	53-55	43	Ether	61.88	7.99		61.73	8.39	
8	4-$O_2NC_6H_4$ (b)	CH_3	H	C_6H_5	0	175-176	38	i-PrOH	62.00	5.82		62.11	6.19	
9	2-$C_2H_5SC_6H_4$ (b)	CH_3	H	C_6H_5	0	118-120	49	EtOAc	66.24	7.02		66.35	7.10	
10	2-$CH_3OC_6H_4$	H	CH_3	CH_3	1	151-153	30	i-PrOH	47.00	6.07	24.05 (c)	47.49	6.54	24.56 (c)

(a) For method of preparation see Experimental. (b) *erythro*-Isomer. (c) Bromine.

TABLE II

Substituted 5,6-Dihydro-4*H*-1,3,4-Oxadiazines



No.	R	R_1	R_2	R_3	y	Method (a)	B.p. or M.p., °C	Yield %	Recrystn. Solvent	Calcd., % C	H	N	Found, % C	H	N
1	cyclo-C_6H_{11} (b)	CH_3	H	C_6H_5	1	HBr-HOAc	183-185	95	MeOH-Et_2O	57.79	7.13	22.62 (c)	57.20	7.27	23.26
2	$C_6H_5CH_2$	H	H	CH_3	0	HBr-HOAc	131-133 (3.5mm.)	32		70.55	7.89	13.71	70.71	7.86	13.89
3	2-ClC_6H_4	H	H	CH_3	0	Tosylate-Displacement	152-153 (3.3mm.)	63		58.79	5.84	15.78 (d)	58.83	6.07	15.82
4	2-$CH_3OC_6H_4$	H	CH_3	CH_3	1	HBr-HOAc	159-160 (dec.)	35	MeOH-Et_2O	49.53	6.07	8.88	50.24	6.34	9.03
5	4-ClC_6H_4	H	H	CH_3	1	HBr-HOAc	206-207 (dec.)	53	i-PrOH	43.23	4.62	26.15 (c)	43.57	4.80	26.53
6	4-$CH_3OC_6H_4$	H	H	CH_3	1	HBr-HOAc	169-170	61	i-PrOH	47.85	5.69	26.53 (c)	47.86	6.02	26.16
7	$C_6H_5OCH_2$	H	CH_3	CH_3	1	HBr-HOAc	150-151 (dec.)	58	MeOH-Et_2O	49.53	6.07	25.35 (c)	49.59	6.97	25.86
8	C_6H_5	H	H	CH_3	1	HBr-HOAc	161-163	55	i-PrOH	48.72	5.58	29.47 (c)	49.49	5.77	29.28
9	*n*-$CH_3(CH_2)_7$	H	CH_3	CH_3	0	HBr-HOAc	111-113 (1.0mm.)	59		69.94	11.74	11.66	69.93	11.69	11.00
10	2,4-$Cl_2C_6H_3$	H	CH_3	CH_3	1	HBr-HOAc (e)	194-195 (dec.)	33	MeOH-Et_2O	40.70	4.27	7.91	40.82	4.47	7.83
11	C_2H_5	H	CH_3	CH_3	0	HBr-HOAc	27-28 (0.6mm.)	37		61.50	10.32	17.93	61.40	10.40	18.44
12	4-$O_2NC_6H_4$ (b)	CH_3	H	C_6H_5	0	HBr-HOAc	120-128	48	CH_3CN	65.58	5.50	13.49	65.32	5.98	13.60
13	$C_6H_5CH_2CH_2$ (b)	CH_3	H	C_6H_5	0	HBr-HOAc	76-77	28	EtOH	77.51	7.53		77.15	7.33	
14	3-$CH_3C_6H_4$ (b)	CH_3	H	C_6H_5	0	HBr-HOAc	91-92	55	i-PrOH	77.11	7.19		77.13	7.55	
15	2-$CH_3C_6H_4$ (b)	CH_3	H	C_6H_5	0	HBr-HOAc	113-114	17	i-PrOH	77.11	7.19		77.27	7.25	
16	3,5-$(CH_3)_2C_6H_3$ (b)	CH_3	H	C_6H_5	0	HBr-HOAc	145-146	57	i-PrOH	77.52	7.53		77.28	7.68	

(a) See Experimental. (b) *cis* Isomer. (c) Bromine. (d) Chlorine. (e) Also prepared in 53% yield in concentrated sulfuric acid cyclodehydration.

There was an extension in the scope of the reaction beyond that delineated by concentrated sulfuric acid as evidenced by the fact that hydroxyl type and acyl type requirements for the successful conversion of 2-(β-hydroxyalkyl)carboxylic acid hydrazide into a substituted 5,6-dihydro-4*H*-1,3,4-oxadiazine were less stringent and extended to include secondary aliphatic hydroxyl and a variety of acyl types, such as, propanoyl, nonanoyl, cyclohexanecarbonyl, phenylacetyl, phenoxyacetyl, and hydrocinnamoyl.

However, although hydrogen bromide-glacial acetic acid does extend the scope of the reaction, it still suffers from some limitations. For example, 2-(β-hydroxyalkyl)carboxylic acid hydrazides possessing a primary hydroxyl group are not cyclodehydrated by hydrogen bromide-glacial acetic acid or, for that matter, by any of the other aforementioned acidic dehydrating agents.

2-Methyl-2-(β-hydroxypropyl)benzoic acid hydrazides (Xc-f) possessing an *ortho* substituent, such as, chlorine or methoxyl are not cyclodehydrated by hydrogen bromide-glacial acetic acid, whereas, the homologous 2-methyl-2-(β-hydroxyisobutyl)-*o*-chloro- or *o*-methoxybenzoic acid hydrazides (Xa-b) are cyclodehydrated into substituted 5,6-dihydro-4*H*-1,3,4-oxadiazines (XIa-d).

The inhibition of cyclodehydration is most likely steric rather than electronic because it is exhibited by both a substituent which is benzene activating (CH_3O) and one (Cl) which is known to deactivate the benzene ring. Also, this inhibition is abolished when these two substituents are moved from the *ortho* position to the *para* position.

Compound Xc was cyclized into the oxadiazine by converting the secondary hydroxyl group to the tosylate ester and then subjecting this to solvolysis. In this case, the hydroxyl is converted to a much better leaving group and the reaction proceeds via attack of the carbonyl oxygen upon the *O*-tosyl bearing carbon. The *ortho* substituent does not sterically retard the ring closure by this method.

The aforementioned results (4) obtained from a study of the effect structural changes, including stereoisomerism, in the 2-(β-hydroxyalkyl)carboxylic acid hydrazide had on the course and rate of this cyclodehydration reaction in various acidic reagents indicate that more than one method of ring closure occurs. It is tempting to speculate that certain reaction conditions cause ring closure to occur via a mechanism which has the net effect of producing a loss of hydroxylic oxygen and other reaction conditions cause ring closure to occur with loss of carbonyl oxygen. In the absence of the results of cyclodehydration studies carried out with 2-(β-hydroxyalkyl)carboxylic acid hydrazides containing labeled oxygen this has not been proved. However, the evidence strongly suggests that concentrated sulfuric acid cyclodehydrates 2-(β-hydroxyalkyl)-

carboxylic acid hydrazides via attack of carbonyl oxygen upon the carbonium carbon resulting from dissociation of protonated hydroxyl and certain other acidic reagents, such as, polyphosphoric acid, phosphorus pentoxide in refluxing toluene, 20% sulfuric acid in acetic acid, hydrogen bromide in acetic acid, and hydrogen chloride in chloroform cyclodehydrate 2-(β-hydroxyalkyl)carboxylic acid hydrazides via attack of hydroxylic oxygen upon carbonyl carbon.

For example, concentrated sulfuric acid converted I, II, and IV into III. Also, the cyclization of I to III did not proceed via I to IV followed by isomerization of IV to III because the conversion of I to III was much faster than the isomerization of IV to III. The conversion of II to IV could occur by either mechanism. All of the other acidic reagents converted I into IV and II into III. Polyphosphoric acid isomerizes IV to III. Therefore at temperatures above ambient polyphosphoric acid cyclodehydration of I yields mainly III.

Treatment of 2-(β-hydroxyalkyl)carboxylic acid hydrazides having differing types of hydroxyl and acyl moieties with concentrated sulfuric acid, and with hydrogen bromide in acetic acid, indicated that for cyclodehydration into an oxadiazine, concentrated sulfuric acid is only effective if the hydroxyl group be the type which yields a relatively stable carbonium ion, whereas hydrogen bromide in acetic acid is also effective when the hydroxyl is secondary aliphatic.

Substituents on the acyl moiety of the 2-(β-hydroxyalkyl)carboxylic acid hydrazide exerted different steric and electronic effects on the cyclodehydration in the different acids. For example, in hydrobromic and polyphosphoric acids, *ortho* substituents greatly retarded cyclodehydration regardless of their electronic character. A similar steric inhibition of the approach of hydroxyl oxygen to carbonyl carbon was noted by Welsh (5) during an investigation of acid-catalyzed N > O acyl migrations in a series of *N*-(*o*-substituted benzoyl)ephedrines and *pseudo*ephedrines. Welsh also reported that *ortho*-substituents retarded the attack of carbonyl oxygen upon hydroxyl bearing carbon to a much lesser degree. In concentrated sulfuric acid electronegative substituents retarded cyclodehydration while electropositive facilitated cyclodehydration. This effect is probably a result of their influence on the basicity of the carbonyl oxygen because, although substituents on the acyl moiety would not be expected to influence the rate determining step (carbonium ion formation), they would be expected to influence the product forming step (attack of carbonyl oxygen upon carbonium carbon). Electropositive substituents should facilitate product formation and electronegative substituents should decrease the rate of product formation allowing the carbonium ion to undergo alternative by-product forming reactions.

We rejected the possibility that hydrogen bromide-glacial acetic acid cyclodehydration may proceed via intramolecular Sn^2 halide displacement because an *ortho*-substituent retarded hydrogen bromide-glacial acetic acid cyclodehydration and it did not retard cyclization via Sn^2 tosyl displacement.

EXPERIMENTAL

The melting points were obtained in a capillary tube with the Thomas-Hoover Uni-Melt and are corrected. The elemental analyses were done by Midwest Microlab., Inc., Indianapolis, Indiana. N.m.r. spectra were obtained at 60Mc., with a Varian A-60 spectrometer, for 10% $CDCl_3$ solutions containing a trace of tetramethylsilane (TMS) as internal standard. Chemical shifts are measured as shielding (ppm) relative to the shielding of the TMS protons, and tabulated as the negative of this value. Infrared absorption spectra were obtained on a Beckman IR5 recording spectrophotometer. Optical rotations were obtained on a Rudolph Laboratory Polarimeter Model No. 62. Certain of the 2-(β-hydroxyalkyl)carboxylic acid hydrazides and substituted 5,6-dihydro-4*H*-1,3,5-oxadiazines discussed in this paper have been reported (2).

2-(β-Hydroxyalkyl)carboxylic Acid Hydrazides Listed in Table I. General Procedure.

To a stirred mixture of 0.5 mole of hydrazinoalcohol, 0.5 mole of triethylamine, and 350 ml. of methylene chloride was added, dropwise, 0.5 mole of acid chloride. The mixture was stirred and refluxed for 6 hours. The cooled mixture was treated with 500 ml. of chloroform, washed (water, sodium carbonate solution, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residual oil was either crystallized using an appropriate solvent, converted to its hydrobromide using ethereal hydrogen bromide, or when *N*-acylation was accompanied by sufficient *O*-acylation (determined by infrared analysis) to prevent crystallization, the *O*-acyl moiety was preferentially hydrolyzed by treatment with 1 *N* sodium hydroxide at 70° for 1.5 hours.

5,6-Dihydro-4*H*-1,3,4-oxadiazines Listed in Table II. General Procedure. A.

Hydrogen Bromide-Glacial Acetic Acid Method.

A solution of 10 g. of a 2-(β-hydroxyalkyl)carboxylic acid in 150 ml. of glacial acetic acid was saturated with gaseous hydrogen bromide. After standing at ambient temperature for 18 hours, the mixture was evaporated *in vacuo*. The residue was either crystallized with an appropriate solvent or treated with a sodium carbonate solution to liberate the free base which was purified either by distillation *in vacuo* or by crystallization with an appropriate solvent.

Tosylate Displacement Method.

A mixture of 22.9 g. (0.058 mole) of 2-methyl-2-(β-*p*-toluenesulfonyloxy-*n*-propyl)-*o*-chlorobenzoic acid hydrazide and 150 ml. of toluene was refluxed for 1 hour, allowed to come to ambient temperature overnight, treated with 500 ml. of chloroform, washed (sodium carbonate solution, water), dried (magnesium sulfate), and evaporated *in vacuo*. Distillation of the residual oil yielded 8.1 g. of clear, colorless oil.

Concentrated Sulfuric Acid Cyclodehydration of a Series of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)carboxylic Acid Hydrazides.

To stirred concentrated sulfuric acid (100 ml.) was added, portionwise, 5 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-carboxylic acid hydrazide. After standing for 1 hour at ambient temperature, the mixture was poured onto crushed ice and extracted thoroughly with chloroform. The chloroform extract was washed (sodium carbonate solution, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was crystallized using an appropriate solvent or converted to the hydrohalide.

trans-(+)-2-(3,4-Dichlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochloride was obtained in 23% yield and after recrystallization from ethanol melted at 225-226° (dec.).

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O \cdot HCl$: C, 54.93; H, 4.61; N, 7.54; Found: C, 54.89; H, 4.66; N, 7.63.

trans-(+)-2-(4-Nitrophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochloride was obtained (3) in 6% yield and after recrystallization melted at 166.5-168° (dec.).

Anal. Calcd. for $C_{17}H_{17}N_3O_3 \cdot HCl$: C, 58.71; H, 5.22; Cl, 10.19. Found: C, 59.62; H, 6.38; Cl, 10.48.

Attempted Cyclodehydration of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic Acid Hydrazide. A. With Dowex-50A Resin.

A mixture of 2.0 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide, 1.2 g. of finely ground Dowex 50-A sulfonic acid resin, and 100 ml. of chlorobenzene was stirred and refluxed, in a flask with a water separator attached, for 24 hours. The chlorobenzene was decanted and evaporated *in vacuo* to give 1.7 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide, m.p. 168-170°.

B. With *p*-Toluenesulfonic Acid.

A mixture of 2.0 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide, 0.3 g. of *p*-toluenesulfonic acid, and 100 ml. of toluene, contained in a flask with a water separator attached, was stirred and refluxed for 6 hours. The cooled mixture was treated with 250 ml. of methylene chloride, washed with sodium hydroxide solution and then with water, and evaporated *in vacuo*. The residue was crystallized with ether and then recrystallized from 1-butanol to give 1.1 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide, m.p. 169-170°.

C. With Thionyl Chloride.

To 50 ml. of cooled, stirred thionyl chloride there was added, portionwise, 12.0 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide. The mixture was stirred for 2 hours, treated with ether, and the solid was dissolved in 100 ml. of dry chloroform. The chloroform solution was filtered, treated with 25 ml. of saturated ethereal hydrogen chloride and then with dry ether until almost turbid, and then allowed to stand in the refrigerator for a few days. The crystalline solid was removed by suction filtration, washed with dry ether, and recrystallized from a 50:50 mixture of chloroform-ether to give 7.2 g. (52%) of 2-methyl-2-(α-methyl-β-chlorophenethyl)benzoic acid hydrazide hydrochloride, m.p. 131-132° (dec.).

Anal. Calcd. for $C_{17}H_{19}ClN_2O \cdot HCl$: C, 60.18; H, 5.94; Cl, 20.90; N, 8.26. Found: C, 60.63; H, 6.22; Cl, 20.66; N, 8.17.

Treatment of *N*-Amino-D-(+)-*pseudo*-ephedrine With Benzoyl Chloride.

To a stirred mixture of 54.0 g. (0.31 mole) of *N*-amino-D-(+)-*pseudo*-ephedrine, 25 g. of pyridine, and 200 ml. of benzene was added, dropwise, a solution of 42.2 g. (0.31 mole) of benzoyl chloride in 150 ml. of benzene. The mixture was stirred and refluxed for 17 hours. The mixture was evaporated *in vacuo*. The residue was dissolved in chloroform and the chloroform solution washed (sodium carbonate solution, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was recrystallized twice from isopropyl alcohol to give 17.7 g. (21%) of *trans*-(+)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 142-143°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.17; H, 6.90; N, 10.53.

Attempted Cyclodehydration of 2-Methyl-2-(β-hydroxyisobutyl)-2,4-dichlorobenzoic Acid Hydrazide With Polyphosphoric Acid.

A mixture of 20 g. of 2-methyl-2-(β-hydroxyisobutyl)-2,4-dichlorobenzoic acid hydrazide and 200 g. of polyphosphoric acid was stirred at 25° for 18 hours. The mixture was treated with crushed ice-water and then extracted with chloroform. The chloroform solution was washed (sodium hydroxide, water), dried (magnesium sulfate), and evaporated *in vacuo* to give 16 g. (80%) of 2-methyl-2-(β-hydroxyisobutyl)-2,4-dichlorobenzoic acid hydrazide, m.p. 104-106°.

2-Methyl-2-(β-*p*-toluenesulfonyloxy-*n*-propyl)-*o*-chlorobenzoic Acid Hydrazide.

To a solution of 31 g. of 2-methyl-2-(β-hydroxy-*n*-propyl)-*o*-chlorobenzoic acid hydrazide in 250 ml. of dry pyridine, cooled to 5°, was added, portionwise, with stirring, 20 g. of *p*-toluenesulfonyl chloride. After standing at 5° for 48 hours, the mixture was diluted with ice-water and the precipitate suction filtered, washed with water, and air-dried. There was obtained 28 g. (64%) of solid, m.p. 105-106°.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_4S$: C, 54.46; H, 5.33; Cl, 8.94; N, 7.06; S, 8.08. Found: C, 54.82; H, 5.47; Cl, 9.33; N, 7.15; S, 7.91.

Hydrogen Chloride-Chloroform Cyclodehydration of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic Acid Hydrazide.

A solution of 1.0 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide in 500 ml. of dry chloroform was saturated with gaseous hydrogen chloride and allowed to stand at ambient temperature for 48 hours. The mixture was evaporated *in vacuo*. The residue was dissolved in a minimum of methanol, basified with methanolic potassium hydroxide, treated with water until turbid, and extracted with methylene chloride. The dried (magnesium sulfate) methylene chloride extract was evaporated *in vacuo*. The residue was recrystallized from isopropyl alcohol to give 0.51 g. (55%) of *cis*-(-)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 101-102°. N.m.r., J (H5-H6) 2.9 c.p.s.; $[\alpha]_D^{28}$ -239±2° (4.17, C_6H_6).

Hydrogen Chloride-Chloroform Cyclodehydration of *threo*-(+)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic Acid Hydrazide.

A solution of 3.0 g. of *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide in 500 ml. of dry chloroform was saturated with gaseous hydrogen chloride and allowed to stand at ambient temperature for 48 hours. The mixture was evaporated *in vacuo*. The residue was dissolved in a minimum of methanol, basified with methanolic potassium hydroxide, treated with water until turbid, and extracted with methylene chloride. The dried (magnesium sulfate) methylene chloride extract was evaporated *in vacuo*. The residue was recrystallized from isopropyl alcohol to give 0.72 g. (77%) of *trans*-(+)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 141-142°. N.m.r., J (H5-H6) 7.5 c.p.s.; $[\alpha]_D^{28}$ +213±2° (3.99, C_6H_6).

Attempted Hydrogen Bromide-Glacial Acetic Acid Cyclodehydration of 2-Methyl-2-(β-hydroxypropyl)-*o*-chlorobenzoic Acid Hydrazide.

A solution of 5.0 g. of 2-methyl-2-(β-hydroxypropyl)-*o*-chlorobenzoic acid hydrazide in 75 ml. of glacial acetic acid was saturated with gaseous hydrogen bromide. After 1 hour the solution was evaporated *in vacuo*. The cooled residual oil was diluted with cold water, basified with sodium carbonate solution, and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* leaving 4.1 g. of a tan oil which by infrared analysis was shown to be a mixture of 2-methyl-2-(β-hydroxypropyl)-*o*-chlorobenzoic acid hydrazide and 2-methyl-2-(β-acetoxypropyl)-*o*-chlorobenzoic acid hydrazide; ν max (film) 3380, 3172 (OH, NH), 1690 (ester carbonyl), and 1655 (hydrazide carbonyl) cm^{-1}.

Attempted Hydrogen Bromide-Glacial Acetic Acid Cyclodehydration of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)-*o*-ethylthiobenzoic Acid Hydrazide.

A solution of 2.0 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-*o*-ethylthiobenzoic acid hydrazide in 75 ml. of glacial acetic acid was saturated with gaseous hydrogen bromide and allowed to remain at ambient temperature for 2 hours. The solution was evaporated *in vacuo*. The residue was dissolved in a minimum of methanol, basified with methanolic potassium hydroxide, treated with water until turbid, and extracted with chloroform. The dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* leaving 2 g. of tan oil which by infrared analysis was shown to be a mixture of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-*o*-ethylthiobenzoic acid hydrazide and *erythro*-(-)-2-methyl-2-(α-methyl-β-acetoxyphenethyl)-*o*-ethylthiobenzoic acid hydrazide; ν max (film) 3390-3180 broad (OH, NH), 1700 (ester carbonyl), and 1650 (hydrazide carbonyl) cm^{-1}.

Attempted Hydrogen Bromide-Glacial Acetic Acid Cyclodehydration of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)-*o*-methoxybenzoic Acid Hydrazide.

A solution of 2.5 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-*o*-methoxybenzoic acid hydrazide in 50 ml. of glacial acetic acid was saturated with gaseous hydrogen bromide and allowed to stand at ambient temperature for 18 hours. The solution was evaporated *in vacuo*. The residue was dissolved in a minimum of methanol, basified with methanolic potassium hydroxide, treated with water until turbid, and extracted with chloroform. The dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* leaving an oil (2.3 g.) which by infrared analysis was shown to be a mixture of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)-*o*-methoxybenzoic acid hydrazide and *erythro*-(-)-2-methyl-2-(α-methyl-β-acetoxyphenethyl)-*o*-methoxybenzoic acid hydrazide; ν max (film) 3298 (OH), 1723 (ester carbonyl), and 1650 (hydrazide carbonyl) cm^{-1}.

Rate of Concentrated Sulfuric Acid Cyclodehydration of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide.

erythro-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide (1.0 g.) was added to 20 ml. of concentrated sulfuric acid (27°) and stirred for 1 minute. The mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*. An n.m.r. spectrum of the residue was identical with a spectrum of authentic *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine; n.m.r. -1.02 (doublet, 5-CH_3), -2.60 (quartet, 5-H), -2.80 (singlet, 4-CH_3), -4.95 (doublet, 6-H), -7.24 and -7.77 (multiplets, aromatic protons), J (5H-6H) = 7.54 c.p.s., J (5H--5CH_3) = 6.58 c.p.s.

Rate of Concentrated Sulfuric Acid Isomerization of *cis*-(-)-into *trans*-(+)-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.

cis-(-)-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (4.0 g.) was added to stirred concentrated sulfuric acid kept at 27°. At intervals 10 ml. aliquots were removed, added to crushed ice, and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* and the residue examined with the aid of n.m.r.; reaction time in minutes, % isomerized - 2, 12; 4, 22; 7, 33; 10, 43; 15, 57; 25, 69; 45, 81; 60, 88; 90, 92.

Attempted Acetic Anhydride Cyclodehydration of *erythro*-(-)-2-Methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic Acid Hydrazide.

A mixture of 5.0 g. of *erythro*-(-)-2-methyl-2-(α-methyl-β-hydroxyphenethyl)benzoic acid hydrazide and 200 ml. of acetic anhydride was refluxed for 18 hours, concentrated *in vacuo*, cooled, diluted with ice water, basified with sodium carbonate solution, and extracted with chloroform. The dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*. An infrared analysis of the oily residue (4.3 g.) indicated it was primarily *erythro*-(-)-2-methyl-2-(α-methyl-β-phenethyl)benzoic acid hydrazide; ν max (CCl_4) 3410 weak (NH), 1720 (ester carbonyl), 1680 (hydrazide carbonyl), and 1245 (acetate C-O) cm^{-1}.

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Received May 1, 1965 Indianapolis, Indiana