N-Phenyl-3,5-bis(methylthio)isothiazolecarboxamide (19).—A mixture of 0.75 g. (0.003 mole) of **16**, 1.75 g. (0.019 mole) of aniline, and 100 ml. of ethyl ether was heated under reflux for 15 min., then was diluted with water and methylene chloride. The organic phase was washed with dilute hydrochloric acid and water. Evaporation and recrystallization from methanol gave 0.69 g. (82% yield) of the anilide, m.p. 162–163°; λ_{max}^{alc} 287 mμ (ε 13,300), 255 (16,500).

Anal. Calcd. for $C_{12}H_{12}ON_2S_3$: C, 48.6; H, 4.1. Found: C, 48.7; H, 4.3.

N-(*o*-Aminophenyl)-3,5-dimethylthio-4-isothiazolecarboxamide (20).—To a solution of 2.7 g. (0.025 mole) of *o*-phenylenediamine and 2.5 g. (0.025 mole) of triethylamine in 75 ml. of tetrahydrofuran was added 6.24 g. (0.025 mole) of **16** in 130 ml. of tetrahydrofuran over 15 min. at room temperature. The mixture was stirred 1 hr., filtered, evaporated to dryness, and triturated with a little methanol to give 6.8 g. (87%) of a solid that melted at 179–180°. A sample recrystallized from a benzene–methanol mixture melted at 182.5–183°; λ_{max}^{alc} 287 mμ (ε 12,300), 233 (10,100).

Anal. Calcd. for $C_{12}H_{13}ON_3S_3$: C, 46.3; H, 4.2. Found: C, 45.6; H, 4.2.

5,6-Dihydro-4*H*-1,3,4-oxadiazines. I. Synthesis and Structure Proof[1]

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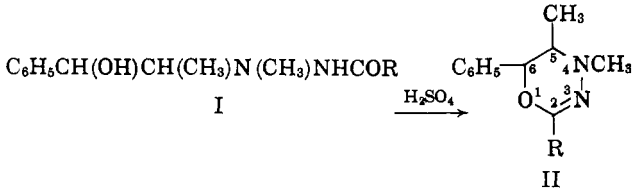
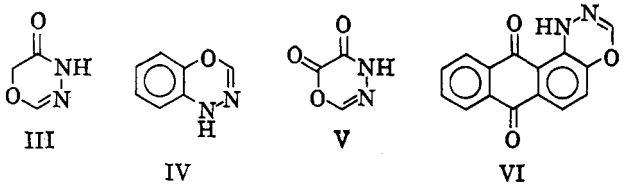
Sulfuric acid dehydration of certain 2-(β-hydroxyalkyl)acid hydrazides has been found to proceed *via* neighboring group participation with concomitant formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine. The structure proof of this novel heterocycle was accomplished by elemental, infrared, and ultraviolet analyses, nuclear magnetic resonance measurements, and chemical degradation.

We have observed that the sulfuric acid dehydration of certain 2-(β-hydroxyalkyl) acid hydrazides (I) proceeds *via* neighboring group participation with concomitant formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine (II). Although much has been reported[3]

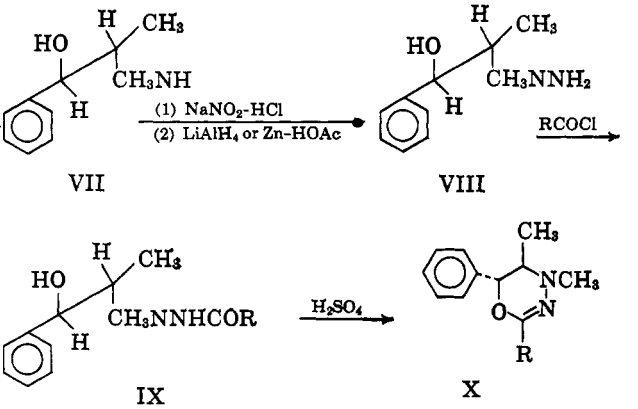


on neighboring group participation between the amido group and the hydroxyl group in the acid-catalyzed cyclodehydration of N-(β-hydroxyalkyl) amides to yield 2-oxazolines, the interaction between the hydrazido group and the hydroxyl group to form 5,6-dihydro-4*H*-1,3,4-oxadiazines has not been explored. Only one example of this novel heterocyclic system has heretofore been reported. Ishidate, *et al.*,[4] reportedly obtained 4-(β-chloroethyl)-2-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine as a by-product (15% yield) from the synthesis of 2,2-bis(β-chloroethyl)benzoic acid hydrazide by the treatment of 2,2-bis(β-hydroxyethyl)-benzoic acid hydrazide with thionyl chloride.

Related heterocycles, such as 5,6-dihydro-4*H*-1,3,4-oxadiazin-5-one (III),[5] 5,6-benzo-4*H*-1,3,4-oxadiazine (IV),[6] 5,6-dihydro-4*H*-1,3,4-oxadiazin-5,6-dione (V),[7] and 1,2-anthraquino-4*H*-1,3,4-oxadiazine (VI),[8] have been reported. Type III has been prepared by base-catalyzed dehydrohalogenation of 2-(β-chloroacetyl) acid hydrazides, type IV by the reaction of substituted 1,2-benzoquinone-2-diazides with ethyl diazoacetate, type V by the reaction of carboxylic acid hydrazides with oxalyl chloride, and type VI by base-catalyzed cyclization of 1-(2-benzhydrazido)-2-nitroanthraquinone.



The 5,6-dihydro-4*H*-1,3,4-oxadiazines listed in Table I of this paper were prepared *via* a four-step synthesis starting with commercially available *l*-ephedrine (VII). It was converted to N-amino-*l*-ephedrine (VIII) by nitrosation and reduction. Acylation of VIII produced the N-acyl derivative (IX) which was cyclized by sulfuric acid to the 5,6-dihydro-4*H*-1,3,4-oxadiazine (X).



Examination of the products of the Zn–HOAc reduction of N-nitroso-*l*-ephedrine by gas–liquid chromatography[9] indicated that VIII was a mixture composed,

(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) U. S. Industrial Chemicals Co., Tuscola, Ill.

(3) (a) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 377; (b) R. H Wiley and L. L. Bennett, Jr., *Chem. Rev.*, **44**, 447 (1949).

(4) M. Ishidate, Y. Sukurai, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **8**, 543 (1960).

(5) J. van Alphen, *Rec. trav. chim.*, **47**, 909 (1928); **48**, 163 (1929); **48**, 417 (1929); **53**, 325 (1934).

(6) R. Huisgen and R. Fleischmann, *Ann.*, **623**, 47 (1959).

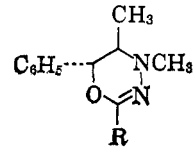
(7) J. van Alphen, *Rec. trav. chim.*, **47**, 673 (1928); **53**, 325 (1934).

(8) W. L. Mosby and W. L. Berry, *Tetrahedron*, **8**, 107 (1960).

(9) The column was 5 ft. × 3/8 in., 15% SE-30, 60/80 AW/Chromosorb W with He flow of 200 ml./min., and temperature programmed at 5°/min. from 100 to 255°. The retention times were VII = 11 min., VIII = 15 min., N-nitroso-*l*-ephedrine = 29 min.

TABLE I

trans-5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES



R	M.p., °C.[a]	Yield, %	Recrystn. solvent	Calcd., % C	H	N	Found, % C	H	N	Ultraviolet absorption,[b] $\lambda_{max}^{CHCl_3}$, mμ (ε × 10⁻³)	Infrared absorption,[c] —OC=N (solvent)
C_6H_5	142–143	32	*i*-PrOH	76.66	6.81	10.52	76.41	7.02	10.10	240 (4.64), 294 (9.08)	1620 (KBr)
2-ClC_6H_4	85–87	56	*i*-PrOH	67.88	5.70	9.31	67.69	5.85	9.37	244 (4.78), 278 (4.53)	1629 (KBr)
$(C_6H_5)_2CH$	133–134	55	*i*-PrOH	80.86	6.79	7.83	80.00	6.70	8.10	244 (6.12),	1640 (KBr)
2-$CH_3OC_6H_4$	94–95	67	*i*-PrOH	72.95	6.80	9.46	73.53	6.83	9.62	244 (5.66), 282 (5.88)	1640 ($CHCl_3$)
4-ClC_6H_4	91–93	58	EtOH	67.89	5.70	9.31	67.78	6.01	9.38	240 (7.42), 300 (11.15)	1612 (KBr)
4-$C_2H_5OC_6H_4$	101–102	57	*i*-PrOH	73.52	7.15	9.03	73.62	7.36	9.17	242 (9.21), 288 (13.42)	1610 (KBr)
2-C_4H_3O	141–142	61	*i*-PrOH	70.29	6.29	10.93	70.28	6.51	11.01	240 (6.04), 290 (11.56)	1640 (KBr)
2-$C_2H_5OC_6H_4$	80–81	67	*i*-PrOH	73.52	7.15	9.03	73.64	7.21	8.90	244 (5.68), 282 (5.91)	1610 (KBr)
4-$CH_3OC_6H_4$	123–124	55	*i*-PrOH	72.95	6.80		72.93	6.92		240 (9.10), 289 (13.60)	1629 (CCl_4)
4-$CH_3C_6H_4$	96–98	65	*i*-PrOH	77.11	7.19		76.79	7.16		242 (7.08), 290 (9.83)	1630 (CCl_4)
2-C_4H_3S	133–135	70	*i*-PrOH	66.14	5.92	10.29	65.93	6.09	10.38	242 (7.40), 308 (9.34)	1610 (Nujol)
3,4-$(CH_3O)_2C_6H_3$	89–92	49	$(i\text{-Pr})_2O$	69.93	6.79		69.54	6.86		244 (7.92), 300 (13.29)	1614 (Nujol)
3,5-$(CH_3)_2C_6H_3$	96–98	53	*i*-PrOH	77 52	7.53		77.15	7.97		242 (6.02), 294 (10.05)	1618 (Nujol)
2-$CH_3C_6H_4$	88–90	57	*i*-PrOH	77.11	7.19		76.72	7.21		244 (4.98), 290 (9.43)	1610 (Nujol)
3-$CH_3C_6H_4$	109–110	65	*i*-PrOH	77.11	7.19		77.07	7.24		242 (4.56), 280 (6.39)	1621 (Nujol)

[a] See ref. 13. [b] Ultraviolet absorption maxima and extinction coefficients measured on a Beckman DU spectrophotometer. [c] Infrared absorption spectra obtained on a Beckman IR5 recording spectrophotometer.

TABLE II

N-ACYLAMINO-*l*-EPHEDRINES

$C_6H_5CH(OH)CH(CH_3)N(CH_3)NHCOR \cdot y HCl$

R	*y*	M.p., °C.[a]	Yield, %[b]	Recrystn. solvent	Method[c]	Calcd., % C	H	N	Found, % C	H	N
C_6H_5	0	169–170.5	59	*n*-BuOH	A	72.11	7.10	9.87	71.92	7.37	10.03
2-ClC_6H_4	1	208–209 dec.	26	*i*-PrOH	C	57.47	5.67	7.89	57.42	5.79	7.86
$(C_6H_5)_2CH$	0	173–174	37	*i*-PrOH	A	76.97	7.00	7.48	76.97	6.90	7.39
2-$CH_3OC_6H_4$	0	116–117	45	$(i\text{-Pr})_2O$	D	68.76	7.06	8.91	69.04	7.33	8.97
4-ClC_6H_4	0	137–138	51	*i*-PrOH	A	64.04	6.01	8.79	64.13	6.02	8.44
2-$C_2H_5OC_6H_4$	0	152–154	44	*i*-PrOH	D	69.49	7.37		69.55	7.40	
2-C_4H_3O	1	184–185 dec.	34	EtOH	B	57.97	6.16		58.55	5.19	
4-$C_2H_5OC_6H_4$	1	216–217 dec.	38	EtOH	B	62.54	6.91		62.80	7.04	
4-$CH_3OC_6H_4$	1	205–206 dec.	33	EtOH	B	61.62	6.61		61.84	7.00	
4-$CH_3C_6H_4$	1	217–218 dec.	37	*i*-PrOH	B	64.56	6.92		64.19	6.91	
4-FC_6H_4	0	139–140	54	*i*-PrOH	A	67.58	6.33		67.72	6.52	
2-C_4H_3S	0	149–151	56	*i*-PrOH	A	62.04	6.25		61.94	6.34	
3,4-$(CH_3O)_2C_6H_3$	1	197–199 dec.	48	EtOH	C	59.62	6.62		60.16	6.67	
3,5-$(CH_3)_2C_6H_3$	1	198–199 dec.	48	*i*-PrOH	C	65.41	7.22		65.00	7.20	
4-$CH_3CH_2OOC_6H_4$	1	203–204	29	EtOH	C	61.14	6.41		61.33	6.65	
2-$CH_3C_6H_4$	0	130–132	29	EtOH	A	72.46	7.43		72.44	7.59	
3-$CH_3C_6H_4$	0	148–149	27	EtOH–H_2O	A	72.46	7.43		72.80	7.66	

[a] See ref. 13. [b] The yield was calculated assuming the N-amino-*l*-ephedrine to be 100% pure; actually g.l.c. indicated 73% purity. [c] The four methods of synthesis are described in the Experimental section.

primarily, of 74% N-amino-*l*-ephedrine, 17% *l*-ephedrine, and 7% N-nitroso-*l*-ephedrine. Although purification of VIII was possible, it was advantageous to treat the impure VIII with an appropriate acyl chloride and then purify the high-melting hydrazide derivative. A variety of acyl chlorides, such as benzoyl, substituted benzoyl, benziloyl, 2-furoyl, and 2-thenoyl, were allowed to react with VIII to prepare the N-(acylamino)-*l*-ephedrines (IX) listed in Table II. Attempted N-acylation of VIII using either esters or carboxylic acids was unsuccessful. When N-acylation of VIII was accompanied by sufficient *O*-acylation (determined by infrared analysis) to prevent crystallization of the desired IX, the O-acyl moiety was preferentially hydrolyzed by treatment with 2 *N* sodium hydroxide at 70° for 1.5 hr. Mild saponification was necessary to prevent concomitant hydrolysis of the N-acyl moiety.

The cyclodehydration of IX was accomplished by the portionwise addition of IX to stirred concentrated sulfuric acid followed by a standing period of 5 min. to 1 day[10] at room temperature. The mixture was then poured onto crushed ice and the 5,6-dihydro-4*H*-1,3,4-oxadiazine (X), being very weakly basic, precipitated and was taken up in chloroform. Basic materials, such as VII, VIII, and IX, remained in the water-

(10) The length of time in contact with sulfuric acid seems to have no effect on the yield of 5,6-dihydro-4*H*-1,3,4-oxadiazine.

sulfuric acid solution and the free carboxylic acid, which was formed due to hydrolysis, was washed out of the chloroform extract with dilute sodium hydroxide solution. Thus, by-products of the cyclodehydration reaction were conveniently removed. Crystallization of the oily or gummy X was induced by trituration with an appropriate solvent.

The proposed structure for the 5,6-dihydro-4*H*-1,3,4-oxadiazines is substantiated by elemental analysis, infrared and ultraviolet spectra, nuclear magnetic resonance measurements, and degradation experiments.

Elemental analysis indicates that treatment of IX with concentrated sulfuric acid causes the loss of one molecule of water.

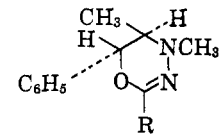
Infrared analysis indicates the absence of NH and OH. No absorption bands of any reasonable intensity are observed in the 1650–1800-cm.$^{-1}$ region, indicating absence of any but the most strongly hydrogen-bonded or conjugated carbonyl groups (the former types being excluded, of course, by absence of OH and NH groups). A fairly intense absorption is always noted in the region 1610–1640 cm.$^{-1}$; this frequency is too high to be the result of phenyl ring fundamental absorption. The frequency is characteristic of C=N, but C=N groups produce only a relatively weak absorption in this region unless an electrophilic polar group is joined to the carbon atom. We may, therefore, regard the reasonably strong absorption near 1625 cm.$^{-1}$ as good evidence for —O—C=N—.

The ultraviolet absorption spectra of the 5,6-dihydro-4*H*-1,3,4-oxadiazines (see Table I) exhibit two maxima, one in the 240–244-mμ region and the other in the 280–300-mμ region, with molar extinction coefficients of 5–9 and 5–14 $\times$ 10^3, respectively. The maximum at 280–300 mμ is indicative of the chromophore C=N in conjugation with an aromatic moiety. When this conjugation is interrupted, as in the case of *trans*-2-benzhydryl-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (compound 3, Table I), there is no absorption in the 280–300-mμ region. Indeed, ultraviolet absorption measurement is the most convenient method for following the course of the reaction in this series of compounds.

Proton n.m.r. analysis detected the expected chemical shifts and coupling constants (Table III). Assuming that the ring takes the likely half-chair form of cyclohexene,[11] a J value of 7.3–7.4 c.p.s. for the –O–CH–CH–N– grouping is indicative of ring protons axial with a dihedral angle approaching 180°. Thus, all the 5,6-dihydro-4*H*-1,3,4-oxadiazines listed in Table I have the *trans* configuration. The 5-CH_3 and 6-C_6H_5 groups always would be equatorial. All compounds listed in Table III, except *trans*-2-benzhydryl-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (compound 2), have nearly identical shifts and couplings, indicating that they have the same ring configuration. Compound 2 [R = $CH(C_6H_5)_2$] deviates from the others but has the same ring configuration. Presumably, the bulky $CH(C_6H_5)_2$ group distorts the ring *via* steric interaction, to make 5-H and 6-H more axial, thereby increasing their coupling constant slightly. The $CH(C_6H_5)_2$ phenyl groups may be close enough to the ring protons and CH_3 groups to cause sizeable shift changes.

TABLE III

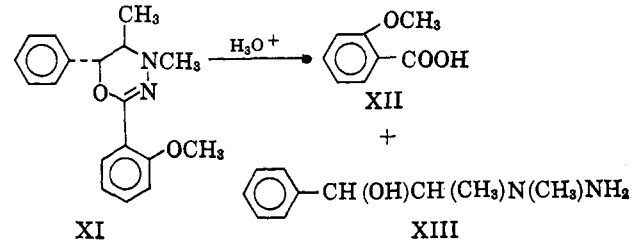
PROTON NUCLEAR MAGNETIC RESONANCE ANALYSIS OF *trans*-5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES[a]



R	Chemical shifts, p.p.m. CCH_3	NCH	OCH	NCH_3	Coupling constants, c.p.s. CH–CH_3	O–CH–CH–N
C_6H_5	1.00	2.60	4.94	2.80	6.4	7.4
$(C_6H_5)_2CH$	0.91	2.36	4.82	2.66	6.4	7.7
4-ClC_6H_4	1.01	2.62	4.94	2.81	6.4	7.3
4-$C_2H_5OC_6H_4$	1.00	2.57	4.92	2.77	6.4	7.4
4-$CH_3OC_6H_4$	1.00	2.56	4.92	2.77	6.4	7.3
4-$CH_3C_6H_4$	1.00	2.59	4.92	2.78	6.4	7.3
2-C_4H_3S	1.00	2.62	4.94	2.77	6.4	7.3
3,5-$(CH_3)_2$-C_6H_3	1.00	2.59	4.92	2.79	6.4	7.3
2-$CH_3C_6H_4$	1.00	2.63	4.95	2.78	6.4	7.3
3-$CH_3C_6H_4$	1.00	2.60	4.93	2.80	6.4	7.4

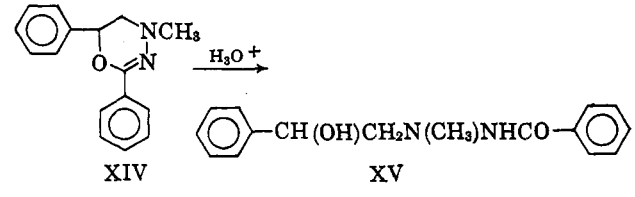
[a] Proton n.m.r. analyses were obtained at 60 Mc., with a Varian Associates A-60 analytical n.m.r. spectrometer, for 10% w./v. carbon tetrachloride solutions containing a trace of tetramethylsilane (TMS) as internal reference. The chemical shifts are given as the negative values of the shielding in p.p.m. relative to TMS at 0.00 p.p.m., and pertinent coupling constants, J, are given in c.p.s.

Acid hydrolysis of *trans*-2-(*o*-methoxyphenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine (XI) yielded *o*-methoxybenzoic acid (XII) and 1-(β-hydroxy-α-methyl-β-phenethyl)-1-methylhydrazine (XIII). No attempt was made to determine



whether or not XIII is a single diastereoisomer. It probably is a mixture of diastereoisomers since it is known that *l*-ephedrine and *d*-pseudoephedrine are interconvertible on heating with hydrochloric acid. W. Mitchell[12] has shown that hydrolysis of acetyl-*l*-ephedrine with 4% hydrochloric acid gave a mixture of two parts of *l* ephedrine and one part of *d*-pseudoephedrine hydrochlorides.

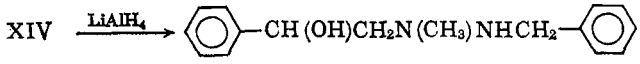
Acid hydrolysis of 4-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (XIV), which does not exhibit *cis–trans* isomerism, yielded 2-methyl-2-(β-hydroxy-β-phenethyl)benzoic acid hydrazide (XV).



(11) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 563.

(12) W. Mitchell, *J. Chem. Soc.*, 1153 (1940).

Lithium aluminum hydride reduction of XIV yielded 1-benzyl-2-methyl-2-(β-hydroxy-β-phenethyl)hydrazine (XVI).



XVI

The 5,6-dihydro-4H-1,3,4-oxadiazine heterocycle forms a high-melting 1:1 acid addition salt when treated with ethereal hydrogen chloride, and a monoquaternary derivative when treated with excess iodomethane or bromomethane. Quaternization changes the ultraviolet spectrum; *e.g.*, *trans*-2-(*o*-methoxyphenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine exhibits maxima at 244 and 282 mμ with molar extinction of 5660 and 5880, respectively; *trans*-2-(*o*-methoxyphenyl)-3,4,5-trimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazinium iodide exhibits maxima at 244, 294, and 364 mμ with molar extinction of 9660, 10,990, and 4730, respectively.

Additional work is in progress to determine the structural requirements of the 2-(β-hydroxyalkyl) acid hydrazide for effective neighboring group participation and to elucidate the mechanism of this ring closure.

Experimental[13]

N-Nitroso-*l*-ephedrine.—To a cooled (0°), stirred solution of 101 g. (0.5 mole) of *l*-ephedrine hydrochloride[14] and 1 ml. of concentrated hydrochloric acid in 500 ml. of water was added, over a period of 20 min., a solution of 35 g. (0.5 mole) of sodium nitrite in 70 ml. of water. During the addition of the sodium nitrite solution, 10 ml. of concentrated hydrochloric acid was added, portionwise, to keep the solution acidic. The mixture was stirred and kept at 0–5° for 6 hr. The solid was removed by suction filtration and allowed to air-dry, m.p. 85–88°; the yield was 82 g. (84%). A 0.5-g. sample of this material was recrystallized twice from water, m.p. 91–92°.[15]

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.43. Found: C, 61.96; H, 7.39; N, 14.51.

Preparation of N-Amino-*l*-ephedrine Using Lithium Aluminum Hydride.—To a stirred suspension of 22.8 g. (0.6 mole) of lithium aluminum hydride in 200 ml. of ether was added, dropwise, a solution of 38.8 g. (0.2 mole) of N-nitroso-*l*-ephedrine in 1 l. of ether.[16] The mixture was stirred and refluxed for 36 hr.[17] The cooled, stirred mixture was treated with 500 ml. of wet ether followed by the dropwise addition of 50 ml. of water. The mixture was suction filtered, and the solid was washed thoroughly with 500 ml. of isopropyl alcohol.[18] The combined filtrate and washings were distilled *in vacuo* to yield 28 g. (78%), b.p. 138–150° (0.05–0.75 mm.). This material solidified in the distillation receiver and melted at 54–57°.

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 67.27; H, 8.60; N, 14.71.

N-Amino-*l*-ephedrine hydrochloride, prepared in ether and recrystallized from isopropyl alcohol, melted at 100–106°.

Anal. Calcd. for $C_{10}H_{16}N_2O \cdot HCl$: C, 55.49; H, 7.91; Cl, 16.40; N, 12.90. Found: C, 55.63; H, 7.71; Cl, 16.61; N, 12.76.

Preparation of N-amino-*l*-ephedrine Using Zn–HOAc.—To a stirred suspension of 130 g. (2.0 moles) of zinc metal dust (Mallinckrodt A.R.) in 200 ml. of water cooled in an ice bath was added, over a period of 45 min., a solution of 97 g. (0.5 mole) of N-nitroso-*l*-ephedrine in 900 ml. of glacial acetic acid. During the addition, the temperature of the reaction mixture was maintained at 20–25° by external cooling. After the addition was completed, the mixture was stirred at 50° for 1 hr., suction filtered, and the zinc residue was washed with a mixture of 150 ml. of water and 50 ml. of glacial acetic acid. The combined filtrate and washings were concentrated to 500 ml. *in vacuo*, 250 ml. of water was added, and the solution was again concentrated to 500 ml. *in vacuo*. The ice-cooled solution was made basic by the addition of a cold solution of 350 g. of sodium hydroxide in 800 ml. of water. The alkaline mixture was extracted four times with 400-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* leaving 83 g. (90% yield) of yellow oil which solidified upon standing overnight at room temperature. A 0.5-g. sample was recrystallized from benzene–hexane, m.p. 55–57°. This material exhibited an infrared spectrum identical with the spectrum of N-amino-*l*-ephedrine synthesized by lithium aluminum hydride reduction of N-nitroso-*l*-ephedrine.

N-Amino-*l*-ephedrine picrate prepared in ethanol was recrystallized from ethanol, m.p. 120–123°.

Anal. Calcd. for $C_{16}H_{19}N_5O_8$: C, 46.94; H, 4.68; N, 17.11. Found: C, 46.85; H, 4.70; N, 17.40.

N-Acylamino-*l*-ephedrines (Compounds in Table II). Method A.—To a stirred mixture of 0.5 mole of N-amino-*l*-ephedrine, 0.5 mole of pyridine, and 250 ml. of toluene was added, dropwise, a solution of 0.5 mole of acid chloride[19] in 200 ml. of toluene. The mixture was stirred and heated on a steam bath for 6 hr. The cooled mixture was treated with a solution of 40 g. of sodium hydroxide in 300 ml. of water and extracted thoroughly with chloroform. The chloroform solution was washed (water), dried (magnesium sulfate), and evaporated to dryness *in vacuo*. The residual viscous oil was crystallized by triturating with the appropriate solvent.[20]

Method B.—To a stirred solution of 0.5 mole of N-amino-*l*-ephedrine in 250 ml. of benzene was added, dropwise, 0.5 mole of acid chloride in 150 ml. of benzene. The mixture was stirred and heated on a steam bath for 6 hr. The cooled mixture was suction filtered and the solid was recrystallized.

Method C.—To a stirred mixture of 0.5 mole of N-amino-*l*-ephedrine, 0.5 mole of pyridine, and 250 ml. of toluene was added, dropwise, a solution of 0.5 mole of acid chloride in 200 ml. of toluene. The mixture was stirred and heated on a steam bath for 6 hr. The cooled mixture was treated with a solution of 40 g. of sodium hydroxide in 300 ml. of water and extracted thoroughly with chloroform. The chloroform solution was washed (water), dried (magnesium sulfate), and evaporated to dryness *in vacuo*. The residual viscous oil was dissolved in ether and treated with ethereal hydrogen chloride until the precipitation of the hydrochloride was complete. The hydrochloride was recrystallized from the appropriate solvent.

Method D.—To a stirred solution of 0.5 mole of N-amino-*l*-ephedrine in 250 ml. of benzene was added, dropwise, 0.5 mole of acid chloride in 150 ml. of benzene. The mixture was stirred and heated on a steam bath for 6 hr. The cooled mixture was treated with a solution of 40 g. of sodium hydroxide in 300 ml. of water and extracted thoroughly with chloroform. The chloroform solution was washed (water), dried (magnesium sulfate), and evaporated to dryness *in vacuo*. The residual viscous oil was dissolved in ether and treated with ethereal hydrogen chloride until the precipitation of the hydrochloride was complete. The hydrochloride was recrystallized from the appropriate solvent.

***trans*-5,6-Dihydro-4H-1,3,4-oxadiazines (Compounds in Table I).**—An appropriate N-acylamino-*l*-ephedrine (10 g.) was added, portionwise, with swirling, to 75 ml. of concentrated sulfuric acid. The mixture was allowed to stand overnight[21] at room temperature and then was poured onto 500 g. of crushed ice and extracted with chloroform. The chloroform extract was washed (sodium carbonate, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was crystallized from an appropriate solvent.

Acid Hydrolysis of *trans*-2-(*o*-Methoxyphenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine.—A mixture of 8.2 g. of *trans*-2-(*o*-methoxyphenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine, 100 ml. of concentrated sulfuric acid, and 200 ml. of water was allowed to stand overnight at room tem-

(13) 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 Microlaboratories, Indianapolis, Ind.

(14) Purchased from Inland Alkaloid, Inc., Tipton, Ind.

(15) See ref. 12, N-nitroso-*l*-ephedrine, m.p. 93°.

(16) Subsequent experiments indicated tetrahydrofuran preferable to ether.

(17) In tetrahydrofuran the reaction time was reduced to 4 hr.

(18) Isopropyl alcohol wash is necessary to remove the N-amino-*l*-ephedrine from the hydride residue.

(19) The acid chlorides were either purchased or prepared from the appropriate acids by refluxing with excess thionyl chloride.

(20) Solvents are listed in Table II.

(21) See ref. 10.

perature, and then was heated (70°) for 1 hr. The cooled mixture was poured onto crushed ice and extracted with chloroform. Evaporation of the washed (water) and dried (magnesium sulfate) chloroform extract yielded 1.7 g. of *o*-methoxybenzoic acid (m.p. 98.5–100.5°). The acidic, aqueous solution was made basic (sodium hydroxide) and extracted with chloroform. Evaporation of the washed (water) and dried (magnesium sulfate) chloroform solution yielded a tan oil (4.6 g.) which was dissolved in ether and treated with ethereal hydrogen chloride until the precipitation of the hydrochloride was complete. After two recrystallizations from isopropyl alcohol–ether, there was obtained 2.8 g. of a white solid, m.p. 129–133°.

Anal. Calcd. for $C_{10}H_{16}N_2O \cdot HCl$, 1-methyl-1-(α-methyl-β-hydroxy-β-phenethyl) hydrazine hydrochloride: C, 55.49; H, 7.91; Cl, 16.40; N, 12.90. Found: C, 55.79; H, 8.07; Cl, 17.31; N, 12.90.

α-(1-Methylhydrazinomethyl)benzyl Alcohol.—A mixture of 460 g. (10.0 moles) of methylhydrazine and 0.5 ml. of 50% aqueous sodium hydroxide solution was warmed and 1 kg. (8.4 moles) of styrene oxide was carefully added over a period of several hours. After the reaction started, the heat source was removed and the mixture was kept refluxing by the addition of the styrene oxide. After the addition was completed, the mixture was refluxed overnight and then distilled *in vacuo*, giving a light yellow oil, 1043 g. (74%), b.p. 140–146° (1.0 mm.).

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.33; H, 8.68; N, 17.14.

2-Methyl-2-(β-hydroxy-β-phenethyl)benzoic Acid Hydrazide (XV).—To a stirred mixture of 253 g. (1.52 moles) of 1-methyl-1-(β-hydroxy-β-phenethyl)hydrazine, 250 ml. of triethylamine, and 500 ml. of methylene dichloride was added, dropwise over a period of 2 hr., a solution of 214 g. (1.52 moles) of benzoyl chloride in 500 ml. of methylene chloride. After the addition was completed, the mixture was stirred overnight at room temperature, washed (water, hydrochloric acid, sodium hydroxide, water), and evaporated *in vacuo*. The residual yellow oil, which would not crystallize (infrared indicated considerable ester C=O at 1706 cm.$^{-1}$), was saponified by heating on a steam bath for 1 hr. with 2 N sodium hydroxide. The mixture was concentrated *in vacuo*, cooled, diluted with water, and extracted with chloroform. Evaporation of the washed (water) and dried (magnesium sulfate) chloroform solution gave a solid which was recrystallized from ethanol, m.p. 148–150°, to yield 267 g. (65%).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 70.83; H, 7.06. Found: C, 71.19; H, 6.82.

4-Methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (XIV).—2-Methyl-2-(β-hydroxy-β-phenethyl)benzoic acid hydrazide (25 g., 0.1 mole) was added, portionwise, to 175 ml. of concentrated sulfuric acid. After 6 hr. the mixture was poured onto crushed ice and extracted with chloroform. Evaporation of the washed (sodium hydroxide, water) and dried (magnesium sulfate) chloroform extract gave a solid which was recrystallized from isopropyl alcohol, m.p. 73–74°, to yield 12.6 g. (51%).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.15; H, 6.39. Found: C, 76.21; H, 6.59.

Acid Hydrolysis of 4-Methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (XIV).—A mixture of 10.0 g. (0.04 mole) of 4-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, 100 ml. of ethanol, 50 ml. of water, and 10 ml. of concentrated hydrochloric acid was refluxed for 17 hr., concentrated *in vacuo*, treated with water, and extracted with chloroform. The chloroform extract was washed (water), dried (magnesium sulfate), and evaporated *in vacuo*. The residual oil was dissolved in hot isopropyl alcohol and allowed to crystallize, m.p. 147–149°, yielding 4.9 g. Recrystallization gave a product of m.p. 148–150°. The melting point of a mixture of this material and authentic 2-methyl-2-(β-hydroxy-β-phenethyl)benzoic acid hydrazide (XV) was 147.5–150°.

Lithium Aluminum Hydride Reduction of 4-Methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (XIV).—To a stirred suspension of 4.2 g. (0.11 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran was added, dropwise over a period of 1 hr., a solution of 25.2 g. (0.10 mole) of 4-methyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (XIV) in 300 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 18 hr. The cooled, stirred mixture was treated, dropwise, with a mixture of 10 ml. of water and 150 ml. of tetrahydrofuran. After stirring for 1 hr., the solid was removed by suction filtration, and the filtrate was evaporated *in vacuo* leaving 24 g. of a light straw-colored oil which by infrared analysis exhibited a broad, intense OH band at 3225 cm.$^{-1}$ and an absence of an —O—C=N— bond in the 1625-cm.$^{-1}$ region.

Anal. Calcd. for $C_{16}H_{20}N_2O$, 1-benzyl-2-methyl-2-(β-hydroxy-β-phenethyl) hydrazine (XVI): C, 74.95; H, 7.87; N, 10.93. Found: C, 74.12; H, 8.06; N, 10.69.

The oxalic acid addition salt, recrystallized from ethanol, melted at 158–159° dec.

Anal. Calcd. for $C_{16}H_{20}N_2O \cdot C_2H_2O_4$: C, 62.41; H, 6.40; N, 8.09. Found: C, 61.61; H, 6.54; N, 7.62.

***trans*-2-(3-Bromophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine Hydrochloride.**—To an ether solution of *trans*-2-(3-bromophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine was added, dropwise, ethereal hydrogen chloride until the precipitation of the hydrochloride was complete. The hydrochloride was recrystallized from methanol, m.p. 224–226° dec.

Anal. Calcd. for $C_{17}H_{17}BrN_2O \cdot HCl$: C, 53.49; H, 4.75. Found: C, 53.31; H, 4.79.

***trans*-2-(*o*-Methoxyphenyl)-3,4,5-trimethyl-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazinium Bromide.**—A mixture of 6.0 g. of *trans*-2-(*o*-methoxyphenyl-4,5-dimethyl-6-phenyl-5,6-dihydro-4-*H*-1,3,4-oxadiazine, 10 ml. of bromomethane, and 50 ml. of acetone was allowed to stand at room temperature in a sealed pressure bottle for 4 days. The crystalline solid that formed was suction filtered, washed with ether, and air-dried, m.p. 160–164° dec., yielding 7.1 g. The material was recrystallized from methanol–ether, m.p. 159–162° dec., to yield 5.5 g. Ultraviolet absorption ($CHCl_3$) showed λ_{max} 244, 294, and 364 mμ ($\epsilon \times 10^{-3}$ 9.66, 10.99, and 4.73).

Anal. Calcd. for $C_{19}H_{23}BrN_2O_2$: C, 58.32; H, 5.92. Found: C, 58.11; H, 6.04.

***trans*-2,6-Diphenyl-3,4,5-trimethyl-5,6-dihydro-4*H*-1,3,4-oxadiazinium Iodide.**—A mixture of 1.0 g. of *trans*-2,6-diphenyl-4,5-dimethyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, 10 ml. of iodomethane, and 150 ml. of methanol was refluxed for 24 hr. The mixture was evaporated and the residue was recrystallized twice from ethanol–ether, m.p. 186–187° dec., to yield 1.0 g.

Anal. Calcd. for $C_{18}H_{21}IN_2O$: C, 52.95; H, 5.18; N, 6.86. Found: C, 52.78; H, 5.28; N, 7.20.

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