5,6-Dihydro-4*H*-1,3,4-oxadiazines. III. *cis–trans* Isomerism[1]

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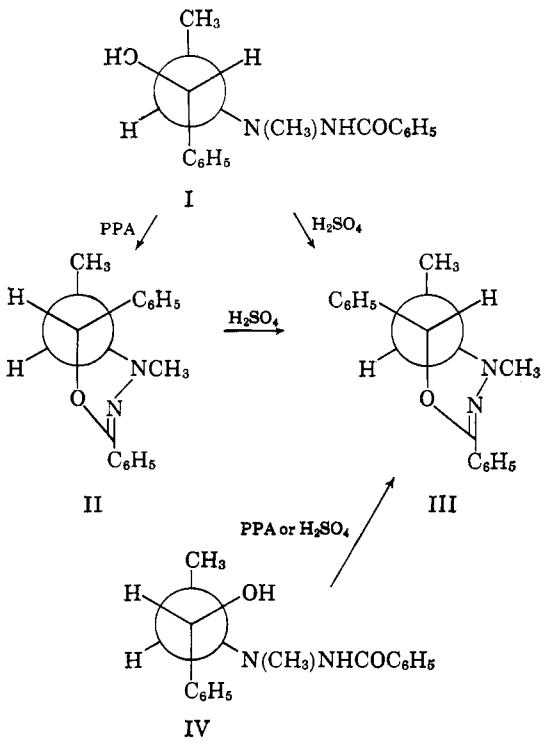
Received February 7, 1964

cis- and *trans*-5,6-dihydro-4*H*-1,3,4-oxadiazines have been synthesized. *cis* isomers have been converted into *trans* isomers. Conformation of the isomers is postulated on the basis of n.m.r. measurements. A proposed mechanism for the formation of *cis* and *trans* isomers is discussed.

We reported[2,3] that sulfuric acid dehydration of certain 2-(β-hydroxyalkyl) acid hydrazides is accompanied by neighboring group participation with the formation of a 5,6-dihydro-4*H*-1,3,4-oxadiazine; and that for effective neighboring group participation the hydroxyl group should be either tertiary or benzyl, and the acyl moiety should be aromatic, heterocyclic, or bulky aliphatic. Even when both the hydroxyl group and the acyl moiety are the most favorable structural types for effective participation, a competing reaction, hydrolysis of the hydrazide linkage, occurs to a significant extent.

In an attempt to retard this competing reaction, cyclodehydration of certain 2-(β-hydroxyalkyl) acid hydrazides was carried out with polyphosphoric acid (PPA) instead of sulfuric acid. Polyphosphoric acid did not increase the yield of 5,6-dihydro-4*H*-1,3,4-oxadiazine, but it did produce an interesting change in the course of the reaction. Cyclodehydration of N-benzoylamino-*l*-ephedrine (I)[4] with PPA gave *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II), whereas cyclodehydration of I with sulfuric acid gave *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III). Cyclodehydration of N-benzoylamino-*d*-pseudoephedrine (IV) with either polyphosphoric acid or sulfuric acid gave III. Treatment of II with concentrated sulfuric acid at 25° converted it to III. Treatment of II with PPA at 25° for 24 hr. produced no change. However, treatment of II with PPA at 65° for 1 hr. gave a mixture of 57% II and 22% III.



Cyclodehydration of a series of N-acylamino-*l*-ephedrines[2] with sulfuric acid gave exclusively the *trans* isomer in every instance. In contrast, polyphosphoric acid cyclodehydration gave either the *cis* or the *trans* isomer or a mixture of both. In fact, cyclodehydration of I with polyphosphoric acid on one occasion gave the *cis* isomer and later, under the same reaction conditions (1 hr. at 60°), yielded the *trans* isomer. In these experiments, a mixture of *cis* and *trans* isomers of varying composition was formed. Higher reaction temperatures (60–70°) gave mixtures richer in *trans* isomer, and a lower reaction temperature (25°) gave mixtures richer in *cis* isomer. The isomers were separated by fractional crystallization from isopropyl alcohol. The *cis* isomers were less soluble.

The best method of synthesis of the *cis* isomer of a 5,6-dihydro-4*H*-1,3,4-oxadiazine was one in which an appropriate N-acylamino-*l*-ephedrine was stirred with excess polyphosphoric acid for 18 hr., unchanged N-acylamino-*l*-ephedrine was removed by adsorption onto alumina, and the mixture of *cis* and *trans* (mostly *cis*) isomers was separated by careful crystallization from a dilute solution at room temperature.

Cyclodehydration of N-benzoylamino-*l*-ephedrine (I) with phosphorus pentoxide in refluxing toluene gave *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II). The *cis*- and *trans*-5,6-dihydro-4*H*-1,3,4-oxadiazines are listed in Table I.

The 4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines, II and III, were designated *cis* and *trans*, respectively, on the basis of n.m.r. data (see Table II). Both II and III exhibit essentially the same chemical shifts regarding their protons—one sharp line (−7.29 for II and −7.30 p.p.m. for III) due to a phenyl group attached to an "ordinary" tetrahedral carbon (C-6), and two structured groups (−7.83 and −7.25 for II and −7.77 and −7.24 p.p.m. for III) caused by a phenyl group with a carboxyl-type substituent (C-2). The N-methyl groups (N-4), having essentially identical shifts (−2.80 for II and −2.81 p.p.m. for III), must be structurally and chemically quite similar. The system $-OCH(C_6H_5)CH(CH_3)-$ is seen in both II and III, but their shifts and couplings differ. Assuming the ring takes the likely half-chair form of cyclohexene,

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

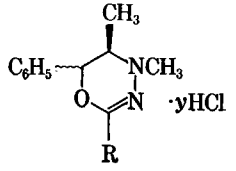
(2) D. L. Trepanier, V. Sprancmanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668 (1964).

(3) D. L. Trepanier and V. Sprancmanis, *ibid.*, **29**, 673 (1964).

(4) We have selected Newman projection formulae I and IV to represent the preferred conformations of N-benzoylamino-*l*-ephedrine and N-benzoylamino-*d*-pseudoephedrine on the basis of reports by L. H. Welsh [*J. Am. Chem. Soc.*, **71**, 3500 (1949)], W. J. Close [*J. Org. Chem.*, **15**, 1131 (1950)], and J. B. Hyne [*J. Am. Chem. Soc.*, **81**, 6058 (1959)].

TABLE I

2-SUBSTITUTED 4,5-DIMETHYL-6-PHENYL-5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES[a]

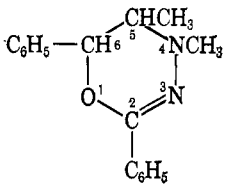


R	*y*	Configuration at C-5 and C-6	M.p., °C.	Method[b] of prepn.	% yield[c]	Recrystn. solvent	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	$[\alpha]^{28}D$ (*c*, solvent)[d]
C_6H_5	0	*trans*	142–143	H_2SO_4, 25°, 18 hr.	46	*i*-PrOH	76.66	6.81	10.52	76.41	7.02	10.10	+213 ± 2° (3.99, C_6H_6)
				PPA, 60°, 1 hr.	49								
C_6H_5	0	*cis*	101–102	PPA, 60°, 1 hr.	32	*i*-PrOH	76.66	6.81	10.52	76.63	6.81	10.62	−239 ± 2° (4.17, C_6H_6)
				PPA, 25°, 24 hr.	67[e]								
				P_2O_5, 110°, 18 hr.	44								
4-$CH_3OC_6H_4$	1	*trans*	159–161		95[f]	2-Butanone–ether	64.95	6.36	8.42	65.59	6.48	8.65	+34.8 ± 2° (4.02, $CHCl_3$)
4-$CH_3OC_6H_4$	1	*cis*	164.5–165.5[g]	PPA, 25°, 18 hr.[h]	50	2-Butanone	64.95	6.36	8.42	64.19	6.31	9.00	−78 ± 3° (4.22, $CHCl_3$)
4-$C_2H_5OC_6H_4$	0	*trans*	101–102	H_2SO_4, 25°, 18 hr.	57	*i*-PrOH	73.52	7.15	9.03	73.62	7.36	9.17	+176 ± 2° (4.10, C_6H_6)
4-$C_2H_5OC_6H_4$	0	*cis*	88–89	PPA, 60°, 1 hr.	25	*i*-PrOH	73.52	7.15		74.12	7.30		−164 ± 2° (4.02, $CHCl_3$)
4-$CH_3OC_6H_4$	0	*trans*	123.5–124.5	H_2SO_4, 25°, 18 hr.	55	*i*-PrOH	72.95	6.80		72.93	6.92		+190 ± 2° (4.11, C_6H_6)
				PPA, 60°, 1 hr.	94								

[a] Compounds listed in Table I were prepared from N-acylamino-*l*-ephedrines and not from diastereoisomeric N-acylamino-*d*-pseudoephedrines. [b] See Experimental section. [c] No attempt was made to obtain optimum yields. [d] Rudolph Laboratory Polarimeter Model No. 62. [e] Also isolated 6.1% yield of the *trans* isomer. [f] Prepared by treating the free base with ethereal hydrogen chloride. [g] A mixture of *cis*- and *trans*-4,5-dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochlorides melted at 132–148°. [h] Free base purified by chromatography on Merck acid-washed alumina (No. 71695). Hydrochloride prepared by treating free base with ethereal hydrogen chloride.

TABLE II

N.M.R. DATA OF *cis*- AND *trans*-4,5-DIMETHYL-2,6-DIPHENYL-5,6-DIHYDRO-4*H*-1,3,4-OXADIAZINES[a]



Substituents	Chemical shifts, – p.p.m. *cis* isomer	*trans* isomer
2-C_6H_5, *o*-H's	7.83	7.77
m- and *p*-H's	7.25	7.24
4-CH_3	2.80	2.81
5-H	3.23	2.61
6-H	5.40	4.95
5-CH_3	0.75	1.02
6-C_6H_5	7.29	7.30
	Coupling constants, c.p.s.	
J (H-5–H-6)	2.90	7.54
J (H-5–CH_3)	6.37	6.58
J (H-6–CH_3)	0	0

[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. CCl_4 solutions containing a trace of tetramethylsilane (TMS) as internal reference. The chemical shifts are given as the negative values of the shielding in parts per million relative to TMS at 0.00 p.p.m., and pertinent coupling constants, *J*, are given in cycles per second.

a value of 2.90 c.p.s. for *J* (H-5–H-6) indicates the dihedral angle between the C–H bonds is approximately 60° and the 5- and 6-protons are gauche. Thus II is the *cis* isomer. The 5-CH_3 and 6-C_6H_5 substituents are axial–equatorial either way with rapid interchange possible, although one might expect the form with 6-C_6H_5 equatorial to be preferred. The *trans* isomer (III) has a coupling constant of 7.54 c.p.s. for *J* (H-5–H-6) indicative of 5- and 6- protons *trans* axial–axial with a dihedral angle approaching 180°, and the 5-CH_3 and 6-C_6H_5 groups always equatorial.

The infrared spectra of *cis*- and *trans*-2-substituted-5,6-dihydro-4*H*-,1,3,4-oxadiazines exhibit a difference in the 1350–1400-cm.$^{-1}$ region (see Fig. 1). The *trans* isomers exhibit bands at 1383 (vs) and 1368 (w), and *cis* isomers exhibit bands at 1380 (s) and 1354 (vs). This consistent difference in infrared absorption provides a basis for easy differentiation of *cis* and *trans* isomers in this series of compounds.

The ultraviolet absorption of *cis*- and *trans*-2-substituted 5,6-dihydro-4*H*-1,3,4-oxadiazines are practically identical. For example, *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II) exhibits $\lambda_{max}^{CHCl_3}$ 240 mμ (ϵ 4840) and 296 mμ (ϵ 9740), and *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III) exhibits $\lambda_{max}^{CHCl_3}$ 240 mμ (ϵ 4640) and 294 mμ (ϵ 9080).

cis- and *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazines (II and III) behaved differently when subjected to acid hydrolysis. The *cis* isomer (II) readily yielded N-benzoylamino-*l*-ephedrine. The *trans* isomer (III) was more difficult to hydrolyze[5] and gave benzoic acid as the only identified product.

The experimental results show that sulfuric acid dehydration gives exclusively the thermodynamically more stable *trans* isomer regardless of whether the starting 2-(β-hydroxyalkyl) acid hydrazide has the *threo* or *erythro* configuration. PPA at 25° gives mainly the kinetically controlled product, whose configuration is determined by the configuration of the starting 2-(β-hydroxyalkyl) acid hydrazide. N-(acylamino)ephedrines give mainly *cis* isomer contaminated with a small amount of *trans* isomer. N-acylaminopseudoephedrines give exclusively *trans* isomer with PPA because this is both the kinetically controlled and the thermodynamically more stable product. As the reaction temperature is elevated to 60–70°, PPA cyclodehydration of N-(acylamino) ephedrines gives a mixture of *cis* and *trans* isomers much richer in *trans* isomer, so much so that it may be the predominant isomer in the mixture.

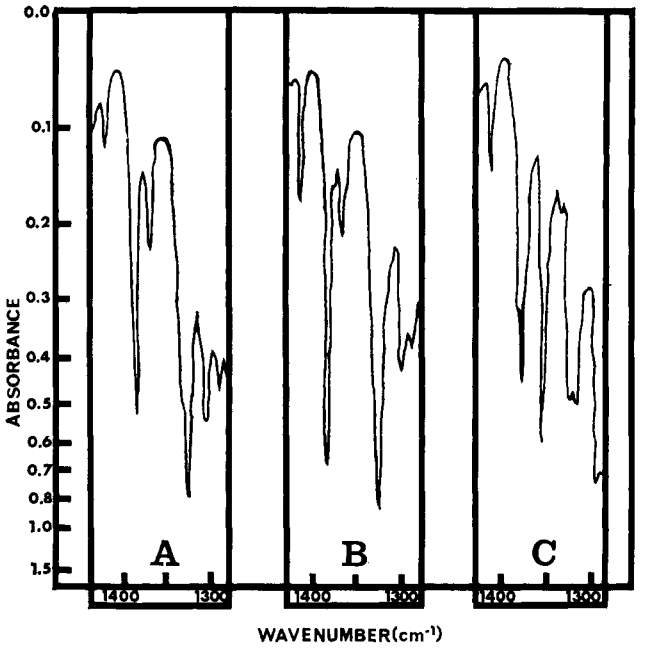


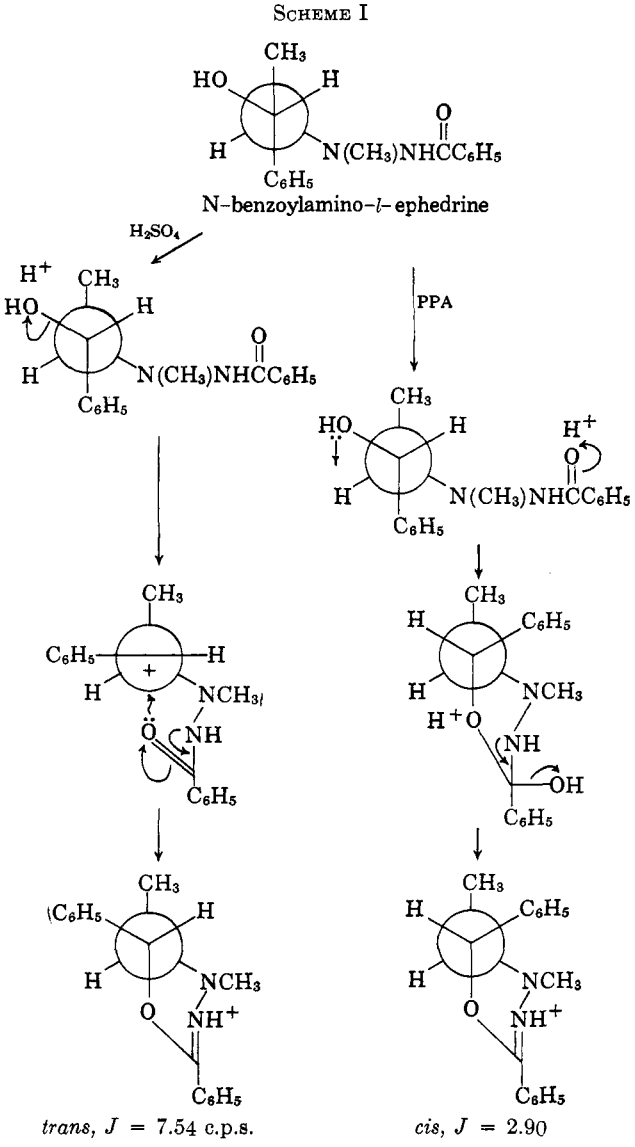
Fig. 1.—Portion of infrared spectra of *trans*-4,5-dimethyl-2-(*o*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (A), *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (B), and *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (C).

We propose the following mechanism (see Scheme I) to account for the different results obtained with sulfuric and polyphosphoric acids. Sulfuric acid protonates the hydroxyl group of the 2-(β-hydroxyalkyl) acid hydrazide and this then dissociates into a water molecule and a carbonium ion. Formation of a trigonal carbonium ion destroys the asymmetry of the hydroxyl-bearing carbon atom and allows the phenyl and hydrogen to assume the most stable configuration. N-benzoylamino-*l*-ephedrine and N-benzoylamino-*d*-pseudoephedrine form the same intermediate carbonium ion because they differ only in configuration about the hydroxyl-bearing carbon atom. The carbonium carbon is attacked by the nucleophilic oxygen of the hydrazide carbonyl giving the conjugate acid of the *trans*-oxadiazine.

Polyphosphoric acid at 25° cyclodehydrates mainly with retention of configuration, and thus either produces no inversion or an equal number of inversions. A reasonable pathway requiring no inversion is one in which PPA protonates the carbonyl oxygen, and this is followed by attack of the hydroxylic oxygen atom upon

(5) Hydrolysis was repeated using either hydrochloric, hydrobromic, or sulfuric acids.

SCHEME I



the carbonyl carbon and subsequent loss of water, giving the conjugate acid of either the *cis*- or *trans*-oxadiazine depending upon the configuration about the hydroxyl-bearing carbon of the starting 2-(β-hydroxyalkyl) acid hydrazide.

Alternatively, both sulfuric acid and PPA may initially cyclodehydrate with retention of configuration followed, in the case of sulfuric acid, by a very rapid isomerization to the more stable *trans* form, and, in the case of PPA, by a slow isomerization to the *trans* form.

Additional work is planned to gain a better understanding of the mechanism and scope of this cyclodehydration reaction.

Experimental[6]

General Procedures for the Preparation of the Compounds Listed in Table I. Sulfuric Acid Method.—The N-acylamino-*l*-ephedrine was added, portionwise, with swirling, to five times its weight of concentrated sulfuric acid. After 18 hr., the mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue was crystallized from an appropriate solvent.

Polyphosphoric Acid Method.—A mixture of the N-acylamino-*l*-ephedrine and twenty times its weight of polyphosphoric acid was kept either at 60° for 1 hr. or at 25° for 18–24 hr. (see Table I). The cooled 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*, and the residue was crystallized from an appropriate solvent.

Phosphorus Pentoxide Method.—A stirred mixture of 6.0 g. N-benzoylamino-*l*-ephedrine, 3.0 g. phosphorus pentoxide, and 150 ml. toluene was refluxed for 18 hr. The cooled mixture was washed (sodium carbonate, water), dried (magnesium sulfate), and evaporated *in vacuo*. The residue was crystallized from an appropriate solvent.

Conversion of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (II) to *trans*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine (III).—A mixture of 1.0 g. of II and 20 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 24 hr. and then was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo*, and the residue was recrystallized from isopropyl alcohol: m.p. 142–143°, yield 0.83 g. (83%).

Conversion of *cis*-4,5-Dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine to *trans*-4,5-Dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.—A mixture of 1.0 g. of *cis*-4,5-dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochloride and 25 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 2 hr. and then was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue recrystallized from isopropyl alcohol gave 1.1 g. (63%) of *trans*-4,5-dimethyl-2-(*p*-methoxyphenyl)-6-phenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 123–124.5°.

Treatment of N-Benzoylamino-*d*-pseudoephedrine Hydrochloride with Sulfuric Acid.—N-Benzoylamino-*d*-pseudoephedrine hydrochloride[7] (2.0 g.) was added, portionwise, with swirling, to 10 ml. of concentrated sulfuric acid. After standing at 25° for 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 *in vacuo*. The residue was crystallized from isopropyl alcohol to give 1.1 g. (65%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine which melted at 142–143.5°, $[\alpha]^{28}D$ +211 ± 2° (*c* 4.07, C_6H_6).

Treatment of N-Benzoylamino-*d*-pseudoephedrine Hydrochloride with Polyphosphoric Acid.—A mixture of 1.0 g. of N-benzoylamino-*d*-pseudoephedrine hydrochloride[7] and 30 g. of polyphosphoric acid was stirred for 15 min. and then allowed to stand at room temperature for 18 hr.[8] The mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue recrystallized twice from isopropyl alcohol gave 0.53 g. (64%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 142–143°, $[\alpha]^{28}D$ +210 ± 2° (*c* 4.12, C_6H_6).

Acid Hydrolysis of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.—A mixture of 1.0 g. of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, 10 ml. of ethanol, and 4 ml. of concentrated hydrochloric acid was refluxed for 20 hr., cooled, treated with 30 ml. of water, extracted with ether, basified with sodium hydroxide solution, and extracted with ether. The ether extract of the alkaline aqueous mixture was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue recrystallized from isopropyl alcohol gave 0.42 g. (40%) of N-benzoylamino-*l*-ephedrine (I), m.p. 168–170°, identical in its melting point and infrared spectrum with authentic I.

Acid Hydrolysis of *trans*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine.—A mixture of 1.0 g. of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, 30 ml. of

(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. Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer.

(7) The same results were obtained when this experiment was repeated with the free base.

(8) Heating at 75° for 1 hr. gave the same result.

concentrated hydrochloric acid,[9] and 30 ml. of water was refluxed for 20 hr. The hot mixture was treated with charcoal and filtered. The cooled filtrate deposited 0.23 g. of benzoic acid, m.p. 121–122°.

Treatment of *cis*-4,5-Dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine with PPA. A. Ambient Temperature.—A mixture of 3.0 g. of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine and 50 g. of PPA was allowed to stand, with occasional stirring, at room temperature for 24 hr. The mixture was poured onto crushed ice and extracted with chloroform. The washed (sodium carbonate, water) and dried (magnesium sulfate) chloroform solution was evaporated *in vacuo*, and the residue was recrystallized from isopropyl alcohol to give 2.5 g. (83%) of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine, m.p. 97.5–101.5°.

B. At 65°.—The reaction was repeated as above, except that the mixture was heated at 65° for 1 hr. instead of being kept at 25° for 24 hr. There was obtained 0.66 g. (22%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4*H*-1,3,4-oxadiazine which melted at 141–142°, and 1.7 g. (57%) of the unchanged *cis* isomer, m.p. 100–101°.

(9) Sulfuric and hydrobromic acids gave benzoic acid as the only identified product.

Acknowledgment.—The authors express their appreciation to Drs. W. J. Potts and J. Heeschen for recording and interpreting infrared and n.m.r. data, respectively.

Reactions of N-Benzylthieno[3,2-*b*]pyrrole. I. Metalation and an Electrophilic Substitution[1]

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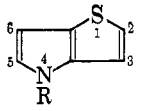
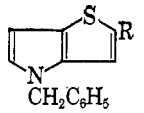
Received January 20, 1964

Treatment of N-benzylthieno[3,2-*b*]pyrrole (Ib) with a slight excess of *n*-butyllithium yielded the 2-lithium compound, IIa, which was converted to the 2-carbomethoxy derivative, IIb. The structure of IIb was shown by nuclear magnetic resonance spectroscopy and by unequivocal chemical evidence. The reaction of Ib with *n*-butyllithium in large excess, followed by carbonation and esterification, afforded a tricarbomethoxy derivative believed to be III. The action of acetyl chloride and stannic chloride on Ib in benzene at 0° led to the 5-acetyl derivative, VIII.

A practical synthesis of thieno[3,2-*b*]pyrrole (Ia) was developed by Matteson and Snyder,[2] but investigations of the chemistry of this compound were severely restricted by its instability. The stability of the ring system of Ia can be increased, however, by placing a benzyl group on the nitrogen atom, and the resulting compound, N-benzylthieno[3,2-*b*]pyrrole (Ib), has been prepared.[3] The chemistry of Ib has not been explored previously; its behavior toward *n*-butyllithium and under Friedel–Crafts acetylation conditions is now described.



Ia, R = H
b, R = $CH_2C_6H_5$



IIa, R = Li
b, R = CO_2Me

When N-benzylthieno[3,2-*b*]pyrrole (Ib) was allowed to react with *n*-butyllithium, 4-benzylthieno[3,2-*b*]-pyrrole-2-lithium (IIa) evidently was formed. The reaction of this lithium derivative with acetyl chloride at −78° led to uncharacterizable products, but carbonation of IIa followed by treatment with diazomethane afforded 2-carbomethoxy-4-benzylthieno[3,2-*b*]pyrrole (IIb) in 70% yield, based on Ib. The lithium compound IIa is the first derivative prepared by direct substitution of N-benzylthieno[3,2-*b*]pyrrole.

The structure of IIb was initially deduced from its nuclear magnetic resonance (n.m.r.) spectrum. The n.m.r. spectrum of N-benzylthieno[3,2-*b*]pyrrole (Ib) has been examined,[4] and the new data obtained in this work are tabulated in Table I.[5] Spin–spin interactions are observed between the α- and β-thiophene protons, and between the α- and β-pyrrole protons. In addition, long-range spin–spin couplings between the α-thiophene and α-pyrrole protons, and between the β-thiophene and β-pyrrole protons, are observed. The former interaction is large enough to be clearly visible, but the latter, being of a magnitude close to the limit of resolution of the instrument, hitherto has been observed only once.[4]

The n.m.r. spectrum of IIb showed a multiplet centered at τ 2.77 (benzene ring protons), a singlet at 4.85 (benzyl methylene protons), and a singlet at 6.19 (carbomethoxy protons). It also had doublets at τ 2.98 and 3.61 (J = 3.0 c.p.s.), and a singlet at 2.47, each having an area corresponding to one proton. Because of the field strengths at which they appeared and the magnitude of their coupling constant, the doublets were assigned to the α- and β-pyrrole protons, respectively. The absence of evidence of interaction between an α-thiophene proton and the α-pyrrole proton indicated that the former proton was missing. The remaining singlet at τ 2.47 was therefore assigned to the β-thiophene proton.

The lowering of the field strength at which the β-thiophene proton in IIb absorbs is not surprising. Gale[6] noted a shift of 0.80 τ-unit to lower field in the position of absorption of the β-thiophene proton in going from 5-carbethoxythieno[3,2-*b*]pyrrole to 2,5-dicarbethoxy-

(1) Supported by a grant (C 3969) from the U. S. Public Health Service.

(2) D. S. Matteson and H. R. Snyder, *J. Am. Chem. Soc.*, **79**, 3610 (1957); *J. Org. Chem.*, **22**, 1500 (1957).

(3) A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 1597 (1960).

(4) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(5) Proton magnetic resonance spectra were obtained by Mr. D. H. Johnson and his associates with a Varian Associates A-60 spectrometer. Tetramethylsilane was employed as an internal standard. Chemical shifts are expressed in τ-units as defined by G. V. D. Tiers [*ibid.*, **62**, 1151 (1958)].

(6) W. W. Gale, Thesis, Doctor of Philosophy, University of Illinois, Urbana, Ill., 1961.