(IXa) remained. It melted at 114–115° after recrystallization from benzene.

The entire crop of IXa (17.8 g., 0.063 mole) was dissolved in 100 ml. of chloroform and a solution of 4.50 ml. (0.063 mole) of thionyl chloride in 50 ml. of chloroform was added. The resulting solution was heated for 3 hr. under reflux. The solvent was evaporated under reduced pressure leaving a semisolid mass. Boiling water was admitted to the flask and the mixture was agitated for a few seconds. The aqueous solution was decanted from the residual oil and quickly cooled. The solution was washed with ether and the ether was discarded. The solution was made basic by the addition of concentrated potassium carbonate solution and the mixture was extracted several times with methylene chloride. The methylene chloride solution was dried over magnesium sulfate and evaporated to a cloudy, colorless oil. The oil was distilled through a short Vigreux column; the material began to boil at 153° (0.30 mm.) and the fraction boiling at 155–156° (0.30 mm.) was collected, yield 8.0 g. (48%).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.60; H, 7.11; N, 10.68.

***d-trans*-3,4-Dimethyl-2-methylimino-5-phenyloxazolidine Hydrochloride (VIIa).**—A solution of hydrous ephedrine alkaloid (Merck and Co., Inc.) in chloroform was dried over magnesium sulfate, and the solvent was evaporated leaving anhydrous ephedrine as a clear oil. A solution of 4.1 g. (0.072 mole) of methyl isocyanate in 25 ml. of chloroform was added to a solution of 11.9 g. (0.072 mole) of the anhydrous ephedrine in 50 ml. of chloroform. The reaction mixture was stirred at 0° for 30 min. and allowed to come to room temperature over a period of 2 hr. The solution was boiled briefly to remove excess methyl isocyanate. To the solution was added 5.2 g. (0.072 mole) of thionyl chloride. The mixture was stirred at room temperature for 1 hr. and heated under reflux for 2 hr. The solvent was evaporated and the white crystals which remained were slurried with ether and collected by filtration, yield 16.5 g. (95%), m.p. 195–196°. The analytical sample was obtained by dissolving the crystals in methanol and precipitating with ether, m.p. 198–199°.

Anal. Calcd. for $C_{12}H_{16}N_2O \cdot HCl$: C, 59.87; H, 7.12; N, 11.63. Found: C, 59.80; H, 7.34; N, 11.58.

The free base for spectral studies was obtained by the following procedure. A solution of 8.0 g. of *d-trans*-3,4-dimethyl-2-methylimino-5-phenyloxazoline hydrochloride in 25 ml. of water was made strongly basic by the addition of 50% sodium hydroxide solution. The mixture was extracted twice with ether, and the ether solution was washed with saturated brine, dried over magnesium sulfate, and concentrated *in vacuo* to give 6.5 g. of a yellow oil. Distillation of the oil through a short Vigreux column afforded 3.14 g. of a colorless, low-melting, hygroscopic solid, b.p. 102° (0.25 mm.), $[\alpha]^{27}D$ +12.1° (*c* 10.0, methanol).

***d-trans*-3,4-Dimethyl-5-phenyl-2-phenyliminooxazolidine (VIIb).**[13] **A. From Ephedrine.**—A solution of 14.3 g. (0.12 mole) of phenyl isocyanate in 50 ml. of chloroform was added to a solution of 20.0 g. (0.12 mole) of anhydrous *l*-ephedrine in 150 ml. of chloroform. The resulting solution was heated under reflux for 2 hr., and the solvent was evaporated under reduced pressure. The residual gum crystallized on standing and was recrystallized from benzene–hexane to give 26.8 g. (78%) of white crystalline *erythro*-1-(β-hydroxy-α-methylphenethyl)-3-methyl-1-phenylurea (Xb), m.p. 130–132°.

The cyclization of Xb (25.0 g., 0.088 mole) by the action of thionyl chloride (10.5 g., 0.088 mole) and boiling water was carried out as described for VIe. The product crystallized without need for distillation and was recrystallized twice from 2-propanol, yield 15.6 g. (68%), m.p. 94–95° (lit.[13] m.p. 187°), $[\alpha]^{27}D$ +46.2° (*c* 10.0, methanol).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.62; H, 6.97; N, 10.30.

B. From VIIa.—A solution of 0.449 g. (0.0022 mole) of *d-trans*-3,4-dimethyl-2-methylimino-5-phenyloxazolidine (VIIa) and 0.239 g. (0.0022 mole) of phenyl isothiocyanate in 5 ml. of hexane was allowed to stand for 4 days at room temperature in a stoppered vessel. The solvent was distilled from the mixture on a steam bath. After several hours the resultant oil was induced to crystallize. The material was recrystallized from hexane, yield 0.319 g. (55%), m.p. 92–94°. Further recrystallization from hexane afforded crystals melting at 94–95°, identical by solid state infrared spectrum and mixture melting point with VIIb prepared by method A.

Deuteration of *dl-cis*-2-Amino-4-methyl-5-phenyl-2-oxazoline (IV).—A suspension of 200 mg. of freshly sublimed *dl-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline (IV) in 2.0 ml. of deuterium oxide was agitated for 18 hr. at 40°. The solid was collected by filtration, dried *in vacuo*, and sublimed. All operations on this material were carried out in a drybox since it is hygroscopic. It was estimated that 79 ± 3% of the two exchangeable hydrogen atoms on nitrogen had been replaced by deuterium by averaging five n.m.r. integral runs measured on a digital voltmeter. A 9.84×10^{-4} *M* solution in deuteriochloroform of the deuterated IV was prepared for infrared analysis by dilution of the solution used for the n.m.r. determination. The infrared spectrum, determined in 1-cm. quartz cells, showed a band at 2.88 μ with only shoulders at 2.83 and 2.92 μ where the undeuterated IV absorbs.

Acknowledgment.—We are indebted to Professor Alan R. Katritzky for a helpful discussion of infrared spectra and to Mrs. M. C. Christie for many of the spectral determinations.

5,6-Dihydro-4H-1,3,4-thiadiazines[1]

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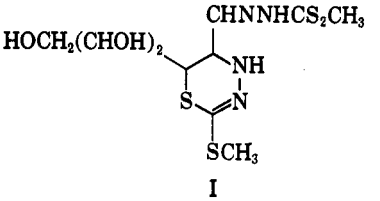
Treatment of 2-(β-hydroxyalkyl)carboxylic acid hydrazides with phosphorus pentasulfide gave substituted 5,6-dihydro-4H-1,3,4-thiadiazines. The scope of this reaction has been explored. *cis* and *trans* isomers have been synthesized and their conformation has been proposed on the basis of n.m.r. data. The mechanism of the reaction is discussed.

As part of a continuing program of exploratory research in heterocyclic chemistry, we turned our attention to the 5,6-dihydro-4H-1,3,4-thiadiazine system.

A survey of the literature showed that Hull, during an investigation of carbohydrate derivatives of alkyl dithiocarbazates, reported[3] that D-glucosamine and methyl dithiocarbazate reacted abnormally to give a product which, on the basis of elemental analysis, could be I.



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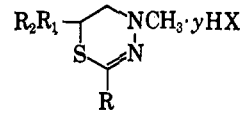
(3) R. Hull, *J. Chem. Soc.*, 2959 (1952).

TABLE I

SUBSTITUTED 5,6-DIHYDRO-4H-1,3,4-THIADIAZINES[a]

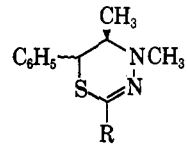


R	R_1	R_2	y	X	B.p. (mm.) or m.p., °C.	Yield, %	Recrystn. solvent	Calcd., % C	Calcd., % H	Calcd., % S	Found, % C	Found, % H	Found, % S
C_6H_5	CH_3	H	1	Cl	126–127	28	MeOH–Et_2O	54.42	6.23	13.21	54.52	6.20	13.77
Cyclo-C_6H_{11}	H	H	1	Cl	131–132	64	EtOAc	51.15	8.16	13.65	50.99	8.38	13.40
$C_6H_5CH_2$	CH_3	H	0		135–144 (0.5)	70		65.41	7.32	14.55	65.31	7.43	14.95
4-ClC_6H_4	CH_3	H	1	Br	156–160	35	MeOH–$(i\text{-Pr})_2O$	41.07	4.39	24.84[b]	41.19	4.72	24.93[b]
4-$CH_3OC_6H_4$	CH_3	H	1	Br	148–149	68	MeOH–$(i\text{-Pr})_2O$	45.43	5.40	25.19[b]	45.40	5.63	25.67[b]
4-ClC_6H_4	C_6H_5	H	0		65–66	27	EtOH	63.46	4.99	10.59	63.19	5.14	10.82
4-$CH_3C_6H_4$	CH_3	CH_3	0		145–148 (0.4)	75		66.62	7.74	13.68	66.51	7.83	13.83
3,4-$Cl_2C_6H_3$	H	H	0		160–163 (0.2)	46		46.00	3.86	12.66	45.92	4.28	11.35
3,4-$Cl_2C_6H_3$	CH_3	H	0		148–150 (0.1)	36		48.00	4.39	10.18	47.81	4.22	10.86

[a] Method A (described in the Experimental section) was used. [b] Bromine.

TABLE II

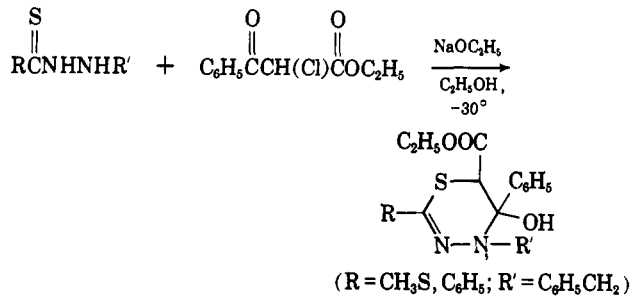
cis AND *trans* 2-SUBSTITUTED 4,5-DIMETHYL-6-PHENYL-5,6-DIHYDRO-4H-1,3,4-THIADIAZINES



R	Configuration at C-5–C-6	M.p., °C.	Yield, %	a	Recrystn. solvent	Calcd., % C	Calcd., % H	Calcd., % S	Found, % C	Found, % H	Found, % S	N.m.r. assignments[b] Chemical shifts, p.p.m. 4-CH_3	5-CH_3	5-H	6-H	$J_{5,6}$, c.p.s.
C_6H_5	*cis*	90–91.5	29	A	EtOH	72.30	6.42	11.35	72.70	6.64	11.29	3.05	0.93	3.42	4.85	3.3
C_6H_5	*trans*	68–69.5	46	B	EtOH	72.30	6.42	11.35	72.51	6.71	11.34	3.03	1.24	3.15	4.26	4.0
4-$CH_3C_6H_4$	*cis*	78–80	42	A	EtOH	72.93	6.80	10.82	72.59	6.91	11.03	3.01	0.90	3.36	4.83	3.2
4-$CH_3C_6H_4$	*trans*	91.5–92.5	46	B	EtOH	72.93	6.80	10.82	72.94	6.85	10.71	3.01	1.23	3.12	4.25	4.2
4-$CH_3OC_6H_4$	*cis*	117–119	31	A	*i*-PrOH	69.20	6.45	10.26	69.09	6.44	10.35	3.01	0.89	3.36	4.84	3.4
4-$CH_3OC_6H_4$	*trans*	88–89	41	B[c]	EtOH	69.20	6.45	10.26	69.27	6.45	10.43	3.00	1.23	3.11	4.26	4.2
4-$C_2H_5OC_6H_4$	*cis*	98–99	35	A	EtOH	69.69	7.08	9.79	69.69	7.01	9.98	3.03	0.91	3.40	4.87	3.3
2-$CH_3OC_6H_4$	*trans*	102–105	23	A	EtOH	69.20	6.45	10.26	70.88	6.36	10.12	2.92	1.26	3.08	4.19	4.2
$C_6H_5CH_2CH_2$	*trans*	111–112	27	A	EtOH	73.50	7.14	10.33	72.93	8.01	10.35	2.80	1.05	2.8	4.11	4.5
4-ClC_6H_4	*cis*	69–70	49	A	EtOH	64.44	5.41	10.12	64.95	5.56	9.74	3.03	0.89	3.39	4.78	3.3
2,4-$Cl_2C_6H_3$	*trans*	117–119	23	A	$(i\text{-Pr})_2O$	58.12	4.59	9.13	58.42	4.86	9.14	2.97	1.32	3.15	4.26	3.7
4-$O_2NC_6H_4$	*trans*	127–128	26	B	EtOH	62.36	5.24	9.80	62.65	5.69	9.78	3.15	1.31	3.33	4.29	3.7
2,3-$(CH_3O)_2C_6H_3$	*trans*	95.5–97	19	B	EtOH	66.63	6.48	9.36	66.86	6.51	9.41	2.96	1.30	3.13	4.23	4.0

[a] Methods A and B are described in Experimental section. [b] N.m.r. spectra were obtained at 60 Mc., with a Varian A-60 spectrometer, for 10% $CDCl_3$ solutions containing a trace of tetramethylsilane (TMS) as an internal standard. Chemical shifts are measured as shielding (p.p.m.) relative to the shielding of the TMS protons, and are tabulated as the negative of this value. [c] Also obtained in 4% yield by method A.

Sandstrom[4] synthesized several dihydrothiadiazines by treating appropriate thiohydrazides with ethyl chlorobenzoylacetate in the presence of sodium ethoxide in absolute ethanol at −30°. Owing to the electron-withdrawing property of the phenyl and carboethoxy groups, these compounds are unstable and darken even at −30°. At higher temperatures they rapidly lose water across the 5,6-positions, followed by the elimination of sulfur, to form the corresponding pyrazoles.



(R = CH_3S, C_6H_5; R′ = $C_6H_5CH_2$)

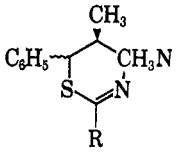
We synthesized 5,6-dihydro-4H-1,3,4-thiadiazines by treating 2-(β-hydroxyalkyl)carboxylic acid hydrazides with 1 mole equiv. of phosphorus pentasulfide in refluxing chloroform for a period of from 4 to 24 hr. and by cyclodehydrating 2-(β-hydroxyalkyl)thiocarboxylic acid hydrazides with concentrated sulfuric acid at 25°.

The phosphorus pentasulfide reaction is quite general and of broad scope as evidenced by the fact the reaction proceeded as expected when the hydroxyl group was primary, secondary, or tertiary aliphatic or secondary benzyl, and the R of the acyl moiety was phenyl, variously substituted phenyl, benzyl, phenethyl, or cyclohexyl (Tables I and II).

(4) J. Sandstrom, *Acta Chem. Scand.*, **16**, 2395 (1962).

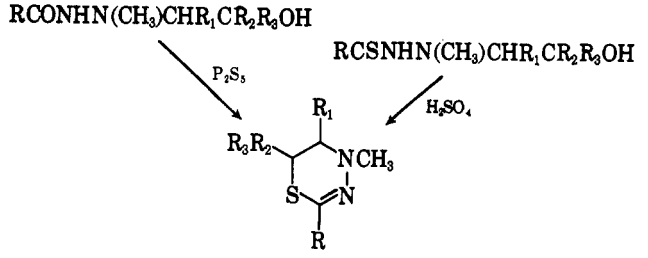
TABLE III

ULTRAVIOLET ABSORPTION AND OPTICAL ROTATION OF *cis*- AND *trans*-4,5-DIMETHYL-6-PHENYL-5,6-DIHYDRO-4H-1,3,4-THIADIAZINES



Compd.	R	Configuration at C-5–C-6	Molar absorption, $\lambda_{max}^{CHCl_3}$, mμ (ε × 10⁻³)[a]	[α]D (c, g./100 ml. of C_6H_6)[b]
1	4-$CH_3OC_6H_4$	*cis*	254 (14.8), 308 (6.6)	−152.7 ± 1.8 (4.078)
2	4-$CH_3OC_6H_4$	*trans*	253 (16.0), 308 (10.2)	−71.8 ± 2.3 (4.288)
3	4-ClC_6H_4	*cis*	245 (17.8), 325 (9.4)	−180.9 ± 2.4 (3.858)
4	4-ClC_6H_4	*trans*	246 (18.6), 324 (9.8)	−55.1 ± 1.8 (3.940)
5	4-$CH_3C_6H_4$	*cis*	246 (19.7), 316 (5.5)	−170.3 ± 1.8 (3.920)
6	4-$CH_3C_6H_4$	*trans*	243 (17.9), 315 (9.2)	−79.5 ± 2.0 (4.080)
7	$C_6H_5CH_2CH_2$	*trans*	262 (3.0)	−255.7 ± 3.2 (3.790)
8	4-$C_2H_5OC_6H_4$	*cis*	254 (15.5), 309 (6.9)	−140.5 ± 2.6 (3.774)
9	C_6H_5	*trans*	245 (15.2), 319 (8.1)	−94.3 ± 2.8 (3.412)

[a] Ultraviolet absorption maxima and molar absorption were measured on a Beckman DU spectrophotometer. [b] Optical rotation was measured on a Rudolph laboratory polarimeter Model No. 62 at room temperature.



R = C_6H_5, cyclo-C_6H_{11}, $C_6H_5CH_2$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 3,4-$Cl_2C_6H_3$, 2-$CH_3OC_6H_4$, $C_6H_5CH_2CH_2$, 2,4-$Cl_2C_6H_3$, 4-$O_2NC_6H_4$, 4-$C_2H_5OC_6H_4$
R_1 and R_2 = H, CH_3
R_3 = H, CH_3, C_6H_5

The scope of the sulfuric acid cyclodehydration reaction was not investigated. The hydroxyl group was a benzyl type in every case. However, the R of the thioacyl moiety was varied to include phenyl, 4-methyl-, 4-nitro-, 4-methoxy-, and 2,3-dimethoxyphenyl (Table II).

The proposed structure for the substituted 5,6-dihydro-4H-1,3,4-thiadiazines is substantiated by elemental analysis, ultraviolet and infrared spectral data, and n.m.r. measurements.

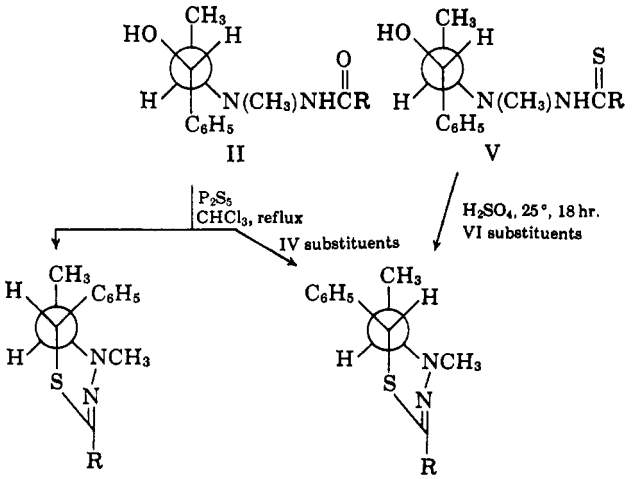
The ultraviolet absorption spectra exhibit two maxima (Table III), one in the 245–262-mμ region and the other in the 308–325-mμ region, with molar absorptions of 3–20 × 10^3 and 4–10 × 10^3, respectively. The maximum at 308-325 mμ is indicative of the chromophore C=N in conjugation with a phenyl or substituted phenyl moiety. When this conjugation is interrupted, as in the case of *trans*-4,5-dimethyl-2-phenethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine (compound **7**, Table III), there is no absorption in the 308–325-mμ region.

Infrared analysis indicates the absence of OH, NH, and hydrazide carbonyl. No absorption bands of any reasonable intensity are observed in the 1650–1800-cm.$^{-1}$ region, indicating the absence of any but the most strongly hydrogen-bonded or conjugated carbonyl groups (the former types being excluded by the absence of OH and NH groups). A fairly intense absorption is noted near 1610 cm.$^{-1}$ which is good evidence for S—C=N.

Proton n.m.r. analysis detected the expected chemical shifts and coupling constants (Table II).

In order to learn more about the mechanism of this reaction, we synthesized 2-(β-hydroxyalkyl)carboxylic and thiocarboxylic acid hydrazides with two asymmetric carbon atoms and treated them with phosphorus pentasulfide and concentrated sulfuric acid, respectively. The 2-(β-hydroxyalkyl)carboxylic acid hydrazides were derived from L-(−)-ephedrine and possess the *erythro* configuration (II).

Upon treatment with phosphorus pentasulfide in refluxing chloroform, II gave either *cis*- or *trans*-5,6-dihydro-4H-1,3,4-thiadiazines (III or IV) or a mixture of both. When R was C_6H_5, 4-$C_2H_5OC_6H_4$, 4-CH_3-C_6H_4, or 4-ClC_6H_4, the *cis* isomer was isolated. When R was 2-$CH_3OC_6H_4$, 2,4-$Cl_2C_6H_3$, or $C_6H_5CH_2CH_2$, the *trans* isomer was isolated. When R was 4-CH_3O-C_6H_4, both isomers were isolated.



cis, $J \sim 3.3$ c.p.s.
III, R = C_6H_5, 4-$C_2H_5OC_6H_4$, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$CH_3OC_6H_4$

trans, $J \sim 4.0$ c.p.s.
IV, R = 2-$CH_3OC_6H_4$, $C_6H_5CH_2CH_2$, 2,4-$Cl_2C_6H_4$, 4-$CH_3OC_6H_4$
VI, R = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$O_2NC_6H_4$, 2,3-$(CH_3O)_2C_6H_5$

The 2-(β-hydroxyalkyl)thiocarboxylic acid hydrazides V, possessing the analogous *erythro* configuration, were prepared by thioacylation of N-amino-L-(−)-

ephedrine with carboxymethyl dithioates in aqueous sodium hydroxide solution. Treatment of V in which R was C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$O_2NC_6H_4$, or 2,3-$(CH_3O)_2C_6H_3$ with concentrated sulfuric acid at 25° for 18 hr. gave the *trans*-5,6-dihydro-4H-1,3,4-thiadiazine (VI) exclusively, in every instance.

Treatment of the diastereoisomeric *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazide, prepared by N-benzoylation of N-amino-D-(+)-pseudoephedrine, with phosphorus pentasulfide in refluxing chloroform gave the *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-thiadiazine together with a small amount of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine.

Treatment of *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)-*p*-chlorothiobenzoic acid with polyphosphoric acid at room temperature gave *trans*-4,5-dimethyl-2-(*p*-chlorophenyl)-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine and *cis*-4,5-dimethyl-2-(*p*-chlorophenyl)-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine.

The method described by Holmberg[5] for the preparation of thiobenzoic acid methylhydrazide was adopted in principle for the thiobenzoylation of N-amino-L-(−)-ephedrine and N-amino-D-(+)-pseudoephedrine. The resulting *erythro*-(−)- and *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazide, however, could only be obtained as yellow to dark colored oils or glasses. Attempts to obtain a crystalline product failed in all but one case.

The carboxymethyl dithiobenzoates needed for the thiobenzoylation of N-amino-L-(−)-ephedrine and N-amino-D-(+)-pseudoephedrine were all prepared by the method described by Jensen and Pedersen,[6] except for carboxymethyl dithiobenzoate, which was prepared by the method of Kajaer.[7]

The assignments of *cis* and *trans* configurations to the isomeric 2-substituted 4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazines in Table II are based on n.m.r. data and comparison with the oxadiazine series. The n.m.r. data consist of measurements of the relative amplitudes of the 5-H–6-H coupling constants and the chemical shifts of 5-H, 6-H, and 5-CH_3. The only strainless conformation of this ring system which could be built with Dreiding stereomodels is one in which carbons 5 and 6 lie above a plane defined by S—C=N—N, with C-6 being nearer to the plane. Presumably, the substituents on C-5 and C-6 are staggered, with the CH_3 and/or C_6H_5 in an equatorial orientation. Thus, a *trans* isomer would have 5-H and 6-H *trans*-axial, and a *cis* isomer would have one axial and the other equatorial. With flattening of the ring because of the longer sulfur bonds, the *trans*-axial–axial coupling should be reduced from a normal value of 6–9 c.p.s. and the *cis*-axial–equatorial coupling may be increased from the normal 2–3 c.p.s. However, one still expects the *trans*-axial–axial coupling to be larger than the *cis*-axial–equatorial coupling. Thus, isomers exhibiting $J \backsim 3$ c.p.s. were designated *cis* and isomers exhibiting $J \backsim 4$ c.p.s. were designated *trans*.

Consistent with the *cis* and *trans* assignments based on $J_{5,6}$ are the chemical shifts of 5-H, 6-H, and 5-CH_3. Generally, but not necessarily always, axial protons are more shielded in the *trans* isomer than in the *cis* isomer.[8] The 5-CH_3, being somewhat axial in the *cis* isomer, should be more shielded in the *cis* isomer than in the *trans*. The assigned configurations show this predicted behavior. Also, we have observed[9] that isomeric *cis* and *trans* 2-substituted 4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazines, which presumably exist in the half-chair form of cyclohexene, exhibit $J_{5,6}$ of 2.9 and 7.5 c.p.s., respectively. In this case, a measured difference of 4.5 c.p.s. in coupling constants between the two isomers can be considered convincing for the assignment. The relative chemical shifts of 5-H, 6-H, and 5-CH_3 in the oxadiazines assigned in this way have the *trans* protons (5 and 6) more shielded than the *cis*, and the *cis* methyl (5) more shielded than the *trans*. This shift behavior is the same as that exhibited by the thiadiazines.

The assignments were further substantiated by the following chemical evidence. Concentrated sulfuric acid cyclodehydration of *erythro*-(−)- and *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazides yielded, exclusively, in every instance, the oxadiazine isomer with the larger 5-H–6-H coupling constant (7.5 c.p.s.). Analogously, concentrated sulfuric acid cyclodehydration of *erythro*-(−)- and *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazides yielded, exclusively, in every instance, the thiadiazine isomer with the larger coupling constant (4 c.p.s.).

Based primarily on the stereochemical results of the reactions of *threo*- and *erythro*-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazides with phosphorus pentasulfide and *threo*- and *erythro*-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazides with sulfuric and polyphosphoric acids and on reported results of reactions of phosphorus pentasulfide with alcohols and hydroxyamides,[10] we postulate that the phosphorus pentasulfide conversion of *erythro*-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazides into *cis*- and *trans*-thiadiazines probably proceeds by the two following mechanisms: (1) the hydroxyl is converted to thiol followed by attack of the thiol sulfur upon the carbonyl carbon, and (2) the carbonyl oxygen is converted to sulfur followed by attack of the thiocarbonyl sulfur upon the hydroxyl-bearing carbon (Scheme I). Ring closure by mechanism 1 proceeds with retention[11] and ring closure *via* mechanism 2 proceeds with inversion.

Certain aroyl substituents may promote predominant retention and others predominant inversion because of steric factors. For example, the 2-methoxy- and 2,4-dichlorobenzoyl may give mainly the *trans* isomer, whereas the 4-methoxy- and 4-chlorobenzoyl give

(5) B. Holmberg, *Arkiv Kemi*, **9**, 47 (1955); *Arkiv Kemi, Mineral., Geol.*, **17A**, 10 (1944).

(6) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 1807 (1961).

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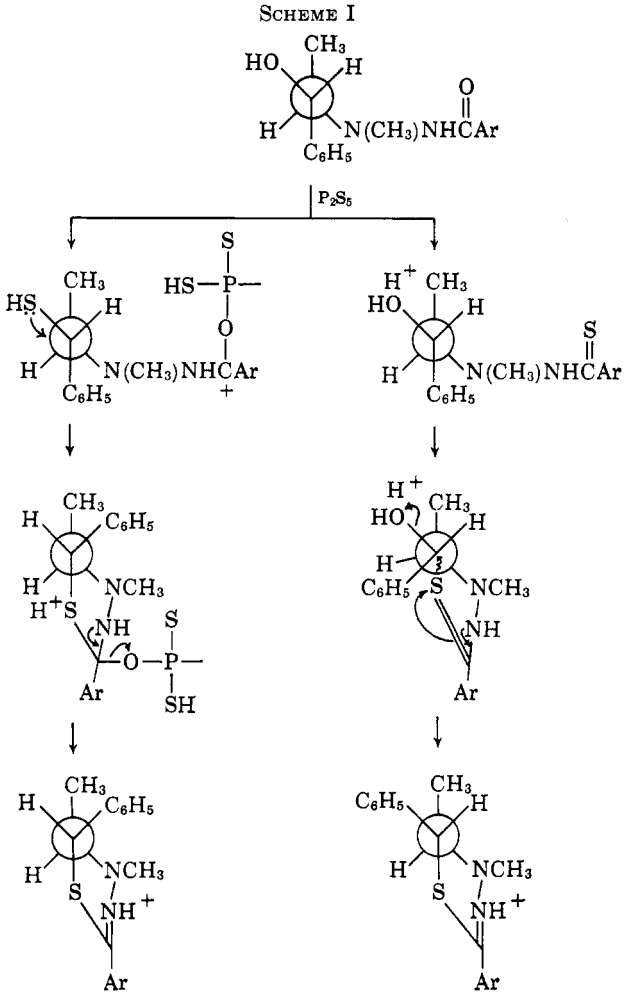
(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y. 1959, p. 116.

(9) D. L. Trepanier, V. Sprancmanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668, 673, 2151 (1964).

(10) S. Tatsuoka, S. Rin, and K. Hirata, *Takeda Kenkyusho Nempo*, **9**, 17 (1950); E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, **72**, 3203 (1950); G. D. Daves, Jr., *ibid.*, **82**, 2633 (1960); E. Montigne, *Bull. soc. chim. France*, [4] **49**, 73 (1931).

(11) The stereochemical consequence of phosphorus pentasulfide conversion of hydroxyl to thiol has not been reported. Our data indicate it likely proceeds with retention analogous to the thionyl chloride conversion of benzylic hydroxyl to chloride.

SCHEME I



mainly the *cis* isomer because the former possess an *ortho* substituent which sterically interferes with the attack of the thiol sulfur upon the carbonyl carbon and thus significantly retards the ring closure *via* the pathway proceeding with retention of configuration.

We prefer two distinctly different methods of ring closure rather than one mode of ring closure followed by an isomerization to account for the formation of *cis*- and *trans*-thiadiazines because of the following observations.

Attempted isomerization of *cis*- and *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine either by treatment with excess phosphorus pentasulfide and polyphosphoric acid in refluxing chloroform or by dissolution in concentrated sulfuric acid at room temperature for 18 hr. was unsuccessful, and a nearly quantitative yield of unchanged starting material was recovered. This indicates that isomerization *after* ring closure is not likely under the conditions of the experiment, as it does not occur under simulated conditions or even under more favorable conditions, such as solution in concentrated sulfuric acid.

Treatment of *threo*-(+)- and *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazide with phosphorus pentasulfide in refluxing chloroform yielded *cis*-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine. No *trans*-thiadiazine was isolated in either case. Since these two hydroxy hydrazides, which differ in configuration about the hydroxyl-bearing carbon, gave the same thiadiazine, more than one mode of ring closure must be operative.

Cyclization of *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)-*p*-chlorothiobenzoic acid hydrazide with polyphosphoric acid yielded *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine and *cis*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine. This indicates polyphosphoric acid produces ring closure by two different methods: (1) attack of the thiohydrazide sulfur upon the hydroxyl-bearing carbon to give the *trans*-thiadiazine, and (2) attack of the hydroxyl oxygen upon the thiocarbonyl carbon to give the *cis*-oxadiazine.. Although this reaction is not identical with the phosphorus pentasulfide cyclization of hydroxy hydrazides, its similarity is sufficiently great to support the postulation that different methods of ring closure occur in the latter reaction.

Undoubtedly, the sulfuric acid cyclodehydration of *threo*- and *erythro*-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazides proceeds by attack of the thiohydrazide sulfur upon the carbonium carbon, produced by dissociation of protonated hydroxyl, because these two diastereoisomeric hydroxy thiohydrazides, which differ only in configuration about the hydroxyl-bearing carbon atom, both gave the same *trans*-thiadiazine.

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 Microlabs., Inc., Indianapolis, Ind. The synthesis of β-(1-methylhydrazino)ethanol, 1-(1-methylhydrazino)-2-propanol, 1-methylhydrazino-*t*-butyl alchol, α-(1-methylhydrazinomethyl)benzyl alcohol, N-amino-L-(−)-ephedrine, and most of the 2-(β-hydroxyalkyl)carboxylic acid hydrazides which were converted to 5,6-dihydro-4H-1,3,4-thiadiazines by method A has been reported.[9]

Substituted 5,6-Dihydro-4H-1,3,4-thiadiazines (Compounds in Tables I and II). Method A.—A mixture of 0.5 mole of a 2-(β-hydroxyalkyl)carboxylic acid hydrazide, 0.5 mole of phosphorus pentasulfide, and 1000 ml. of chloroform was stirred and refluxed for 6–24 hr., cooled, washed twice with a 20% aqueous sodium hydroxide solution, washed twice with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residual oil was purified either by crystallization from an appropriate solvent, by distillation, or, when necessary, by chromatography on acid-washed alumina (Merck 71695) using chloroform or benzene as solvent. In some cases, hydrochlorides or hydrobromides were prepared by treating an ether solution of the base with either gaseous hydrogen chloride or gaseous hydrogen bromide.

Method B.—To 600 ml. of stirred, cold concentrated sulfuric acid was added slowly a solution of 0.5 mole of a 2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazide in about 100 ml. of methylene chloride. The mixture was stirred for 15 hr. at room temperature and was then poured into a stirred mixture of 4–5 kg. of ice and 1000 ml. of chloroform. The chloroform layer was separated and the aqueous solution was extracted three times with chloroform. The washed (water, sodium bicarbonate solution, water) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* leaving an oil which crystallized in most cases upon standing. The product was purified by recrystallization or, when necessary, by chromatography on acid-washed alumina (Merck 71695) using chloroform or benzene as solvent.

Treatment of *threo*-(+)-2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic Acid Hydrazide with Phosphorus Pentasulfide.—A mixture of 42 g. (0.15 mole) of *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazide (obtained from N-amino-D-(+)-pseudoephedrine and benzoyl chloride), 32g. of phosphorus pentasulfide, and 300 ml. of chloroform was stirred and refluxed for 4 hr. After cooling to room temperature, the

mixture was washed with three portions (total 1000 ml.) of 1 *N* sodium hydroxide solution, washed twice with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* leaving a yellow, viscous oil. This material was chromatographed on a 70 × 6.5 cm. column of acid-washed alumina (Merck 71695) using benzene as an eluent and taking cuts every 250 ml. Evaporation of fractions 1, 2, and 3 gave a residue which, after recrystallization twice from ethanol, yielded 4.7 g. (11%) of *cis*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-thiadiazine as white crystals, m.p. 89–90°. The residues of fractions 5 and 6 solidified on standing, were combined and recrystallized several times from ethanol to give 0.8 g. (0.2%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine as white crystals, m.p. 137–139.5°.[12]

Polyphosphoric Acid Cyclodehydration of *erythro*-(−)-2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)-*p*-chlorothiobenzoic Acid Hydrazide.—A mixture of 100 g. (0.3 mole) of crude *erythro*-(−)-2-(α-methyl-β-hydroxy-β-phenethyl)-*p*-chlorothiobenzoic acid hydrazide and 1455 g. of polyphosphoric acid was stirred at room temperature for 18 hr. Ice–water was added and the resulting mixture was extracted with methylene chloride. The methylene chloride solution was washed once with water and twice with a saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residual dark oil was chromatographed on a 60 × 6.5 cm. column of activated alumina (Alcoa) using benzene as a solvent. Fractions 2, 3, and 4 (250 ml. each) yielded 12.3 g. (13%) of *trans*-4,5-dimethyl-2-(*p*-chlorophenyl)-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 112–114°. Fractions 6 and 7 gave 5.0 g. (5.5%) of *cis*-4,5-dimethyl-2-(*p*-chlorophenyl)-6-phenyl-5,6-dihydro-4H-1,3,4-oxadiazine, m.p. 70–71.5°.

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.32. Found: C, 68.09; H, 5.70; N, 9.11.

Attempted Isomerization of *cis*-2-(*p*-Chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine. A. With Concentrated Sulfuric Acid.—*cis*-2-(*p*-Chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine (1.0 g.) was added, portionwise, to 10 ml. of concentrated sulfuric acid. The clear solution was allowed to stand at room temperature for 18 hr. It was poured onto crushed ice and extracted with chloroform. The chloroform extract was washed (sodium carbonate, water), dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residual oil was crystallized with ethanol. Recrystallization from ethanol gave 0.95 g. (95%) of *cis*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 69–70°.

B. **With Phosphorus Pentasulfide and Polyphosphoric Acid.**—A mixture of 1.0 g. of *cis*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, 2.0 g. of phosphorus pentasulfide, 5.0 g. of polyphosphoric acid, and 100 ml. of chloroform was refluxed for 18 hr. The cooled mixture was treated with 100 ml. of 2 *N* aqueous sodium hydroxide solution, and then stirred for 1 hr. The chloroform solution was separated, washed twice with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residual oil was crystallized with ethanol. Recrystallization from ethanol gave 0.89 g. (89%) of *cis*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 69–70°.

Thiobenzpiperidides.—To a mixture of 1 mole of a benzaldehyde and 48 g. of powdered sulfur was added 150 ml. of piperidine. Sometimes a vigorous reaction occurred when the piperidine was added and cooling was required. The mixture was stirred and heated under reflux for 1 hr. The hot mixture was poured onto 2 kg. of crushed ice and acidified with concentrated hydrochloric acid. The solid was suction filtered, washed with water, air dried, and recrystallized from a suitable solvent.

p-Methylthiobenzpiperidide[13] (m.p. 102–103.5°), *p*-chlorothiobenzpiperidide[8] (m.p. 112–113.5°), *p*-methoxythiobenzpiperidide[8] (m.p. 106–108°), and *p*-nitrothiobenzpiperidide[8] (m.p. 176–178°) have been reported.

2,3-Dimethoxythiobenzpiperidide, recrystallized from ethanol–methylcyclohexane, m.p. 64–66°, was obtained in 53% yield.

Anal. Calcd. for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22. Found: C, 63.47; H, 7.28.

S-Carboxymethylthiobenzpiperidinium Bromides.—To a solution or stirred suspension of 1 mole of a thiobenzpiperidide in about 1200 ml. of dry benzene was added 155 g. of bromoacetic acid. A short time after the addition of the bromoacetic acid an oil separated which often crystallized on standing for several hours. The mixture was allowed to stand at room temperature usually for about 24 hr., although in the case of *p*-nitrothiobenzpiperidide, about 2 weeks was required. About 2.5 l. of dry ether was added to precipitate the product completely. In some cases the product had to be induced to crystallize by scratching the oil in the presence of ether. Only in the case of S-carboxymethyl-2,3-dimethoxythiobenzpiperidinium bromide was it not possible to obtain a crystalline product. The solid was then collected by filtration, washed with ether, and dried. The crude product was used directly for the preparation of the carboxymethyl dithiobenzoates.

S-Carboxymethyl-*p*-methoxythiobenzpiperidinium bromide (m.p. 153–156° dec.) and S-carboxymethyl-*p*-chlorothiobenzpiperidinium bromide (m.p. 161–163° dec.) have been reported.[8]

S-Carboxymethyl-*p*-methylthiobenzpiperidinium bromide had m.p. 171–172° dec.

Anal. Calcd. for $C_{15}H_{20}BrNO_2S$: C, 50.28; H, 5.63. Found: C, 50.32; H, 5.58.

S-Carboxymethyl-*p*-nitrothiobenzpiperidinium bromide had m.p. 170–172 dec.

Anal. Calcd. for $C_{14}H_{17}BrN_2O_4S$: C, 43.19; H, 4.40. Found: C, 44.24; H, 4.41.

Carboxymethyl Dithiobenzoates.—A stirred solution or suspension of 1 mole of an S-carboxymethylthiobenzpiperidinium bromide in 1000 ml. of dry ethanol was cooled in an ice bath, and hydrogen sulfide was bubbled in over a period of 4–6 hr. The mixture was stirred overnight and permitted to warm slowly to room temperature. The resulting solution or suspension was concentrated *in vacuo*. The solid residue was either extracted with water to remove the piperidinium hydrobromide and the remaining orange to dark red solid was collected by filtration, or the carboxymethyl dithiobenzoate was dissolved in ether, the piperidinium hydrobromide was removed by filtration, and the filtrate was concentrated *in vacuo*. The crude carboxymethyl dithiobenzoate was then recrystallized from a suitable solvent such as benzene–Skellysolve (b.p. 60–70°), methylcyclohexane, or ethanol.

Carboxymethyl *p*-methyldithiobenzoate (m.p. 117–118°), carboxymethyl *p*-chlorodithiobenzoate (m.p. 115–117°), and carboxymethyl *p*-methoxydithiobenzoate (m.p. 122.5–124.5°) have been reported.[8]

Carboxymethyl *p*-nitrodithiobenzoate had m.p. 113–115°.

Anal. Calcd. for $C_{11}H_{12}O_4S_2$: C, 48.51; H, 4.44. Found: C, 48.55; H, 4.61.

Carboxymethyl Dithiobenzoate.—A Grignard solution prepared from 33 g. of magnesium and 203 g. of bromobenzene in 600 ml. of ether was added, over a period of 1.5 hr., to a cooled solution of 153 g. of carbon disulfide in 300 ml. of ether. After standing overnight at room temperature, the mixture was poured onto 800 g. of crushed ice and then filtered to remove a small amount of brown precipitate. The ether layer was removed and the aqueous portion was washed twice with ether. To the aqueous part was added a solution of 128.5 g. of chloroacetic acid in 500 ml. of water neutralized with 76 g. of sodium carbonate. The resulting mixture was placed in a refrigerator for about 50 hr. The solution was then acidified with a cold mixture of 90 ml. of concentrated sulfuric acid and 100 ml. of water. A red precipitate (71 g.) formed, which was collected by filtration, washed with water, and dried *in vacuo*. The compound was recrystallized from benzene–Skellysolve (b.p. 60–70°) to give 63 g. (23%) of red crystals, m.p. 125.5–127°.

2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic Acid Hydrazides.—To a stirred solution of 0.5 mole of a carboxymethyl dithiobenzoate and 20 g. of sodium hydroxide in about 1800 ml. of water (20–50°) was added 90 g. (0.5 mole) of N-amino-L-(−)-ephedrine. The resulting mixture was stirred until further stirring became difficult because of the formation of a gummy solid. After standing at room temperature for about 1 week the aqueous layer was decanted, and the gummy product was dissolved in chloroform. The chloroform solution was washed several times with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* leaving a yellow to brown viscous oil. Attempts to obtain a crystalline product failed in all cases. The crude product was used directly for the preparation of the *trans* 2-substituted 4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazines listed in Table II.

***threo*-(+)-2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic Acid Hydrazide.**—To a stirred solution of 10 g. of sodium

(12) Previously described in ref. 3.

(13) J. Goerdeler and H. Horstman, *Ber.*, **93**, 671 (1960).

hydroxide in 900 ml. of water was added 52 g. of carboxymethyl dithiobenzoate and 45 g. of N-amino-D-(+)-ephedrine. The mixture was stirred and heated at 50° for 3 hr. and then allowed to stand at room temperature overnight. The aqueous layer was decanted and the residual gummy solid was dissolved in 1000 ml. of chloroform. The chloroform solution was washed (water), dried (magnesium sulfate), and evaporated *in vacuo* to yield 66 g. of red oil. The red oil was cyclodehydrated without further purification as described in the following experiment.

Sulfuric Acid Cyclodehydration of *threo*-(+)-2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic Acid Hydrazide.—To 300 ml. of cold, stirred, concentrated sulfuric acid was added a solution of 66 g. of *threo*-(+)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)thiobenzoic acid hydrazide in 100 ml. of methylene chloride. The mixture was stirred at room temperature for 3 hr., poured onto 2 kg. of crushed ice, and extracted with four 500-ml. portions of chloroform. The chloroform solution was washed (sodium bicarbonate), dried (magnesium sulfate), and evaporated *in vacuo* leaving 37 g. of red oil. The 37 g. of red oil was chromatographed on a 40 × 5.5 cm. column of aluminum oxide powder (Baker 0537) using benzene as a solvent. Fractions 3–6 (130 ml. each) yielded 31.3 g. (49%) of *trans*-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 67.5–69°.

Attempted Isomerization of *trans*-2-(*p*-Chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine. A. With Concentrated Sulfuric Acid.—*trans*-2-(*p*-Chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine (1.0 g.) was added, portionwise, to 10 ml. of concentrated sulfuric acid. The mixture was allowed to stand at room temperature for 18 hr. It 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 residual oil was crystallized with ethanol. Recrystallization from ethanol gave 0.88 g. (88%) of *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 112–114°.

B. With Phosphorus Pentasulfide and Polyphosphoric Acid.—A mixture of 1.0 g. of *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, 2.0 g. of phosphorus pentasulfide, 5.0 g. of polyphosphoric acid, and 100 ml. of chloroform was refluxed for 8 hr. and then allowed to stand at room temperature overnight. The cooled mixture was treated with 100 ml. of 2 *N* aqueous sodium hydroxide solution, and then stirred for 1 hr. The chloroform solution was separated, washed twice with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The pale yellow solid was recrystallized from ethanol to give 0.78 g. (78%) of *trans*-2-(*p*-chlorophenyl)-4,5-dimethyl-6-phenyl-5,6-dihydro-4H-1,3,4-thiadiazine, m.p. 111–113°.

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The Reaction of 16-Hydroxymethylene-17-keto Steroids with Semicarbazide and Thiosemicarbazide to Give 17α-Hydroxy[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline Derivatives. 17α-Hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline, a Potential Nonfeminizing Hypocholesterolemic Agent

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16-Hydroxymethylene-17-keto steroids react with semicarbazide and various thiosemicarbazides to give 17α-hydroxy[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline derivatives. Similar results are obtained with the 16-ethoxalyl-17-keto system. With hydroxylamine the 17α-hydroxy[16β,17β-*d*]-$\Delta^{2'}$-isoxazolines are obtained. The structure of one of the pyrazolines was established by X-ray analysis. 17α-Hydroxy-3-methoxy-2′-thiocarbamoylestra-1,3,5(10)-trieno[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazoline (III) shows good hypocholesterolemic action as well as a low uterotropic effect and therefore is of interest as a potential nonfeminizing hypocholesterolemic agent. The synthesis and structure of several open-chain analogs are reported.

The possibility of developing nonfeminizing, hypocholesterolemic estratriene derivatives has received considerable research attention in recent years.[1] We now wish to report the preparation of several 17α-hydroxyestra-1,3,5(10)-trieno[17β,16β-*c*]-$\Delta^{1'(5')}$-pyrazolines and-[16β,17β-*d*]-$\Delta^{2'}$-isoxazolines, certain of which are of interest in this respect.

The pyrazolines III of this study were readily prepared in high yield by treating 16-hydroxymethylene-17-keto steroids (I) with semicarbazide, thiosemicarbazide, and certain N^4-substituted derivatives of the latter reagent. The formation of the pyrazoline derivative rather than the fully aromatic pyrazole II was not anticipated, inasmuch as hydrazine and certain substituted hydrazines were known to react with the 16-hydroxymethylene-17-keto system (I) to give the corresponding pyrazoles (II),[2] although we also were aware of the fact that reaction of this system (androstane series) with hydroxylamine gives isoxazolines (IV).[2c,3] Formation of the pyrazoline structures was indicated by combustion analyses, the infrared spectra (hydroxyl absorption, no band attributable to a 17-carbonyl group), and enhanced ultraviolet absorption corresponding to that anticipated for isolated semicarbazone or thiosemicarbazone chromophores.[4] Similarly, condensation of 16-hydroxymethylenestrone 3-methyl ether[5] with hydroxylamine afforded the 17-hydroxyisoxazoline XIX, which structure is supported by combustion analysis, infrared data, and ultraviolet evidence (no absorption attributable to an isoxazole chromophore).

In order to determine unequivocally all structural aspects of these interesting compounds, one of the pyrazolines, the 4-bromo derivative XVIII, was subjected to single-crystal X-ray analysis. For this purpose,

(1) See V. A. Drill and B. Riegel [*Recent Progr. Hormone Res.*, **14**, 50 (1958)] for a brief resume of the rationale to this approach.

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