ester in anhydrous Et_2O. Anhydrous MeOH (1 ml) was added and the solution was permitted to stand at room temperature. The precipitated salt was collected by filtration over a period of several weeks. This was the method utilized for the preparation of all of the methobromides reported in Table I. Quantitative yields were obtained but the salts were very hygroscopic (except the *cis* acetate) and generally resisted purification by recrystallization (see Table I).

Method E.—The methiodides were prepared in quantitative yield by refluxing for 12 hr a solution of the ester in Na-dried C_6H_6 with an excess of MeI.

Pharmacological Procedure. Toxicity in Mice.—All compounds were injected intraperitoneally in aqueous solution (made with aid of dilute HCl in the case of **6**) over a range of at least four dosages. Five albino mice were used at each dosage level and the proportion of animals dying was used to determine approximate LD_{50}'s, and confidence limits when the data permitted, by the method of Horn.[24]

Cardiovascular Effects in Rats.—Recordings of arterial blood pressure, respiration, and the electrocardiogram were made by means of an E & M Physiograph and appropriate transducers. Blood pressure was recorded *via* the cannulated carotid artery. Injections were made *via* a needle-cannula in the femoral vein. All materials administered were flushed in with a small volume of 0.9% saline solution.

(24) H. J. Horn, *Biometrics*, **12**, 311 (1956).

Male albino rats of the Holtzmann strain weighing 275–375 g were anesthetized with urethan (1.26 g/kg ip). The test compounds and a standard consisting of protoveratrines A and B were administered at dosages constituting 3, 10, and 30% of the approximate LD_{50} for mice. Observations for changes in the physiological parameters were made after each of these dosages. Then, upon equilibration from any changes evoked, standard doses of histamine, epinephrine, and methacholine were administered successively. Responses to these agents after the test compound were compared to responses to like quantities that had been observed prior to any administration of the test substance. In several cases the 30% dosage was lethal. In some others it was repeated or even a 60% dosage was administered if the preparation was still functioning.

Smooth Muscle Effects.—The compounds were tested on sections of rabbit ileum which were suspended in an oxygenated Ringer's solution in a 30-ml muscle bath maintained at 37°. The muscle strip was attached to a myograph transducer to record muscular activity on an E & M physiograph. Response to solutions of the test compound were observed in comparison to responses to 0.5-ml quantities of standard solutions of acetylcholine chloride (1:100,000) and epinephrine (1:10,000), or in conjunction with the cholinergic receptor blocking action of atropine sulfate (1:400). The two solutions (1:100 and 1:1000) of each compound which were tested yielded upon addition to the bath in 0.5-ml quantities final drug concentrations of about 15 and 150 μg/ml, respectively.

Synthesis and Pharmacological Evaluation of Some Tetrahydrooxadiazinones and Some Dihydroaminooxadiazines

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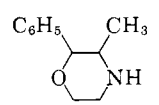
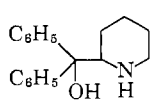
The synthesis of *cis*-(+)- and *cis*-(−)-tetrahydrooxadiazinone derivatives of (+)- and (−)-ephedrines and two related tetrahydrooxadiazinones is reported. The results of an attempted synthesis of a dihydroaminooxadiazine derivative of ephedrine and the successful synthesis of three related dihydroaminooxadiazines is also reported. The *cis*-(−)-tetrahydrooxadiazinone derived from (−)-ephedrine was found to be a monoamine oxidase inhibitor in pharmacological testing.

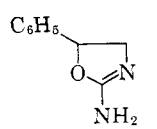
One widely used approach for the synthesis of new compounds that possess some type of central nervous system stimulant activity is the cyclization of substituted phenethanolamines into heterocycles, such as morpholine, piperidine, and 2-oxazoline in such a manner that more or less of the phenethanolamine skeleton becomes part of the heterocyclic ring. Well-known drugs of this type are phenmetrazine,[1] pipradol,[2] and aminorex.[3]



phenmetrazine



pipradol



aminorex

The ephedrines and norephedrines are useful starting materials for a study of this type because they possess some central activity and because all eight of the isomers are readily available. Morpholine,[1] 2-oxazoline,[4] oxazolidine,[5] di- and tetrahydro-1,3,4-oxadiazines,[6,7] 2-thiazoline,[8] thiazolidine,[9] dihydro-1,3,4-thiadiazine,[10] tetrahydro-*as*-triazine,[11] and imidazolidine[12] heterocyclic derivatives of the ephedrines and norephedrines have been reported. Certain of these heterocycles exhibit central-stimulating appetite-depressing,[1,4] monoamine oxidase inhibiting antidepressant,[6g,10b] central nervous system depressant,[6e,f,7,11] analgetic,[11] hypocholesterolemic,[7] antiinflammatory,[7] antimicro-

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, The Macmillan Co., New York, N. Y., 1965, p 516.

(2) R. F. Gould, "Molecular Modification in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 116.

(3) C. K. Cain, "Annual Reports in Medicinal Chemistry, 1965," Academic Press Inc., New York, N. Y., 1966, p 54.

(4) G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelly, and J. McGowin, *J. Med. Chem.*, **6**, 266 (1963).

(5) H. Pfanz and G. Kirchner, *Ann.*, **614**, 149 (1958).

(6) (a) D. L. Trepanier, V. Spranemanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668 (1964); (b) D. L. Trepanier and V. Spranemanis, *ibid.*, **29**, 673 (1964); (c) *ibid.*, **29**, 2151 (1964); (d) D. L. Trepanier, V. Spranemanis, D. S. Tharpe, and P. E. Krieger, *J. Heterocyclic Chem.*, **2**, 403 (1965); (e) D. L. Trepanier, P. E. Krieger, and J. N. Eble, *J. Med. Chem.*, **8**, 802 (1965); (f) D. L. Trepanier, V. Spranemanis, and J. N. Eble, *ibid.*, **9**, 753 (1966); (g) D. L. Trepanier, U. S. Patent 3,122,537 (1964).

(7) M. J. Kalm, U. S. Patent 3,251,838 (1966).

(8) M. Kojima, *Yakugaku Zasshi*, **79**, 1 (1959).

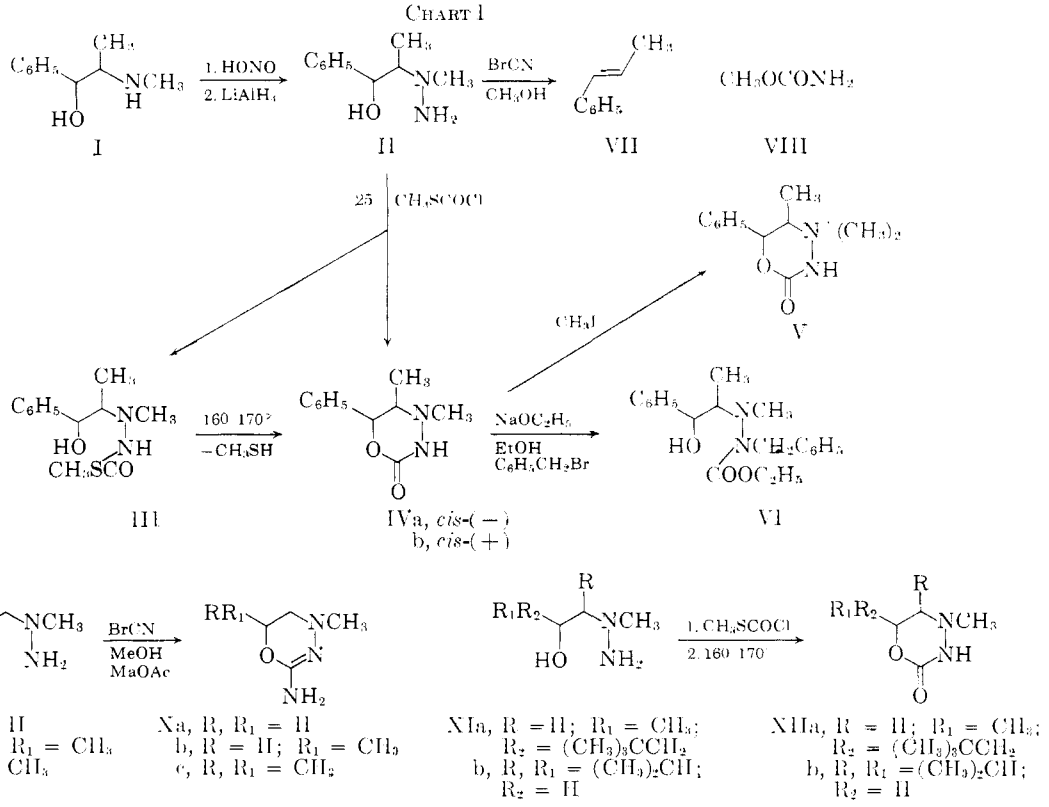
(9) A. P. Roszkowski and G. B. Koelle, *J. Pharmacol. Exp. Ther.*, **128**, 227 (1960).

(10) (a) D. L. Trepanier, W. Reifschneider, W. Shumaker, and D. S. Tharpe, *J. Org. Chem.*, **30**, 2228 (1965); (b) D. L. Trepanier, U. S. Paten 3,290,303 (1966).

(11) D. L. Trepanier, E. R. Wagner, G. Harris, and A. D. Rudzik, *J. Med. Chem.*, **9**, 881 (1966).

(12) M. Murakami and T. Fukumoto, *Nippon Kagaku Zasshi*, **76**, 270 (1955).

CHART I



bial,[7,10b] or catecholamine-potentiating[9] activity when subjected to pharmacological screening in lower animals.

This paper describes the synthesis of tetrahydrooxadiazinone derivatives of (−)- and (+)-ephedrines and of two related tetrahydrooxadiazinones, the results of an attempted synthesis of a dihydroaminooxadiazine derivative of ephedrine, and the successful synthesis of three related dihydroaminooxadiazines. It also reports the results of pharmacological evaluation of these new tetrahydrooxadiazinones and dihydroaminooxadiazines.

Chemistry.—Treatment of N-amino-(−)-ephedrine[6a] in anhydrous ether with methyl chlorothiolformate in the presence of triethylamine at ambient temperature gave S-methyl 3-(β-hydroxy-α-methylphenethyl)-3-methylthiocarbazate (III) (43% yield) and *cis*-(−)-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-2H-1,3,4-oxadiazin-2-one (IV) (7% yield). The *cis* configuration was assigned to this novel oxadiazinone because J_{5H-6H} is 3.0 cps and because it was synthesized from *erythro*-hydrazino alcohol II by a conversion which would not be expected to break any bonds about either of the asymmetric carbons of II. Greater significance can be attached to the meaning of the magnitude of the 5H–6H coupling because it has been reported[6c] that in the closely related 5,6-dihydro-4H-1,3,4-oxadiazine system that *cis*-(−)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine exhibited a J_{5H-6H} = 2.90 cps and the corresponding *trans*-(+) isomer a J_{5H-6H} = 7.54 cps.

Pyrolysis of thiocarbazate ester III neat at 160–170° for 2 hr caused elimination of methyl mercaptan and cyclization in high yield to oxadiazinone IVa. This same sequence of reactions was repeated in order to prepare the *cis*-(+)-oxadiazinone IVb from (+)-ephedrine. Also, as shown in Chart I, thiocarbazate ester formation followed by pyrolytic cyclization was used to convert hydrazino alcohols XIa and b to oxadiazinones XIIa and b.

Allowing oxadiazinone IVa to react with iodomethane in refluxing acetone resulted in the formation of 3,4,5,6-tetrahydro-4,4,5-trimethyl-6-phenyl-2H-1,3,4-oxadiazin-2-onium iodide (V). Oxadiazinone IVa was alkylated at N^3 instead of N^4 by allowing it to react with sodium ethoxide in ethanol followed by treatment of the refluxing mixture with benzyl bromide. However, because the alkylation at N^3 was accompanied by ethanolysis of the C–O bond the product isolated and purified as the hydrochloride was ethyl 2-benzyl-3-(β-hydroxy-α-methylphenethyl)-3-methylcarbazate (VI).

Treatment of hydrazino alcohols IXa–c[6b] in methanol at 10° in the presence of sodium acetate with slightly more than 1 equiv of cyanogen bromide gave aminooxadiazines Xa–c, respectively. Structures were substantiated by elemental analysis and ir and pmr spectra.

Reaction of N-amino-(−)-ephedrine (II) in methanol in the presence of sodium acetate with cyanogen bromide yielded after concentration and basification a chloroform-soluble oil which upon distillation in an oil bath heated to 110° gave a mixture that boiled at 45–65° (0.3 mm) and partially solidified in the receiver. The liquid was pipetted from the solid and passed through filter paper. Glpc indicated the liquid to be approximately 98% pure. Ir and pmr analyses indicated the liquid was principally *trans*-β-methylstyrene (VII). Comparison with spectra of authentic *trans*-β-methylstyrene verified this structure assignment. The solid portion of the distillate was purified by recrystallization. Melting point, elemental, ir, and pmr analyses indicated the solid was methyl carbamate (VIII).

Pharmacology.—To measure potential antidepressant activity of these compounds they were tested for an-

TABLE I

Compd	Screening dose, mg/kg	Reserpine–pentylenetetrazole treated/control
IVa	8.9	1.9
	12.5	3.2
	25	2.5
	50	4.7
IVb	10	.9
	20	1.5
	40	1.1
V	100	1.2
Xa	100	1.3
Xb	100	1.2
Xc	100	1.0
XIIa	100	1.0
XIIb	100	1.0
Clidinium bromide	12.5	3.5
	25	2.8
	50	3.5

tagonism to the threshold effect of reserpine[13] on convulsions induced by intravenous infusions of pentylenetetrazole.[14] Monoamine oxidase inhibitors are known to be active in this test.[13] Groups of ten mice were dosed intraperitoneally with test compound at 48, 24, and 2 hr before a 5-mg/kg dose of reserpine. Two hours after reserpine they were infused through a tail vein with a 0.5% solution of pentylenetetrazole at the rate of 0.2 ml/min. The time, in seconds, to extensor convulsions was measured; the average time of each group is expressed as a ratio of the average time of the saline-treated group of the same day in Table I.

Because of the novelty of the structure, the one compound showing activity in this test, the *cis*-(−)-oxadiazinone IVa, was then further evaluated pharmacologically. The LD_{50} by intraperitoneal injection in mice was 540 mg/kg (500 mg/kg, 4/10 dead; 562 mg/kg, 5/10 dead; 631 mg/kg, 8/10 dead). Death followed a period of prostration, difficult respiration, and cyanosis.

Compound IVa was inactive as an analgetic in the HCl writhing test[11] at a dose of 100 mg/kg ip. It was inactive at 100 mg/kg in an amphetamine aggregate toxicity test,[15] a measure of potential tranquilizing activity. The compound afforded no protection at a dose of 100 mg/kg against tremorine-induced tremors, a test for potential antiparkinsonism activity.[16]

The compound was tested for antagonism to the lethal effects of strychnine as a measure of potential muscle relaxant and mild tranquilizing activity.[17] Mice were dosed intraperitoneally at 48, 24, and 1 hr before a challenge with 2 mg/kg ip of strychnine. At a dose of 100 mg/kg of IVa there were 3/10 dead in the experimental group; in the controls there were 10/10 dead. Since Kato[18] has demonstrated the possibility of an antagonism to strychnine by means of an induction of hepatic microsomal enzymes (rather than central muscle relaxation) the experiment was repeated using the protein biosynthesis inhibitor ethionine. When 250 mg/kg of ethionine was given simultaneously with each 100-mg/kg dose of IVa, no protection (10/10 dead) from the lethal effects of strychnine was obtained, suggesting the strychnine antagonism of IVa initially observed was the result of increased metabolism of strychnine rather than a central nervous system mechanism.

IVa was tested for *in vivo* monoamine oxidase activity in rats. Groups of three animals were given IVa intraperitoneally at 50 and 100 mg/kg daily for 4 days. On the 5th day the animals were sacrificed, liver homogenates were prepared, and MAO activity was determined by the method of Weissbach, *et al.*,[19] measuring rate of disappearance of kynuramine. Liver MAO was found to be 2% of control at the higher dose, 35% of control at the lower dose.

Cardiovascular studies were done in two pentobarbital-anesthetized dogs. Cumulative intravenous doses of 50 mg/kg of IVa were without effect on artertial blood pressure or respiratory rate, nor did they produce any alteration of the response of the arterial pressure to epinephrine, norepinephrine, acetylcholine, or histamine. However, the response to dopamine was enhanced and that to reserpine was reversed, changes characteristic of known MAO inhibitors in this species.[20,21] In summary, IVa is a relatively nontoxic MAO inhibitor devoid of cardiovascular activity in the dog and devoid of activity in all of the other CNS screening tests in the mouse except for the strychnine lethality test. The absence of MAO inhibitory activity for enantiomer IVb is another example of enzyme inhibitor specificity.

Experimental Section

The melting points were obtained in a capillary tube with the Thomas–Hoover Uni-Melt and are corrected. Elemental analyses were performed by Midwest Microlabs., Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values. The pmr spectra were obtained at 60 Mc, with a Varian A-60 spectrophotometer, for 10% $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard; ir spectra, with a Perkin-Elmer 337 grating spectrophotometer; the glpc analyses, on an Aerograph Autoprep A-700.

S-Methyl 3-(β-Hydroxy-α-methylphenethyl)-3-methylthiocarbazate (III) and *cis*-(−)-3,4,5,6-Tetrahydro-4,5-dimethyl-6-phenyl-2H-1,3,4-oxadiazin-2-one (IVa).—To a stirred mixture of 36 g (0.20 mole) of N-amino-(−)-ephedrine, 28 ml of Et_3N, and 500 ml of Et_2O was added, dropwise, over a period of 2 hr, a solution of 22 g (0.20 mole) of methyl chlorothiolformate in 100 ml of Et_2O. The mixture was stirred at ambient temperature overnight, washed with one 350-ml portion of H_2O, extracted three times with 250-ml portions of dilute HCl, washed with 350 ml of aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was recrystallized twice from $(i\text{-Pr})_2O$ to give 22 g (43%) of white crystalline III, mp 145–146°. *Anal.* ($C_{12}H_{18}N_2O_2S$) C, H, N, S.

The combined dilute HCl extracts of the Et_2O solution were basified with K_2CO_3. The precipitate was filtered and recrystallized twice from hexane to give 2.9 g (7%) of white long needles of IVa: mp 119–120°; $[\alpha]^{25}D$ −8.0° (*c* 4.00, $CHCl_3$); λ_{max} (KBr) 3.11 (NH) and 5.94 μ (C=O); pmr, 52 (5-CH_3, doublet, J = 6.9 cps), 171 (NCH_3 singlet), 190 (5 H, multiplet), 348 (6 H, doublet, J = 3.0 cps), 433 (singlet, 5 phenyl protons), and 539 cps (NH proton, singlet). *Anal.* ($C_{11}H_{14}N_2O_2$) C, H, N.

(13) A. W. Lessin and M. W. Parkes, *Brit. J. Pharmacol.*, **14**, 108 (1959).
(14) G. Chen, C. R. Ensor, and B. Bohner, *Proc. Soc. Exp. Biol. Med.*, **86**, 507 (1954).
(15) L. C. Weaver and T. L. Kerley, *J. Pharmacol. Exp. Ther.*, **135**, 240 (1962).
(16) G. M. Everett, *Nature*, **177**, 1238 (1956).
(17) E. L. Anderson, J. E. Casey, Jr., L. C. Greene, J. J. Lafferty, and H. H. Reiff, *J. Med. Chem.*, **7**, 259 (1964).
(18) R. Kato, *Arzneimittel-Forsch.*, **11**, 797 (1961).
(19) H. Weissbach, T. E. Smith, J. W. Daly, B. Witkop, and S. Udenfriend, *J. Biol. Chem.*, **235**, 1160 (1960).
(20) L. I. Goldberg, *Ann. N. Y. Acad. Sci.*, **80**, 639 (1959).
(21) M. Chessin, R. R. Kramer, and C. C. Scott, *J. Pharmacol. Exp. Ther.*, **119**, 453 (1957).

Pyrolytic Conversion of III to IVa.—A 2-g sample of III was heated at 160–170° until the evolution of MeSH was completed (2 hr). The cooled residue was recrystallized from *i*-PrOH–$(i\text{-Pr})_2O$ to give 1.1 g (68%) of IVa, mp 119–120°.

Treatment of N-Amino-(−)-ephedrine with BrCN.—To a stirred mixture of 16 g (0.90 mole) of N-amino-(−)-ephedrine, 15 g of NaOAc, and 75 ml of MeOH cooled to 10° was added, dropwise, over a period of 0.5 hr a solution of 10 g (0.94 mole) of BrCN in 25 ml of MeOH. The mixture was allowed to come to ambient temperature and was stirred overnight. It was concentrated *in vacuo*, cooled, basified with 25 ml of cold aqueous 10 *N* NaOH solution, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give 11.4 g of brown oil. A rapid vacuum distillation with an oil bath at 110° yielded 9 g of oil, bp 45–65° (0.3 mm). The oil partially solidified. The liquid was pipetted from the solid and passed through a filter paper. Glpc (130°, 4% SE 30/Chromosorb W/AW, He 250 cc/min, t = 90 sec) indicated that the liquid was ~98% pure. Ir and pmr analyses indicated the oil was principally *trans*-β-methylstyrene (VII): λ_{max} (film) 5.81, 6.32, 10.45, 13.6, and 14.5 μ; pmr ($CDCl_3$), 103 (CH_3 doublet, J = 5 cps), 371 (multiplet, 2 vinyl protons), and 430 cps (multiplet, 5 aromatic protons). The solidified portion of the distillate was recrystallized from Et_2O–hexane to give white crystals of methyl carbamate (VIII): mp 55–56°; λ_{max} (Nujol) 2.91, 3.01, 3.10, 3.15, 6.01, 6.25 μ; pmr ($CDCl_3$), 218 cps (CH_3O singlet).

Ethyl 2-Benzyl-3-(β-hydroxy-α-methylphenethyl)-3-methylcarbazate (VI).—To a stirred solution of 0.05 mole of NaOEt in absolute EtOH, prepared by dissolving 1.2 g (0.05 g-atom) of Na in 50 ml of absolute EtOH, was added, dropwise, a solution of 10.3 g (0.05 mole) of IVa in 100 ml of absolute EtOH. After the addition was completed, the mixture was heated and the temperature gradually was elevated to the reflux temperature over a period of 1 hr. To the stirred, refluxing mixture was added, dropwise, 8.6 g (0.05 mole) of benzyl bromide. The mixture was stirred and heated at reflux temperature overnight. The cooled mixture was diluted with a 300-ml portion of H_2O and extracted with CH_2Cl_2. The washed (H_2O) and dried ($MgSO_4$) CH_2Cl_2 extract was evaporated *in vacuo* and the residual tan oil was dissolved in dry Et_2O and treated with ethereal HCl until the precipitation of the hydrochloride was complete. Three recrystallizations of the hydrochloride from MeOH–Et_2O gave 8.5 g (45%) of white crystalline solid: mp 144–145°; λ_{max} (Nujol) 3.00 (broad, w, OH), 3.80 (broad, m, NH^+), and 5.82 μ (s, C=O). *Anal.* ($C_{20}H_{26}N_2O_3 \cdot HCl$) C, H, Cl, N.

3,4,5,6-Tetrahydro-4,4,5-trimethyl-6-phenyl-2H-1,3,4-oxadiazin-2-onium Iodide (V).—A mixture of 5.0 g of VI, 10 ml of MeI, and 50 ml of Me_2CO was heated at reflux temperature for 7 hr and then allowed to come to room temperature overnight. The precipitate was suction filtered, washed with Et_2O, and recrystallized twice from MeOH–Et_2O to give 3.9 g (53%) of white solid, mp 143–144° dec. *Anal.* ($C_{12}H_{17}IN_2O_2$) C, H, N.

2-Amino-5,6-dihydro-4-methyl-4H-1,3,4-oxadiazine (Xa).—To a stirred, cooled (10°) mixture of 81 g (0.90 mole) of β-(1-methylhydrazino)ethanol (IXa),[13] 154 g (1.9 moles) of NaOAc, and 750 ml of MeOH was added, dropwise, over a period of 2 hr a solution of 100 g (0.94 mole) of BrCN in 300 ml of MeOH. The mixture was stirred at ambient temperature overnight, concentrated *in vacuo*, cooled, basified with a solution of 60 g of NaOH in 150 ml of H_2O, and extracted with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ extract was distilled *in vacuo* to give 19.8 g (22%) of sparkling, colorless oil that solidified but was too soft and hygroscopic for a melting point determination: bp 90° (0.3 mm); λ_{max} (Nujol) 2.88 (w) and 2.96 (w) (NH_2) and 6.02 μ (s) (C=N). *Anal.* ($C_3H_5N_3O$) C, H, N.

2-Amino-5,6-dihydro-4,6-dimethyl-4H-1,3,4-oxadiazine (Xb) was obtained as a colorless, viscous oil in 42% yield: bp 94–96° (2.0 mm); pmr (CCl_4), 74 (CH_3 doublet, J = 6 cps), 129 (multiplet, 2 protons), 144 (NCH_3 singlet), 172 (multiplet, 1 proton), and 270 cps (NH_2 singlet). *Anal.* ($C_4H_9N_3O$) C, H, N.

2-Amino-5,6-dihydro-4,6,6-trimethyl-4H-1,3,4-oxadiazine (Xc) was obtained as a colorless, viscous oil in 19% yield which solidified and gave white needles from ether–hexane: bp 85–88° (0.8 mm); mp 85–86.5°; λ_{max} (Nujol) 3.03 (w) and 3.17 (w) (NH_2) and 6.01 μ (s) (C=N); pmr ($CDCl_3$), 81 (geminal dimethyl singlet), 148 (CH_3 singlet), 154 (NCH_3 singlet), and 255 cps (broad NH_2). *Anal.* ($C_6H_{13}N_3O$) C, H, N.

2-(1-Methylhydrazinomethyl)-4,4-dimethyl-2-pentanol (XIa).—A mixture of 23 g (0.18 mole) of 1,2-epoxy-2,4,4-trimethylpentane, 83 g (1.8 moles) of methylhydrazine, and 2 drops of 1 *N* NaOH solution was heated at reflux temperature for 24 hr. The mixture was distilled through a 30-cm vacuum enclosed Vigreux column using a H_2O pump. After distillation of excess methylhydrazine, the colorless oily product was collected, bp 133–135° (35 mm), yield 16.5 g (53%), $n^{20}D$ 1.4564. *Anal.* ($C_9H_{22}N_2O$) C, H, N.

4-(1-Methylhydrazino)-2,5-dimethyl-3-hexanol (XIb).—A mixture of 40.0 g (0.31 mole) of 3,4-epoxy-2,5-dimethylhexane, 143 g (3.1 mole) of methylhydrazine, and 5 drops of 1 *N* NaOH solution was heated at reflux temperature for 60 hr. The mixture was distilled through a 30-cm vacuum enclosed Vigreux column as above. After distillation of excess methylhydrazine, the colorless, oily product was collected, bp 143–146° (35 mm), yield 32 g (59%), $n^{20}D$ 1.4581. *Anal.* ($C_9H_{22}N_2O$) C, H, N.

4,6-Dimethyl-6-(β,β-dimethylpropyl)-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-one (XIIa).—To a stirred mixture of 8.0 g (0.046 mole) of 2-(1-methylhydrazinomethyl)-4,4-dimethyl-2-pentanol (XIa), 10 ml of Et_3N, and 50 ml of C_6H_6 was added, dropwise, a solution of 6.6 g (0.060 mole) of methyl chlorothiolformate in 20 ml of C_6H_6. The mixture was stirred and heated at reflux temperature for 18 hr. The cooled mixture was diluted with 150 ml of $CHCl_3$, washed (twice with H_2O, twice with NaOH, and twice with H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The 10.1 g of residual tan oil was heated in an oil bath at 160–170° for 5 hr. After approximately 3 hr the weight of the remaining residue was 7.9 g. The solidified residue after washing with $(i\text{-Pr})_2O$ weighed 6.3 g and melted at 111–116°. After three recrystallizations from $(i\text{-Pr})_2O$ the melting point was 119–120.5°, yield 4.8 g (52%). *Anal.* ($C_{10}H_{20}N_2O_2$) C, H, N.

5,6-(Diisopropyl)-4-methyl-3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-one (XIIb).—Methyl chlorothiolformate (9.5 g, 0.086 mole) dissolved in 50 ml of C_6H_6 was added, dropwise, to a stirred mixture of 15 g (0.086 mole) of 4-(1-methylhydrazino)-2,5-dimethyl-3-hexanol (XIb), 15 ml of Et_3N, and 50 ml of C_6H_6. The mixture was stirred and refluxed for 6 hr, cooled, diluted with 200 ml of $CHCl_3$, washed (twice with H_2O, twice with 10% NaOH, twice with H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The 15.6 g of tan oil was heated in an oil bath at 160–170° for 4 hr. The residue (13 g) was crystallized with $(i\text{-Pr})_2O$; mp 114–118°. Two recrystallizations from $(i\text{-Pr})_2O$ gave a white crystalline solid, mp 118–120°, yield 7.6 g (46%). *Anal.* ($C_{10}H_{20}N_2O_2$) C, H, N.