The hydroxyl protons appear as a broad band at δ 2.7, H_1 is a multiplet at 6.5, H_2 at 2.3, H_3 at 4.5, H_4 at 4.0, and H_5 at 3.7.

It was found that the α and β anomers of **12** could be separated by repeated chromatography on silica gel using $CHCl_3$ and $CHCl_3$–methanol as the solvents. The first fraction was **12a**, $[\alpha]^{24}D$ +45° (*c* 10.6, CH_3OH), and the second fraction was **12b**, $[\alpha]^{24}D$ −10° (*c* 4.26, CH_3OH).

6-Trifluoromethyl-2-(2′-deoxy-D-ribofuranosyl)-*as*-triazine-3,5(2H,4H)-dione (5-Trifluoromethyl-6-aza-2′-deoxyuridine, 7).—The mixture of anomers **12a** and **12b** (0.10 g, 0.22 mmole), 10 ml of methanol, and approximately 50 mg of prereduced 5% palladium on carbon in methanol (20 ml) was hydrogenated at room temperature and pressure. After the mixture had taken up 10 ml of hydrogen (99% of theory), the reduction was stopped. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to yield a transparent, semisolid mass (81 mg) which was chromatographed on silica (Merck AG., silica gel, 0.05–0.2 μ) with $CHCl_3$. The first fraction contained diphenylmethane (identified by nmr). Changing to 15% methanol in $CHCl_3$ gave a fraction containing 54 mg (82%) of the anomers of **7** as a clear glass. After passing an aqueous solution through a Dowex 50 W (H^+ form) column, the fractions absorbing in the ultraviolet were evaporated, and the residue was redissolved in methanol, filtered, and evaporated to give **7** as a glass, softening at 78°. The presence of methanol was confirmed by nmr.

Anal. Calcd for $C_9H_{10}F_3N_3O_5 \cdot CH_3OH$: C, 36.48; H, 4.28; N, 12.76. Found (two samples): C, 36.83, 36.12; H, 3.86, 4.18; N, 13.22.

Similar reduction of the anomer **12a** gave anomer **7a**, purified on silica, $[\alpha]^{24}D$ +76° (*c* 2.3, CH_3OH), λ_{max} (pH 1.0) 269 mμ (ε 5000), (pH 12.4) 264 mμ (ε 5000).

The anomer **12b** gave **7b**, $[\alpha]^{24}D$ −36° (*c* 2.4, CH_3OH), λ_{max} (pH 1.0) 269 mμ (ε 4900), (pH 12.4) 264 mμ (ε 4900), after chromatography with methanol. Compound **7b** gives the following signals in the sugar portion of the molecule: H_1, δ 6.6; H_2, 2.5; H_3, 4.5; H_4, 4.0; and H_5, 3.7. The integral is consistent with the structure.

Inhibition Studies. Dihydrofolate Reductase Assay.—The stock solution of NADPH was prepared by dissolving NADPH (Sigma Chemical Corp.) in 0.02 *M* Tris buffer at a pH of 8.5 to give a final concentration of 0.5 μmole/ml. Dihydrofolic acid, prepared by dithionite reduction of folic acid according to Futterman,[35] was dissolved in 0.005 *M* acetate buffer containing 0.01 *M* mercaptoethanol at a pH of 4.5 to give a final concentration of 0.5 μmole/ml. The assay was that of Friedkin and co-workers[36] and contained 0.2 ml of the NADPH stock solution, 0.1 ml of the dihydrofolic acid stock solution, 0.75 ml of 0.02 *M* mercaptoethanol in 0.1 *M* phosphate buffer at pH of 7.5 and enzyme, inhibitor, or inhibitor solvent, and water to a total of 1.5 ml. Dihydrofolic acid was replaced by 0.005 *M* acetate buffer containing 0.01 *M* mercaptoethanol at a pH of 4.5 in the reference cell.

The change in absorbance at 340 mμ (32°) in a Beckman DB spectrophotometer was recorded with 10 × expansion of the transmission scale and was linear for 10 min. After conversion to absorbance units, 52% of the change in absorbance represents the utilization of dihydrofolic acid, and this change was used in determining the specific activity of the enzyme.

Inhibitors were dissolved in water, alcohol, or 0.02 *M* NaOH to give stock solutions containing 1 μmole/0.1 ml. When base or alcohol was used as the solvent the effect of the solvent on the uninhibited reaction was examined, and these rates were compared to the inhibited reaction.

Thymidylate Synthetase.—The assay solution contained 0.05 μmole of deoxyuridine 5′-monophosphate (Sigma Chemical Corp.), 0.22 μmole of tetrahydrofolic acid (General Biochemicals Corp.), 15 μmoles of formaldehyde, 25 μmoles of $MgCl_2$, 130 μmoles of mercaptoethanol, 0.9 μmole of disodium ethylenediaminetetraacetic acid, 45 μmoles of Tris buffered at a pH of 7.4, and enzyme to a total volume of 1.2 ml. Tetrahydrofolic acid was added to 1 *M* mercaptoethanol and adjusted to pH 7.4 and this solution containing approximately 20 μmoles/ml was divided into small fractions and frozen. Deoxyuridine 5′-monophosphate was dissolved in water to give a stock solution containing approximately 1 μmole/ml and was stored, frozen. The assay stock solution (minus mix) contained 12 mmoles of mercaptoethanol, 27 μmoles of tetrahydrofolic acid, 1.8 mmoles of formaldehyde, and 3 mmoles of $MgCl_2$ in a total volume of 30 ml. The assay sample cell contained 0.25 ml of the minus mix and 0.05 ml of the deoxyuridine 5′-monophosphate stock solution and enzyme, inhibitor solution, or inhibitor solvent and buffer A were added to a total of 1.2 ml. Deoxyuridine 5′-monophosphate was replaced by water in the reference cell.

The change in absorbance at 340 mμ was read at 30° in a Beckman DB spectrophotometer and recorded with 10 × expansion of the transmission scale and converted to absorbance. Under these conditions the change in absorbance usually was linear for the first 10 min.

Acknowledgment.—The authors wish to acknowledge the assistance of Mrs. William Riggs for enzyme studies, Messrs. Larry Hare, Donald Thompson, and Quentin Gilman for synthesis of starting materials, and Professor Morris Friedkin and associates for helpful discussions.

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1,4,5,6-Tetrahydro-*as*-triazines. I. Sulfuric Acid Catalyzed Condensation of Nitriles and Hydrazino Alcohols[1]

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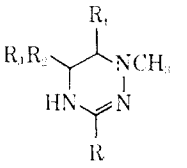
Variously substituted 1,4,5,6-tetrahydro-*as*-triazines were prepared by treating nitriles with hydrazino alcohols in the presence of concentrated sulfuric acid. The scope and mechanism of this reaction was investigated. The spectral properties and pharmacological activity of the compounds are discussed. *trans*-(−)-3-(*o*-Chlorophenyl)-1,6-dimethyl-5-phenyl-1,4,5,6-tetrahydro-*as*-triazine was found to possess analgetic activity as measured by the inhibition of hydrochloric acid induced writhing and by a modified hot plate procedure. Five other compounds were found to inhibit maximal electroshock seizures in mice indicating anticonvulsant activity.

We observed that N-amino-(−)-ephedrine (I) reacted with benzonitrile in concentrated sulfuric acid at ambient temperature to give *trans*-(+)-1,6-dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine (II). A literature search revealed the absence of any reports on the acid-catalyzed condensation of hydrazino alcohols and nitriles. In fact, the only example of a

(1) Presented in part before the Division of Medicinal Chemistry at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

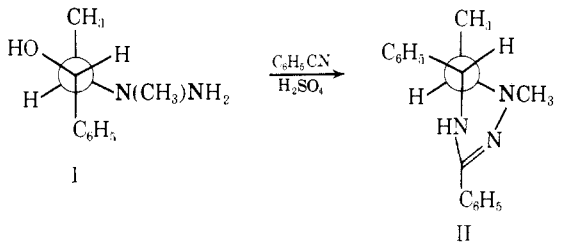
TABLE I

SUBSTITUTED 1,4,5,6-TETRAHYDRO-*as*-TRIAZINES



No.	R	R_1	R_2	R_3	Bp (mm) or mp, °C	% yield	Meth-od	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	4-ClC_6H_4	CH_3	H	C_6H_5	134–135	23	A	68.11	6.05	14.02	67.88	6.24	13.80
2	C_6H_5	CH_3	H	C_6H_5	146–147	35	A	76.95	7.22	15.83	76.73	7.46	15.80
3	4-$CH_3OC_6H_4$	CH_3	H	C_6H_5	133–134	10	A	73.19	7.17	14.23	73.29	7.20	14.19
4	2-ClC_6H_4[e]	CH_3	H	C_6H_5	256–257	26	A	60.72	5.70	12.50	60.47	5.72	12.15
5	3-$CH_3C_6H_4$	CH_3	H	C_6H_5	147–148	30	A	77.38	7.58	15.04	77.19	7.68	14.48
6	4-$CH_3C_6H_4$	CH_3	H	C_6H_5	142–143	34	A	77.38	7.58	15.04	77.27	7.52	14.57
7	2-$CH_3C_6H_4$[c]	CH_3	H	C_6H_5	227–229	15	A	68.23	7.32	13.26	68.52	7.14	13.00
8	C_6H_5	H	H	C_6H_5	133–134	52	B	76.47	6.82	16.72	76.00	7.12	16.31
9	3-NC_5H_4	CH_3	H	C_6H_5	146–147	15	A	72.14	6.76	21.03	71.82	7.00	20.58
10	C_6H_5	H	CH_3	CH_3	95–96	12	B	70.89	8.43	20.67	71.04	8.54	20.15
11	2-ClC_6H_4	H	H	C_6H_5	92–93	20	B	67.25	5.60	14.72	67.17	5.65	14.02
12	4-$CH_3OC_6H_4$	H	H	C_6H_5	103–105	8	B	72.74	6.76	14.94	72.47	7.02	14.57
13	4-$F_3CC_6H_4$	H	H	C_6H_5	80–83	6	B	62.94	5.01	13.16	62.61	5.17	12.44
14	4-ClC_6H_4	H	H	C_6H_5	107–108	17	B	67.25	5.60	14.72	67.20	5.41	14.38
15	2-ClC_6H_4[g]	H	CH_3	CH_3	183–185	13	B	45.22	5.34	13.50	45.22	5.42	15.73
16	4-$F_3CC_6H_4$	CH_3	H	C_6H_5	119–120	6	B	64.88	5.44	12.90	65.02	5.40	12.73
17	4-FC_6H_4	CH_3	H	C_6H_5	118–121	14	B	72.04	6.40	14.82	72.09	6.47	14.43
18	4-$O_2NC_6H_4$	CH_3	H	C_6H_5	110–111	7	B	65.77	5.84	18.05	65.47	5.75	17.15
19	CH_3	H	CH_3	CH_3	126–127	19	B	59.54	10.71	29.76	59.66	10.98	29.59
20	CH_3	H	H	C_6H_5	84–85	67	B	69.81	7.99	22.20	69.86	8.29	22.31
21	$(C_2H_5)_2NCH_2$	H	H	C_6H_5	143 (0.24)	9	B	69.19	9.29	21.52	68.59	9.20	21.95
22	$H_2C{=}CH$	H	H	C_6H_5	145 (0.15)	16	C	71.61	7.51	20.89	71.24	7.83	20.68

[a] Pmr spectra were obtained at 60 Mc with a Varian A-60 spectrometer. Spectra for **4**, **7**, and **15** were obtained for 10% D_2O solutions containing a trace of 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (TMSPS) as an internal standard and spectra for all the other compounds were obtained for 10% $CDCl_3$ solutions containing a trace of tetramethylsilane as an internal standard. [b] Ultraviolet



1,4,5,6-tetrahydro-*as*-triazine is 3-methoxy-5,6-diphenyl-1,4,5,6-tetrahydro-*as*-triazine.[2] Related heterocycles, such as 1,2,5,6-tetrahydro-,[3] 2,3,4,5-tetrahydro-,[4] 3-thiono-2,3,4,5-tetrahydro-,[5] 3,5-dioxo-2,3,4,5-tetrahydro-,[6] 3-oxo-2,3,4,5-tetrahydro-,[7] 5-oxo-1,4,5,6-tetrahydro-,[8] and 6-oxo-1,4,5,6-tetrahydro-*as*-triazines[9] have been reported.

Because of the uniqueness of both the heterocyclic ring and its formation *via* a modified Ritter reaction and because certain isosteric 5,6-dihydro-4H-1,3,4-oxadiazines have been reported[10] to possess biological activity, a study was initiated to determine the scope of the reaction and to synthesize a series of variously substituted 1,4,5,6-tetrahydro-*as*-triazines for pharmacological screening.

The 1,4,5,6-tetrahydro-*as*-triazines listed in Table I (except **12**) were prepared either by method A or B (see Experimental Section). A significant difference in the two methods is that attempts to prepare triazines with an aliphatic substituent in the 3 position failed by method A and succeeded by method B.

Infrared analysis indicates the presence of NH at around 3350 cm^{-1} and –NHC=N– near 1625 cm^{-1}. This is analogous to the reasonably strong absorption near 1625 cm^{-1} exhibited by the –OC=N– and –SC=N– groupings present in the isosteric 5,6-dihydro-4H-1,3,4-oxa- and -thiadiazines.[11,12]

The ultraviolet absorption spectra of the 1,4,5,6-tetrahydro-*as*-triazines (see Table I) containing an aromatic moiety attached to the triazine heterocycle at the 3 position all exhibit a maximum in the 280–320-mμ region except for **4**, **7**, **11**, **15**, and **18**. This maximum at 280–320 mμ is indicative of the chromophore C=N in conjugation with an aromatic moiety. Compounds **4**, **7**, **11**, and **15** all have as the aromatic moiety attached at the 3 position of the triazine ring either *o*-chlorophenyl or *o*-tolyl. Stewart–Briegleb models indicate steric interaction between the *o*-chloro and *o*-methyl group and the hydrogen attached to the 4 position of the triazine ring that prevents free rotation about the triazine–phenyl bond. Although this steric

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Nmr assignments[a]								Molar absorption[b]	$[\alpha]_D$, deg
Chemical shifts, –ppm						Coupling, cps			(c in g/100 ml,
NCH_3	NH	R_3	R_2	R_1	6-H	H_5–H_6	H_5–H_4	$\lambda_{max}^{CH_3OH}$, mμ ($\epsilon \times 10^{-3}$)	CH_3OH)[c]
2.81	4.61	7.26	4.24	1.03	2.52	6.8	1.6	230 (17.5), 304 (4.7)	+35.9 (4.004)
2.88	4.72	7.27	4.22	1.00	2.50	6.68	1.58	*d*	
2.80	4.61	7.27	4.24	1.03	2.49	7.0	1.4	239 (14.7), 279 (6.5)	+42.1 (3.776)
2.90	...	7.50	4.69	1.18	3.37	7.75	...	*f*	−132.7 (4.018)
2.82	4.62	7.26	4.24	1.05	2.50	6.85	1.55	289 (4.2)	+27.6 (4.010)
2.81	4.63	7.28	4.25	1.05	2.50	6.8	1.4	227 (16.1), 289 (4.8)	+33.4 (4.004)
2.89	...	7.51	4.68	1.14	3.35	7.9 ± 0.4	...	*f*	−138.2 (4.004)
2.79	4.74	7.29	4.75	3.10	2.57	7.4	1.5	292 (4.2)	
2.83	5.00	7.27	4.27	1.05	2.56	6.65	1.65	314 (4.0)	+30.4 (4.006)
2.83	4.23	1.29	1.29	2.48	2.48	...	...	293 (4.0)	
2.77	4.66	7.3	4.79	3.10	2.62	7.1	1.7	*f*	
2.79	4.74	7.35	4.80	3.14	2.56	7.0 ± 0.5	>0	238 (14.8), 280 (6.7)	
2.83	4.79	7.35	4.81	3.14	2.64	7.15	1.6	317 (3.9)	
2.80	4.75	7.35	4.78	3.12	2.60	6.9	1.8	230 (15.9), 300 (4.9)	
2.95	...	1.48	1.48	3.13	3.13	...	...	260 (4.3)	
2.87	4.75	7.34	4.32	1.07	2.60	6.6	1.75	224 (6.6), 322 (3.4)	+26.6 (4.014)
2.84	4.68	7.35	4.29	1.05	2.54	6.8	1.2 ± 0.2	287 (4.3)	+30.2 (4.010)
2.90	4.78	7.35	4.34	1.09	2.66	6.25	1.9	265 (13.5), 395 (4.2)	−109.3 (4.010)
2.70	4.10	1.39	1.39	2.36	2.36	...	...	*d*	
2.65	4.5	7.29	4.62	2.98	2.43	7.35	<2	*d*	
2.70	5.54	7.30	4.69	3.06	2.41	7.5	1.2	*d*	
2.75	4.60	7.29	4.69	3.07	2.45	~7	~1	*d*	

absorption maxima and molar absorption were measured on a Beckman DU spectrophotometer. [c] Optical rotation was measured on a Rudolph laboratory polarimeter Model No. 62 at room temperature. [d] Not measured. [e] Hydrochloride. [f] Data were not obtained because the wavelength of maximum absorbance was 220 mμ or less. [g] Hydrobromide.

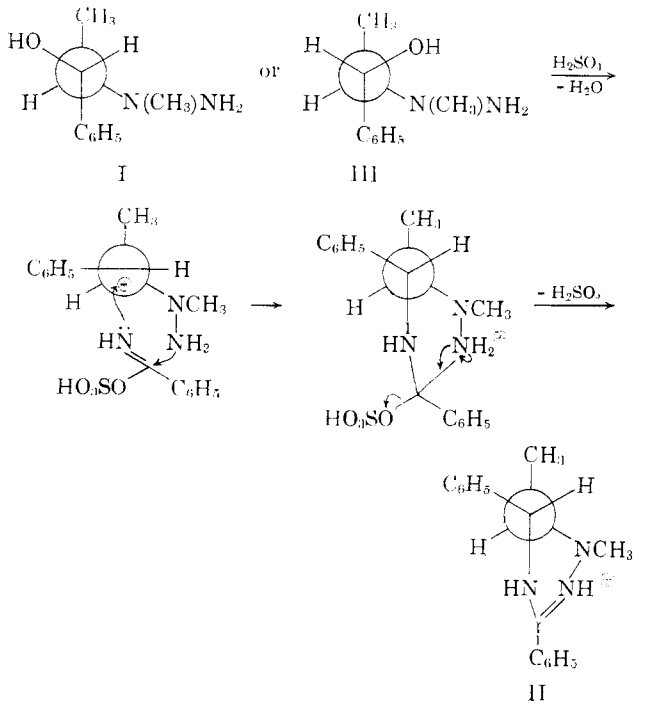
interaction does not prevent coplanarity of the rings, it may be responsible for lack of ultraviolet absorption maximum at 280–320 mμ because (a) when the chloro or methyl group is in the *para* position (**6** and **14**) there is a maximum at 280–320 mμ, and (b) both the isosteric oxa- and thiadiazines having *o*-chlorophenyl or *o*-tolyl substituents exhibit a maximum in the 280–320-mμ-region and Stewart–Briegleb models indicate free rotation about the oxa- and thiadiazine–phenyl bond, since there is a lack of steric interaction of the *o*-chloro or *o*-methyl group with either the oxygen or sulfur atoms of the oxa- or thiadiazine ring.[11,12]

The nmr spectra exhibited the expected chemical shifts and coupling constants (Table I). The 3-substituted 1,6-dimethyl-5-phenyl-1,4,5,6-tetrahydro-*as*-triazines in Table I exhibited $J_{5,6} \sim 7$ cps. This coupling indicates these protons most likely are *trans*-axial-axial. Comparing with the isosteric oxidiazines where both the *cis* and *trans* isomers were available it is seen that the couplings compare favorably with the *trans*-oxadiazine which has a $J_{5,6} \sim 7.2$ cps and not with the *cis*-oxidiazine which has a $J_{5,6} \sim 2.5$ cps.[13] Thus, all of the 3-substituted 1,6-dimethyl-5-phenyl-1,4,5,6-tetrahydro-*as*-triazines in Table I are *trans* isomers. The double bond is probably between N-2 and C-3 rather than between C-3 and N-4 because of the complex splitting of the C-5 proton which indicates a proton at N-4 and because the H_5–H_4 splitting is ~1.6 cps. Placement of the double bond between C-3 and N-4 is very unlikely because the consequent coupling between H-5 and H-2 would be expected to be unobservably small.

In order to determine the scope of the reaction various hydrazino alcohols, such as, N-amino-(−)-ephedrine, N-amino-(+)-pseudoephedrine, 1-(1-methylhydrazino)-2-propanol, 1-methylhydrazino-*t*-butyl alcohol, and α-(1-methylhydrazinomethyl)benzyl alcohol, were allowed to react with a variety of aliphatic and aromatic nitriles in concentrated sulfuric acid according to method B. Hydrazino alcohols possessing a tertiary aliphatic or secondary benzyl hydroxyl, *i.e.*, a type that yields a relatively stable carbonium ion in concentrated H_2SO_4, condensed with a variety of nitriles to give triazines. Hydrazino alcohols containing a secondary or primary aliphatic hydroxyl would not condense with a nitrile in concentrated H_2SO_4 to give a triazine. Instead the nitrile was converted to an amide. Treatment of the diastereoisomeric hydrazino alcohols, N-amino-(−)-ephedrine (I) and N-amino-(+)-pseudoephedrine (III), with benzonitrile in concentrated H_2SO_4 yielded *trans*-(+)-1,6-dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine (II), exclusively. The necessity of the hydrazino alcohol possessing a hydroxyl group that forms a relatively stable carbonium ion and the fact that both I and III, which are diastereoisomeric hydrazino alcohols that differ only in configuration about the hydroxyl-bearing carbon atom, reacted with benzonitrile to give II, exclusively, indicate that the reaction most likely proceeds *via* attack of the nitrilium sulfate upon the carbonium ion resulting from the dehydration of the hydrazino alcohol (Scheme I).

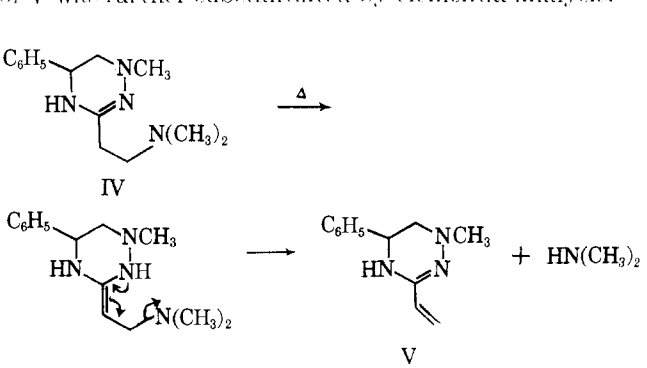
(13) D. L. Trepanier and V. Spranemanis, *J. Org. Chem.*, **29**, 2151 (1964).

SCHEME I



A variety of nitriles were used successfully in this condensation reaction. However, chloroacetonitrile gave a polymeric amorphous product and hydrogen cyanide gave an oily product which distilled readily, but gave an extremely complex nmr spectrum and was not further characterized. Nevertheless, the scope of the reaction is broad in relationship to the structural requirements of the nitrile.

An interesting triazine was **22** (Table I) prepared from β-dimethylaminopropionitrile and α-(1-methylhydrazinomethyl)benzyl alcohol in concentrated H_2SO_4. Initially, a viscous light brown oil was isolated which gave an nmr spectrum corresponding to the expected 3-β-dimethylaminoethyl-1-methyl-5-phenyl-1,4,5,6-tetrahydro-*as*-triazine (IV). Distillation of IV gave a moderate yield (16%) of a viscous yellow oil having an nmr spectrum considerably different from the spectrum of IV. This new material possessed only one N-methyl group and along with the typical patterns of the C-6, C-5, and N-4 triazine protons there occurred nine sharp peaks at −5 to −7 ppm representing three protons. This pattern, typical of a vinyl group, indicated that probably distillation had produced a thermal elimination of dimethylamine to form 1-methyl-5-phenyl-3-vinyl-1,4,5,6-tetrahydro-*as*-triazine (V). The structure of V was further substantiated by elemental analysis.



Pharmacology. Analgetic Test. Adult male mice (Cox) weighing 18–22 g were used in these tests. Analgesia was measured by the ability of the compounds to antagonize the HCl-induced writhing response. Writhing was induced by the intraperitoneal injection of 10 ml/kg of a 0.1% HCl solution. The compounds to be tested were administered intraperitoneally, 30 min prior to the HCl. The results are expressed as a ratio of the number of animals not writhing/the number of animals tested.

Maximal Electroshock Test. Maximal electroshock seizures were produced by the method of Swinyard, *et al.*,[14] by delivering a current of 50 ma of 0.2-sec duration *via* corneal electrodes to mice injected intraperitoneally with the test compounds 1 hr prior to electroshock. The results are expressed as a ratio of the number of animals protected from the tonic hind limb extensor phase of the seizure/the number of animals tested.

Hexobarbital Sleeping Times. Adult male mice were injected intraperitoneally with the test compound 30 min prior to injection of 100 mg/kg of hexobarbital. The time (min) between injection of the hexobarbital and the regain of the righting reflex was taken as the duration of sleeping time. The results are expressed as a ratio of the treated group over the control group.

Results. The results of the pharmacological tests are summarized in Table II. Five (**3**, **5**, **6**, **12**, and **13**) of the 14 compounds tested were found to possess analgetic activity as measured by the inhibition of HCl-induced writhing. One of these (**3**) was also found to possess activity in a modified hot plate procedure. Compound **14**, which is the optical antipode of **3**, was devoid of analgetic activity.

Activity in the maximal electroshock test was found in five (**3**, **5**, **6**, **8**, **14**) of the 14 compounds tested. The most potent of the five was **6**.

Compounds **1**–**9** were potent potentiators of hexobarbital sleep time. The potentiation was most marked with **3**, **6**, **8**, and **14**. Only three of the compounds tested (**10**, **11**, **13**) failed to alter hexobarbital sleep time.

Experimental Section

The melting points were obtained in a capillary tube with the Thomas–Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlaboratories, Inc., Indianapolis, Ind. The synthesis of 1-(1-methylhydrazino)-2-propanol, 1-methylhydrazino-*t*-butyl alcohol, α-(1-methylhydrazinomethyl)benzyl alcohol, and N-amino-(−)-ephedrine has been reported.[9,12]

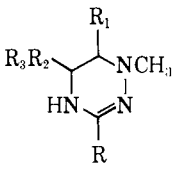
Substituted 1,4,5,6-Tetrahydro-*as*-triazines (see Table I). Method A.—To 250 ml of cooled (5°), stirred concentrated H_2SO_4 was added, dropwise, a solution of 36 g (0.2 mole) of N-amino-(−)-ephedrine in 100 ml of methylene chloride. To this mixture was added 23 g (0.2 mole) of *m*-tolunitrile. After stirring at 5° for 1 hr and at ambient temperature overnight, the mixture was poured onto crushed ice and extracted with chloroform to remove nonbasic by-products (mainly *m*-toluamide). The acidic, aqueous solution was made strongly basic (Na_2CO_3, NaOH), and then was extracted with $CHCl_3$. The chloroform extract of the basic, aqueous mixture was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from an appropriate solvent.

Method B.—To 100 ml of cooled (5°), stirred concentrated H_2SO_4 was added, dropwise, over a period of 5 min, 10.3 g (0.1 mole) of benzonitrile. To this mixture was added, dropwise, over a period of 1.5 hr, a solution of 16.6 g (0.1 mole) of α-(1-methylhydrazinomethyl)benzyl alcohol in 10 ml of CH_2Cl_2.

(14) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Expll. Therapy.*, **106**, 319 (1952).

Table II

Pharmacological Activity of Substituted 1,4,5,6-Tetrahydro-*as*-triazines



No.	R	R_1	R_2	R_3	Screening dose, mg/kg	Toxicity LD_{50}, mg	Hydrochloric acid writhing test[c]	Max electric shock test[c]	Hexobarbitol sleep time test[c]
1	4-ClC_6H_4	CH_3	H	C_6H_5	200	>400	0/4	0/4	206/53
2	C_6H_5	CH_3	H	C_6H_5	50	>200	0/4	0/4	82/48
3	2-ClC_6H_4[a]	CH_3	H	C_6H_5	50	>200	4/4	2/4	210/32
							10/10	8/10	
4	3-$CH_3C_6H_4$	CH_3	H	C_6H_5	400	>400	1/4	0/4	140/32
5	4-$CH_3C_6H_4$	CH_3	H	C_6H_5	50	>200	3/4	3/4	168/32
								7/10	
6	2-$CH_3C_6H_4$[a]	CH_3	H	C_6H_5	50	>50	4/4	3/4	213/33
							6/10	10/10	
7	C_6H_5	H	H	C_6H_5	200	>200	1/4	1/4	137/45
8	3-NC_5H_4	CH_3	H	C_6H_5	200	>400	2/4	4/4	300/33
							3/10	9/10	
9	C_6H_5	H	CH_3	CH_3	100	>100	1/4	1/4	87/32
10	CH_3	H	CH_3	CH_3	50	>100	1/4	0/4	33/30
11	CH_3	H	H	C_6H_5	50	>200	1/4	0/4	27/30
12	$(C_2H_5)_2NCH_2$	H	H	C_6H_5	100	>200	3/4	0/4	68/39
							6/10		
13	$H_2C{=}CH$	H	H	C_6H_5	100	>200	4/4	0/4	44/39
							8/10		
14	2-ClC_6H_4[b]	CH_3	H	C_6H_5	50	>200	1/4	4/4	350/53

[a] Hydrochloride. [b] Optical antipode of **3**. Compound **3** is *trans*-(−) and **14** is *trans*-(+). [c] See Pharmacology for an explanation of these ratios.

After the addition was completed, the mixture was poured onto crushed ice and the product was isolated as described in method A.

Method C.—To 200 ml of cooled (5°), stirred concentrated H_2SO_4 was added, dropwise, 19.6 g (0.2 mole) of 3-dimethylaminopropionitrile. To this mixture was added, dropwise, a solution of 33.2 g (0.2 mole) of α-(1-methylhydrazinomethyl)-benzyl alcohol in 15 ml of CH_2Cl_2. The mixture was poured onto crushed ice, basified (Na_2CO_3, NaOH), and extracted with a 1:1 methylene chloride–ether mixture. The dried (Na_2SO_4) organic extract was evaporated *in vacuo* leaving 34 g of an orange oil. Distillation of this oil yielded 6.3 g (16%) of 1-methyl-5-phenyl-3-vinyl-1,4,5,6-tetrahydro-*as*-triazine: bp 145° (1.5 mm); nmr ($CDCl_3$) 2.2–2.7 (CH_2, multiplet, two protons), 2.7 (NCH_3, singlet, three protons), 4.5–4.9 (CH and NH multiplet, two protons), 5.12 and 5.27 ($C{=}CH_2$ two doublets, two protons), 5.9–6.5 (C=CH– multiplet, one proton), and 7.28 ppm (five aromatic protons).

Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.89. Found: C, 71.24; H, 7.82; N, 20.68.

Attempted Preparation of 1,5-Dimethyl-3-phenyl-1,4,5,6-tetrahydro-*as*-triazine.—A solution of 20 g (0.18 mole) of 1-(1-methylhydrazino)-2-propanol in 10 ml of CH_2Cl_2 was added, dropwise, over a period of 2 hr, to a cooled (10°), stirred solution of 20.6 g (0.2 mole) of benzonitrile in 250 ml of concentrated H_2SO_4. After the addition was completed, the mixture was poured onto crushed ice and extracted thoroughly with chloroform. The washed (H_2O) and dried (Na_2SO_4) chloroform solution was evaporated *in vacuo* leaving 22 g (90%) of benzamide, mp 127–128°.

Condensation of Benzonitrile and N-Amino-(+)-pseudoephedrine in Concentrated H_2SO_4.—A solution of 36 g (0.2 mole) of N-amino-(+)-pseudoephedrine in 50 ml of CH_2Cl_2 was added, dropwise, to cooled (5°), stirred concentrated H_2SO_4 (250 ml). After the addition was completed, 20.6 g (0.2 mole) of benzonitrile was added and the mixture was stirred at ambient temperature overnight. The mixture was poured onto crushed ice, washed with chloroform, basified with Na_2CO_3 solution and the precipitated solid was removed by suction filtration. The solid was recrystallized from isopropyl alcohol to yield 18.5 g of white crystalline solid, mp 146–147°. An admixture with authentic *trans*-1,6-dimethyl-3,5-diphenyl-1,4,5,6-tetrahydro-*as*-triazine melted at 146–147°. Also, the nmr spectra were identical.

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