1,4,5,6-Tetrahydro-*as*-triazines. II. Condensation of β-Aminoalkylhydrazines with Iminoesters and Orthoesters

DONALD L. TREPANIER, JACK E. RICHMAN, AND ALLAN D. RUDZIK

Chemistry Research and Pharmacology Departments, Human Health Research and Development Center, The Dow Chemical Company, Indianapolis, Indiana

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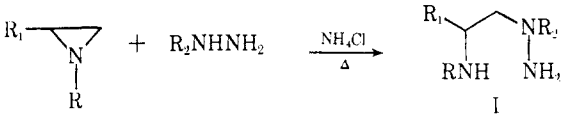
Variously substituted 1,4,5,6-tetrahydro-*as*-triazines were prepared *via* the condensation of β-aminoalkylhydrazines with iminoesters and orthoesters. The scope of these reactions and the pharmacological activity of the compounds is discussed.

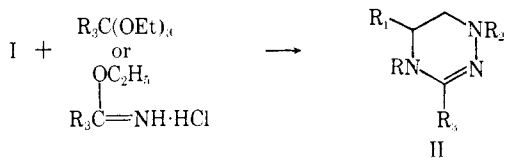
Previously, we reported[1] the results of an investigation of the synthesis of substituted 1,4,5,6-tetrahydro-*as*-triazines *via* condensation of nitriles with hydrazino alcohols catalyzed by concentrated sulfuric acid. During this investigation we found that the condensation could be effected only if the hydrazino alcohol possessed a hydroxyl group which yielded a relatively stable carbonium ion. This stringent requirement as to the types of hydrazino alcohols that could be condensed with nitriles to give triazines limited the scope of this synthetic method. Therefore, in order to synthesize other structurally diverse types of triazines, we studied the condensation of β-aminoalkylhydrazines with a variety of iminoesters and orthoesters. This paper describes our study of these reactions which led to the synthesis of new substituted 1,4,5,6-tetrahydro-*as*-triazines, and it also reports the pharmacological activity of these compounds.

The required β-aminoalkylhydrazines were prepared by treating either aziridine, N-ethylaziridine, or 2-methylaziridine with a 10-mole excess of either hydrazine or methylhydrazine in the presence of a catalytic amount of ammonium chloride. The large excess of the hydrazine reactant was necessary to minimize the formation of polymeric products. Also, slow, dropwise addition of the aziridine to the rapidly stirred, heated hydrazine reactant containing the ammonium chloride gave a higher yield of the β-aminoethylhydrazine.



Ia, R, R_1, R_2 = H
b, R, R_1 = H; R_2 = CH_3
c, R = H; R_1, R_2 = CH_3
d, R = C_2H_5; R_1 = H; R_2 = CH_3

The four β-aminoethylhydrazines (Ia–d) were allowed to react with either an iminoester hydrochloride or an orthoester to give the desired substituted 1,4,5,6-tetrahydro-*as*-triazines (II).



The iminoester hydrochlorides were prepared using the Pinner synthesis[2] which consists of condensing the nitrile and the alcohol under anhydrous conditions in the presence of HCl at 0–5°. Ethanol was used in all cases. However, both methyl and ethyl benzimidate hydrochloride were prepared. The iminoester hydrochlorides were not purified and characterized. They were used as crude products that were washed thoroughly with anhydrous ether and dried *in vacuo* at ambient temperature.

The iminoester hydrochlorides were condensed with the β-aminoalkylhydrazines by slowly adding the β-aminoalkylhydrazine to a stirred solution or suspension of the iminoester hydrochloride in absolute ethanol (method A), chloroform (method B), or methanol (method C) at ambient temperature and then heating the stirred mixture so that it refluxed for 6 hr. Method F is the same as method B except that methyl iminoester hydrochloride was used instead of the ethyl iminoester hydrochloride. A survey of Table I which lists the results obtained using these four methods with a variety of iminoester hydrochlorides and the aminoalkylhydrazines Ia–d indicates that (1) the yield of triazine varied considerably, (2) generally higher yields were obtained with aminoalkylhydrazine Ib and lower yields were obtained with aminoalkylhydrazine Ia, (3) iminoester hydrochlorides of lower alkylnitriles (aceto- or propionitrile) or cyanopyridines gave low yields of triazines, and (4) the reaction proceeded equally well in either ethanol, methanol, or chloroform. The fact that the condensation proceeds as well in chloroform as it does in ethanol or methanol indicates that alcoholysis of the iminoester hydrochloride to the orthoester is not a necessary intermediate step.

Three commercially available orthoesters (triethyl orthoformate, -acetate, and -propionate) were allowed to react with the various aminoalkylhydrazines. Just as with the iminoester hydrochlorides, yields varied considerably. The condensation was effected by heating at reflux for 20 hr either neat or in the presence of a solvent, such as ethanol, chloroform, or ethyl acetate. Condensation of β-aminoethylhydrazine and triethyl orthoformate gave the unsubstituted 1,4,5,6-tetrahydro-*as*-triazine.

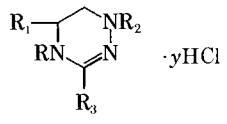
We previously reported[1] the preferred position of the double bond in this heterocyclic system to be between N_2–C_3 rather than between C_3–N_4. To further substantiate this assignment we compared the nmr spectra

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

(2) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

Table I

Substituted 1,4,5,6,-Tetrahydro-*as*-triazines



No.	R_3	R_2	R_1	R	y	Bp (mm) or mp, °C	% yield	Method[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Screening dose, mg/kg ip	Hexobarbital sleep time test[b]	Hydrochloric acid writhing test[c]	Maximal electric shock test[d]	*d*-Amphetamine aggregation toxicity test[b]
1	C_6H_5	CH_3	H	H	0	88–89	55	F	68.54	7.48	23.98	68.60	7.61	24.18	100	45/31	1/4	0/4	0/4
							23	G											
2	$2,3,6\text{-}Cl_3C_6H_2CH_2$	CH_3	H	H	0	167–168	81	A	45.15	4.14	36.35[e]	45.09	4.20	36.21[e]	100	139/40	2/4, 4/10	2/4, 8/10	2/4, 2/10
3	$2,3,6\text{-}Cl_3C_6H_2CH_2$	CH_3	CH_3	H	0	161–163	88	A	47.00	4.60	34.69[e]	46.91	4.66	34.30[e]	100	88/41	2/4, 1/10	4/4, 4/10	0/4
4	$2,6\text{-}Cl_2C_6H_3CH_2$	H	H	H	0	159–160	39	A	49.20	4.54	29.05[e]	49.20	4.73	29.06[e]	25	51/59	2/4, 6/10	0/4	0/4
5	$2,6\text{-}Cl_2C_6H_3CH_2$	CH_3	H	H	0	128–130	65	A	51.18	5.08	16.28	51.32	4.92	16.05	50	28/59	3/4, 8/10	1/4	0/4
6	C_6H_5	CH_3	CH_3	H	0	135–137 (0.8)	59	F	69.81	7.99	22.20	69.66	7.97	22.01	100	60/32	2/4, 6/10	0/4	1/4
7	$2,6\text{-}Cl_2C_6H_3CH_2$	CH_3	CH_3	H	0	158–159	39	A	52.95	5.56	15.44	52.78	5.62	15.40	50	36/32	1/4	0/4	0/4
8	$3,4,5\text{-}(CH_3O)_3C_6H_2$	H	H	H	0	132–133	35	A	57.36	6.82	16.72	57.21	6.84	16.44	200	73/33	1/4	0/4	2/4, 0/10
9	CH_3	H	H	H	0	82–85 (0.12)	16	A	48.46	9.15	42.39	48.71	9.10	42.01	400	79/47	1/4	0/4	1/4
							16	B											
							0	C											
10	C_2H_5	H	H	H	0	99–101 (0.3)	30	D	53.07	9.80	37.14	52.58	10.01	36.60	400	62/47	0/4	0/4	2/4, 3/10
							58	E											
							0	A											
11	CH_3	CH_3	H	H	0	73–75 (0.5)	11	A	53.07	9.80	37.14	52.68	10.03	37.20	400	44/47	1/4	0/4	1/4
							75	C											
12	C_2H_5	CH_3	H	H	0	80–83 (0.7)	37	A	56.66	10.30	33.04	56.65	10.14	32.84	200	57/47	0/4	0/4	2/4, 5/10
13	CH_3	CH_3	CH_3	H	0	74–76 (0.7)	34	A	56.66	10.30	33.04	56.43	10.42	32.94	200	55/47	2/4, 3/10	0/4	1/4
							20	D											
14	$4\text{-}ClC_6H_4$	H	H	H	0	136-137	39	A	57.28	5.77	20.04	57.55	5.82	19.30	25	48/47	1/4	0/4	2/4, 7/10
15	$4\text{-}ClC_6H_4CH_2$	CH_3	H	H	0	133–134	73	A	59.06	6.31	18.78	58.52	6.46	18.71	50	56/47	2/4, 3/10	1/4	4/4, 10/10
16	$3,4,5\text{-}(CH_3O)_3C_6H_2$	CH_3	CH_3	H	0	148–149	47	A	60.20	7.58	15.04	60.02	7.67	14.91	200	96/60	0/4	0/4	0/4
17	C_6H_5	CH_3	H	C_2H_5	0	118–119 (0.2)	40	A	70.90	8.43	20.67	70.72	8.50	20.98	100	98/30	3/4, 8/10	0/4	0/4
18	$4\text{-}ClC_6H_4CH_2$	CH_3	H	C_2H_5	0	63–64	14	A	62.02	7.21	14.08	62.48	7.70	14.10	25	109/30	1/4	0/4	0/4
19	$3,4\text{-}Cl_2C_6H_3OCH_2$	CH_3	H	H	0	83–85	16	A	48.19	4.77	25.86[e]	48.20	4.82	26.07[e]	100	133/39	4/4, 7/10	3/4, 6/10	3/4, 0/10
20	$3,4\text{-}Cl_2C_6H_3OCH_2$	H	H	H	1	223–224 dec	19	A	40.49	4.08	35.86[e]	40.73	4.27	35.67[e]	100	77/39	3/4, 10/10	0/4	0/4
21	$3,4\text{-}Cl_2C_6H_3OCH_2$	CH_3	CH_3	H	1	181–183 dec	19	A	44.39	4.96	32.76[e]	44.51	5.37	32.82[e]	100	>147/40	3/4, 8/10	0/4	1/4
22	$(CH_3)_2NCH_2CH_2$	CH_3	H	H	0	113–115 1.7	41	A	56.43	10.66	32.91	56.03	10.60	33.23	100	58/49	3/4, 6/10	0/4	3/4, 3/10

[a] See Experimental Section. [b] See Pharmacology. [c] Writhing was induced by intraperitoneal injection of 10 ml/kg of 0.1% HCl. The results are expressed as a ratio of the number of animals not writhing over the number of animals tested. [d] The results are expressed as a ratio of the number of animals protected from the tonic hind limb extensor phase of the seizure over the number of animals tested. [e] Chlorine.

of **15** and **18**. The position of the double bond in **18** is unambiguous. It must be between N_2–C_3 because N_4 bears an ethyl substituent. The nmr spectrum of **18** showed the two ring CH_2 groups at −2.79 (sharp) and −3.33 ppm (sharp) and the spectrum of **15** showed these groups at −2.64 (sharp) and −3.36 ppm (broadened by NH). The lack of significant shift change of these ring CH_2 protons in the NH (**15**) and the NC_2H_5 compound (**18**) can be taken as good support for assigning the same double bond position to both compounds.

Results.—Table I shows the results of the pharmacological evaluation of the 22 *as*-triazines in this series. Five (**2**, **17**–**19**, **21**) of the 22 compounds tested were found to be potentiators of hexobarbital-induced sleep (greater than threefold increase). Compound **5** produced a significant shortening of hexobarbital-induced sleep.

Eight of the compounds (**4**–**6**, **17**, **19**–**22**) tested were found to inhibit the writhing response induced by HCl in mice. These eight compounds were subsequently tested for antiinflammatory activity using the carrageen-induced rat paw edema test.[3] None of these compounds exhibited significant antiinflammatory activity in this test (not shown). One of them (**4**) was also tested for analgetic activity in a modified hot plate procedure and was found to be inactive (Table II). However, when administered simultaneously with 2 mg/kg of morphine sulfate it was found to enhance the analgetic activity of morphine.

TABLE II

RESULTS OF MODIFIED HOT PLATE TEST ON COMPOUND **4** OF TABLE I[a]

Compd[b]	Dose, mg/kg sc	Reaction times of mice, sec		
		Pre-control	Control	30 min after compd	60 min after compd
Control (saline)	..	40.99	11.39	13.12	12.64
Morphine sulfate	5	37.94	10.41	22.48	20.45
4	10	26.47	12.06	9.68	12.25
	25	36.78	11.76	12.99	11.66
	50	23.22	11.41	11.98	10.25
Morphine sulfate	2	26.36	8.98	12.84	16.17
4 +	25	32.81	6.70	18.84	19.67
morphine sulfate	2				
4 +	50	40.01	8.75	22.96	22.92
morphine sulfate	2				

[a] See Pharmacology section. [b] Compound **4** of Table I is 3-(2,6-dichlorobenzyl)-1-methyl-1,4,5,6-tetrahydro-*as*-triazine.

In the maximal electroshock test only two compounds (**2**, **19**) showed significant activity. Both of these compounds were also potentiators of hexobarbital sleep time.

Three compounds (**12**, **14**, **15**) decreased the toxicity of *d*-amphetamine in the aggregated situation. It is of interest that these compounds did not show significant activity in any of the other screening procedures employed. In control experiments with *d*-amphetamine itself only $^1/_{30}$ of the animals survived the aggregation procedure.

(3) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

Experimental Section

Pharmacology. Analgetic Tests.—Adult male mice (CD-1) weighing 18–22 g were used in these tests. In the hydrochloric acid writhing tests, the method of Eckhardt, *et al.*,[4] was used, and the modified hot plate method of Marshall, *et al.*,[5] was used. Maximal electroshock seizures were produced by the method of Swinyard, *et al.*[6]

For the hexobarbital sleep time test, adult male mice were injected intraperitoneally with the test compound 30 min prior to injection of 100 mg/kg of hexobarbital. The time in minutes 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.

In the *d*-amphetamine aggregation toxicity test, female albino mice (19–25 g) of the Swiss–Webster strain (laboratory Supply Co.) were used in all experiments. The test compounds were administered 30 min prior to the injection of 20 mg/kg of *d*-amphetamine. Immediately after the administration of *d*-amphetamine the mice were aggregated in groups of four for initial screening or in groups of ten. In the retests (groups of ten) the wire mesh cages for aggregation measured 15 cm on each side. The number of animals that died during 24 hr of aggregation was recorded. The results are expressed as the number of animals surviving over the number of animals tested.

Chemistry. Melting points were determined in open capillary tubes using the Thomas-Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlab., Indianapolis, Ind.

General Preparation of Aminoalkylhydrazines (Ia–d).—To a rapidly stirred, refluxing mixture of 10 moles of the hydrazine and 1 g of NH_4Cl was added, dropwise, over a period of 4 hr, 1 mole of the aziridine compound. After the addition was completed, the mixture was stirred and heated at reflux for 16 hr. Most of the excess hydrazine compound was removed by distillation at atmospheric pressure using a 40-cm Vigreux column.

2-Aminoethylhydrazine (Ia) was obtained in 71% yield; bp 73–80° (8 mm); λ_{max}^{film} 3.05, 3.15, and 6.20 μ; nmr (50% in $CDCl_3$), −2.65 (5 H) and −2.78 ppm (4 H).

1-(2-Aminoethyl)-1-methylhydrazone (Ib) was obtained in 75% yield, bp 155–161°. *Anal.* Calcd for $C_3H_{11}N_3$: C, 40.42; H, 12.44; N, 47.14. Found: C, 39.73; H, 12.53; N, 46.88.

1-(2-Aminopropyl)-1-methylhydrazine (Ic), was obtained in 52% yield, bp 51–54° (10 mm). *Anal.* Calcd for $C_4H_{13}N_3$: C, 46.56; H, 12.70; N, 40.73. Found: C, 45.97; H, 12.67; N, 39.48.

1-(2-Ethylaminoethyl)-1-methylhydrazine (Id), was obtained in 53% yield, bp 103–105° (75 mm). *Anal.* Calcd for $C_5H_{15}N_3$: C, 51.24; H, 12.90; N, 35.86. Found: C, 50.29; H, 12.58; N, 35.56.

General Procedure for the Preparation of Methyl and Ethyl Iminoester Hydrochlorides.—A stirred, cooled (5°) mixture of 0.20 mole of the nitrile, 0.26 mole of either methanol or ethanol, and 100 ml of anhydrous ether was saturated with dry HCl. After standing for an additional 3 hr at 5°, the mixture was concentrated to about one-half the original volume under a stream of dry nitrogen. The precipitated iminoester hydrochloride was removed by suction filtration, washed with anhydrous ether, and allowed to dry in a vacuum desiccator. When the iminoester hydrochloride separated as an oil, anhydrous ether was added and the evaporation was repeated. This usually caused the oil to crystallize. When this failed crystallization was induced by scratching with a glass rod or allowing the oil to stand overnight at ambient temperature in a vacuum desiccator.

Methods Used to Prepare the Compounds Listed in Table I. Method A.—To a stirred mixture of 0.10 mole of ethyl iminoester hydrochloride and 250 ml of absolute ethanol was added, dropwise, over a period of 0.5 hr, a solution of the β-aminoethylhydrazine in 50 ml of absolute ethanol. The mixture was stirred and refluxed for 6 hr, concentrated *in vacuo*, cooled, diluted with 150 ml of ice water, acidified to approximately pH 2 with HCl, and washed twice with 150-ml portions of CH_2Cl_2. The

(4) E. T. Eckhardt, F. Chaplovitz, M. Lipo, and W. M. Govier, *Proc. Soc. Exptl. Biol. Med.*, **98**, 186 (1958).

(5) F. N. Marshall, W. B. Jones, and L. C. Weaver, *ibid.*, **116**, 912 (1964).

(6) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

washed acidic, aqueous solution was made strongly basic with cold aqueous NaOH and extracted $CHCl_3$. The washed (water) and dried ($MgSO_4$) chloroform solution was evaporated *in vacuo*, and the residue was purified either by distillation or crystallization.

Method B is identical with method A except that chloroform is used as the reaction solvent instead of absolute ethanol.

Method C.—A mixture of 0.10 mole of orthoester, 0.10 mole of β-aminoethylhydrazine, and 50 ml of ethyl acetate was refluxed for 20 hr and then distilled *in vacuo*.

Method D is identical with method C except that $CHCl_3$ is used as the reaction solvent instead of ethyl acetate.

Method E is the same as method C except that absolute ethanol is used as the reaction solvent instead of ethyl acetate.

Method F is the same as method B except that the methyl iminoester hydrochloride is used instead of the ethyl iminoester hydrochloride.

Method G is the same as method F except that methanol is used as the reaction solvent instead of $CHCl_3$.

1,4,5,6-Tetrahydro-*as*-triazine.—A mixture of 30 g (0.40 mole) of β-aminoethylhydrazine and 80 g (0.54 mole) of ethyl orthoformate was heated at reflux temperature for 24 hr and then distilled, bp 98–100° (0.3 mm), yield 20%. *Anal.* Calcd for $C_3H_7N_3$: C, 42.34; H, 8.29; N, 47.37. Found: C, 41.82; H, 8.57; N, 47.27.

1,4,5,6-Tetrahydro-*as*-triazine monopicrate was prepared in ethanol and after recrystallization from water; mp 136–138°. *Anal.* Calcd for $C_9H_{10}N_6O_7$: C, 34.40; H, 3.21; N, 26.75. Found: C, 34.61; H, 3.47; N, 26.95.

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The Synthesis and Pharmacology of ^{131}I-Labeled 1,10-Bis(trimethylammonium)-5-chloro-6-iodo-5-decene Dihalide and Related Neuromuscular Blocking Agents[1]

OVE A. NEDERGAARD[2] AND DERMOT B. TAYLOR

Department of Pharmacology, School of Medicine, and Brain Research Institute, University of California, Los Angeles, California 90024

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Synthesis of ^{131}I-labeled 1,10-bis(trimethylammonium)-5-chloro-6-iodo-5-decene dihalide has been accomplished by several different methods. It is a stable depolarizing neuromuscular blocking agent. Some related unsaturated diquaternary amines of interest in structure–activity relationships were also prepared.

Stable depolarizing neuromuscular blocking agents such as 1,10-bis(trimethylammonium)decane dihalide [decamethonium (I)] characteristically produce a dual block on isolated nerve–muscle preparations.[3] It has been suggested[4] that the second phase of this biphasic block is related to the penetration of the drug into the skeletal muscle fiber. This hypothesis can be studied most conveniently by using labeled depolarizing drugs.

Decamethonium (I) labeled with N-methyl-^{14}C has been prepared.[5] However, labeling with ^{131}I

$$(^{14}CH_3)_3N^+(CH_2)_{10}N^+(^{14}CH_3)_3$$

I

would be advantageous, since γ-emitting isotopes permit easier and more accurate counting than is possible with β emitters. Furthermore, the counting is simplified since no disintegration of the tissue or extraction of the drug is necessary. Hence ^{131}I-labeled 1,10-bis(2-iodoethyldimethylammonium)decane dichloride [iodocholinium (II)] was synthesized[4a,b,6] However,

$$^{131}ICH_2CH_2 \qquad CH_2CH_2{}^{131}I$$
$$(CH_3)_2N^+(CH_2)_{10}N^+(CH_3)_2$$

II

it is difficult to obtain pure iodocholinium by the method employed; the product appears to be unstable and a biphasic block is not observed consistently. These difficulties have been overcome largely by the synthesis of 1,10-bis(trimethylammonium)-5-chloro-6-iodo-5-decene dihalide [TID-5[1d] (III)].

$$(CH_3)_3N^+(CH_2)_4CI{=}CCl(CH_2)_4N^+(CH_3)_3$$

III

Some unsaturated diquaternaries related to I, which are of interest in structure–activity studies, have been prepared also. These compounds and some of the intermediaries can serve as a convenient starting material for specific tritium labeling of neuromuscular blocking agents.

Partial hydrogenation of 1,10-dichloro-5-decyne (IV)[7] gave 1,10-dichloro-5-decene (V), which, when heated with anhydrous trimethylamine, gave 1,10-bis(trimethylammonium)-5-decene dichloride (VI). Addition of iodine monochloride to VI in glacial acetic acid or methanol–dimethylformamide failed to give the expected 1,10-bis(trimethylammonium)-5-chloro-6-io-

(1) (a) This work was supported in part by U. S. Public Health Service Grant B-738(C7). (b) Some of the results contained in the present report have been submitted by one of us (O. A. N.) in partial fulfillment of the requirements for the degree of M.Sc. in Pharmacology, University of California at Los Angeles, 1961. (c) Presented in part at the American Pharmacological Society Meeting, Nashville, Tenn., Aug 1962. (d) D. B. Taylor and O. A. Nedergaard, *Pharmacologist*, **4**, 183 (1962).

(2) Investigation carried out during the tenure of U. S. Public Health Service Predoctoral Fellowship.

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(5) (a) P. G. Waser and U. Lüthi, *Nature*, **178**, 981 (1956); (b) U. Lüthi and P. G. Waser, *Arch. Intern. Pharmacodyn.*, **156**, 319 (1965).

(6) R. Creese, D. B. Taylor, and B. Tilton, *Science*, **125**, 494 (1957).

(7) D. L. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, **78**, 2518 (1956).