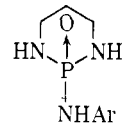
TABLE I

2-(N-ARYLAMINO)-1,3,2-DIAZAPHOSPHORINANE 2-OXIDES



	Ar	Yield, % crude	M.p., °C.	Yield, % pure	M.p., °C.	% nitrogen Calcd.	% nitrogen Found
VIII	Phenyl	53	217–219	24	217–219	19.92	19.94
IX	*p*-Methoxyphenyl[a]	59	181.5–183	14	190–190.5	17.45	17.51
X	*p*-Chlorophenyl[b]	53	205–215	17	214–215	17.12	17.13
XI	*p*-Tolyl[c]	27	...	14	224–225	18.68	18.84
XII	*m*-Tolyl	85	228–233	30	233–234	18.68	18.63
XIII	*o*-Chlorophenyl[d]	...	...	18	165–166	17.12	17.31

[a] Recrystallized from absolute ethanol. [b] Recrystallized from benzene–methanol (4:1). [c] Recrystallized from ethanol–water (2:1). [d] Recrystallized from water.

interesting that the first compound of this series to undergo the screening (IX, Table I) exhibited 66% and 78% inhibition in the first two trials against Carcinoma 755 even though this compound does not contain the nitrogen mustard moiety. However, no activity was indicated for the compound in further screening against Carcinoma 755 or the other tumor systems. The other compounds listed in Table I were also found to be inactive.

Experimental

1,3-Diaminopropane was obtained from the Union Carbide Chemicals Company.

N-Arylphosphoramidic Dichlorides.—These intermediates were prepared by refluxing the arylamine hydrochloride in phosphorus oxychloride, a method described by Michaelis and Schulze.[9]

2-(N-Arylamino)-1,3,2-diazaphosphorinane 2-Oxides (Table I).—The general preparative method was to add approximately 0.1 mole of the phosphoramidic dichloride in 500 ml. of benzene to a stirred solution of approximately 0.2 mole of the 1,3-diaminopropane in 500 ml. of benzene. The addition took about 2 hr., with the reaction mixture remaining near 35°. The mixture was stirred for an additional 1 hr. and then the white solids which had precipitated during the reaction were collected on a Buchner funnel. This residue was allowed to dry thoroughly in the air. The separation of the product from the 1,3-diaminopropane dihydrochloride was accomplished either by method A or method B.

A.—This method was used in obtaining compounds VIII and IX. For example, with compound VIII there was 37 g. of dry solid collected from the reaction. This was boiled with 400 ml. of water until almost all of the material had dissolved. The hot solution was filtered through a fluted filter and then allowed to cool to room temperature. A total of 20 g. of sodium carbonate was slowly added to the solution, with stirring, and 3.5 g. of white solid separated. Cooling the solution overnight furnished an additional 3.5 g. of this material. A final 4.1-g. portion of crude product was obtained by distilling one-half of the solvent and cooling the remaining solution. Three recrystallizations from methanol gave 5.1 g. (24%) of crystals, m.p. 217–219°.

B.—This general method was used for compounds X-XIII and is given for compound XII, prepared in a reaction with a theoretical yield of 0.135 moles of product. The dried solids from this reaction weighed 51.4 g. They were powdered and stirred into 300 ml. of water containing 17.5 g. of sodium carbonate. The mixture was stirred for 0.5 hr. and then the suspended material was collected and dried in a vacuum desiccator. It was again powdered and stirred for 0.5 hr. in 150 ml. of warm water containing 3.5 g. of sodium carbonate. The suspended solid, after collecting and drying, weighed 25.5 g. (85%) with a 228–233° m.p. range.

An 8-g. portion of the crude material was stirred in 120 ml. of refluxing ethanol and 20 ml. of 5% sodium carbonate solution was added. Then 40 ml. of ethanol was gradually added to the mixture. The resulting cloudy solution was filtered while hot. The clear filtrate was cooled and 4.8 g. of colorless crystals, m.p. 230–231°, separated. A final recrystallization was accomplished from 80 ml. of 90% ethanol which contained 0.15 g. of sodium carbonate. There was obtained 2.9 g. (30% of theory, by proportion) of solid, m.p. 233–234°.

The recrystallization solvents for other compounds are listed under Table I.

Acknowledgment.—Mr. Stephen Johnson for preparing some of the intermediates, Drs. H. W. Bond, R. B. Ross, and J. E. Leiter of the CCNSC for their cooperation and for making screening data available. We also wish to thank the Union Carbide Chemicals Company for supplying some of the 1,3-diaminopropane used in this research.

(9) A. Michaelis and G. Schulze, *Ber.*, **26**, 2937 (1893).

Monoamine Oxidase Inhibitors. Hydrazine Derivatives

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The monoamine oxidase (MAO) inhibitory activity in an earlier series of acylated and carbalkoxylated aralkyl hydrazines appeared to be dependent upon hydrolysis of the blocking groups to the free aralkyl hydrazines.[1] Since the relative degree of MAO inhibition in the brain and liver caused by some inhibitors of the hydrazine type depends on the route of drug administration,[2] the possibility was considered that specificity of inhibition, independent of route of administration, could be achieved if the hydrolysis of a blocked hydrazine were catalyzed by an enzyme, esterase or amidase, specific to a particular organ, for example, the brain. Table I shows the results of a study of brain *vs.* liver localization of the inhibition with several new MAO inhibitors injected subcutaneously or given orally.

One of the compounds, VIII in Table I, the least potent of the group, exhibited greater inhibition in the

(1) F. E. Anderson, D. Kaminsky, B. Dubnick, S. R. Klutchko, W. A. Cetenko, J. Gylys, and J. A. Hart, *J. Med. Pharm. Chem.*, **5**, 221 (1962).

(2) A. Horita, *Toxicol. Appl. Pharmacol.*, **3**, 474 (1961).

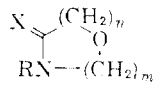
TABLE I

MAO INHIBITION IN BRAIN AND LIVER WITH A SERIES OF INHIBITORS RELATED TO BENZYLHYDRAZINE

	Compd.	Dose, mg./kg.	Route	% Inhibition of MAO[a] — Brain	Liver
I	$C_6H_5CH_2NHNH_2$[b]	1	s.c.	77	31
		1	p.o.	24	74
II	$C_6H_5CH_2NHNHCOCH_3$[b]	5	s.c.	24	86
		5	p.o.	10	100
III	$C_6H_5CH_2NHNHCOOCH_3$[b]	5	s.c.	60	75
		5	p.o.	16	85
IV	$C_6H_5CH_2NHNHCOOC_2H_5$[b]	5	s.c.	51	88
		5	p.o.	50	100
V	$C_6H_5CH_2NHNHCOOC_2H_4OH$[b]	7	s.c.	30	100
		7	p.o.	26	95
VI		8	s.c.	39	45
		8	p.o.	35	63
VII		40	s.c.	40	10
		40	p.o.	32	50
VIII		50	s.c.	30	5
		50[c]	p.o.	35	10

[a] Average of 2-3 experiments. Tissues of 2 mice were pooled 1 hr. after drug administration and homogenized, and MAO activity was measured compared to normal by disappearance of tyramine.[d] [b] Reported previously.[1] [c] In an additional experiment, using a dose of 100 mg./kg., p.o., brain MAO was inhibited by 56% and liver MAO by 25%, 18 hr. after drug administration. [d] B. Dubnick, G. A. Leeson, R. Leverett, D. F. Morgan, and G. E. Phillips, *J. Pharmacol. Exptl. Therap.*, **140,** 85 (1963).

TABLE II



R	M.p. [b.p.], °C.	Formula	% Carbon — Calcd.	Found	% Hydrogen — Calcd.	Found	% Nitrogen — Calcd.	Found
A. 3-Aminooxazolidinone Derivatives (n = 0, m = 2, X = O)								
$C_6H_5CH{=}N{-}$	143–144[a]	$C_{10}H_{10}N_2O_2$	63.15	63.03	5.30	5.41		
$C_6H_5CH_2NH{-}$	149.5–151[b]	$C_{10}H_{12}N_2O_2 \cdot HCl$	52.52	52.57	5.73	5.88	(15.50	15.18)[c]
$C_6H_5CH_2CH{=}N{-}$	96–98	$C_{11}H_{12}N_2O_2$	64.69	64.82	5.92	6.07	13.72	13.80
$C_6H_5CH_2CH_2NH{-}$	125–127	$C_{11}H_{14}N_2O_2 \cdot HCl$	54.43	54.04	6.23	6.48	11.54	11.72
p-$ClC_6H_4CH{=}N{-}$	172–174	$C_{10}H_9ClN_2O_2$						
p-$ClC_6H_4CH_2NH{-}$	90–92	$C_{10}H_{11}ClN_2O_2$	52.94	52.76	4.89	4.96	12.36	12.31
$CH_3CH_2C(CH_3){=}N{-}$	[94–96 (2.5 mm.)][d]	$C_7H_{12}N_2O_2$						
$CH_3CH_2CH(CH_3)NH{-}$	133–134[e]	$C_7H_{14}N_2O_2 \cdot HCl$	43.19	42.94	7.77	7.87	14.39	14.25
B. 3-Aminomorpholine Derivatives (n = 1, m = 2, X = H_2)								
$C_6H_5CH{=}N{-}$	91–92	$C_{11}H_{14}N_2O$	69.44	69.50	7.42	7.54	14.73	14.65
$C_6H_5CH_2NH{-}$	231–233[f]	$C_{11}H_{16}N_2O \cdot HCl$	57.76	58.02	7.49	7.55	12.25	12.19
$C_6H_5CH_2CH{=}N{-}$	[124 (0.7 mm.)][g]	$C_{12}H_{16}N_2O$	70.56	70.84	7.90	8.15	13.72	14.00
$C_6H_5CH_2CH_2NH{-}$	168–170	$C_{12}H_{18}N_2O \cdot HCl$	59.37	59.54	7.89	7.86	(14.61	14.49)[c]
p-$CH_3C_6H_4C_6H_4CH(CH_3)NH{-}$	162–163[h]	$C_{18}H_{22}N_2O_2 \cdot HCl$	57.24	57.42	7.76	7.70	10.27	10.07
C. 1-Aminomorpholinone-2 Derivatives (n = 1, m = 2, X = O)								
$C_6H_5CH{=}N{-}$	152–154	$C_{11}H_{12}N_2O_2$	64.69	64.81	5.92	6.05	13.72	13.56
$C_6H_5CH_2NH{-}$	67–69	$C_{11}H_{14}N_2O_2$	64.06	64.31	6.84	6.83	13.58	13.39

[a] Lit.[1] m.p. 143–145°. [b] Base, lit.[5] m.p. 70°. [c] Chlorine analysis. [d] $n^{25}D$ 1.4812. [e] Base, b.p. 74–76° (0.2 mm.). [f] Base, b.p. 115–117° (0.45 mm.). [g] $n^{25}D$ 1.5555. [h] Intermediate hydrazone not isolated.

brain than in the liver, when given orally. Whether this is a result of greater hydrolysis of the compound within the brain is a matter of speculation.

With several of the disubstituted hydrazines the per cent inhibition in the brain and liver was similar by both routes of administration, a pattern rather different from that observed with benzylhydrazine and other monosubstituted hydrazines, but similar to nialamid.[2,3]

The hydrazones were prepared, in most cases, by condensing an aldehyde or ketone with the appropriate N-amino compound in an alcoholic solution. Catalytic reduction (Paar hydrogenator, 5–10% Pd/C) of the intermediate hydrazones yielded the trisubstituted hydrazines in 80–90% yields. The physical properties and analyses are listed in Tables II and III.

The N-amino compounds were prepared by published procedures[4-6] with the exception of N-aminomorpholine which was commercially available and 1-amino-5,5-dimethylhydantoin, which was prepared *in situ* by the electrolytic reduction of 1-nitro-5,5-dimethylhydantoin. This method was required since catalytic and chemical reduction methods caused either cleavage of the N–N bond (isolation of 5,5-dimethylhydantoin) or caused no reduction to occur.

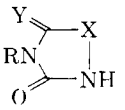
(3) B. Dubnick, unpublished observations in these laboratories.

(4) G. Gever, C. O'Keefe, G. Drake, F. Ebetino, J. Michels, and K. Hayes, *J. Am. Chem. Soc.*, **77**, 2277 (1955).

(5) R. Delaby, C. Warolin, and F. Brustlein, *Compt. rend.*, **238**, 1714 (1954).

(6) O. Diels and H. Grube, *Ber.*, **53**, 854 (1920).

TABLE III



R	M.p., °C.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
A. 1-Amino-5,5-dimethylhydantoin Derivatives (Y = $(CH_3)_2$, X = O)								
$C_6H_5CH{=}N-$	190–192[a]	$C_{12}H_{13}N_3O_2$						
$C_6H_5CH_2NH-$	132–133	$C_{12}H_{15}N_3O_2$	61.78	61.55	6.48	6.55	18.02	17.91
B. 4-Aminourazole Derivatives (Y = O, X = NH)								
$C_6H_5CH{=}N-$	255–257[b]	$C_9H_8N_4O_2$						
$C_6H_5CH_2NH-$	249–251	$C_9H_{10}N_4O_2$	52.42	52.33	4.89	4.83	27.17	27.08

[a] Lit.[12] m.p. 191–192. [b] Lit.[10] m.p. 253–254.

Experimental[7]

The 1-aminomorpholine used was a commercial sample obtained from Food Machinery Corp. Published procedures were used to prepare 3-aminooxazolidinone,[8] 1-amino-2-morpholinone,[9] and 4-aminourazole.[10] The 3-benzylideneamino-2-oxazolidinone and 3-phenethylidineamino-2-oxazolidinone were also prepared by the method of Gever, *et al.*,[4] starting from the hydrazino alcohol. The 1-benzylidineamino-5,5-dimethylhydantoin was also prepared by the method of Bailey and Read.[11] Condensation of *p*-chlorobenzyl chloride with 3-amino-2-oxazolidinone in alcoholic solution resulted in a 10% yield of 3-(*p*-chlorobenzylamino)-2-oxazolidinone.

1-Benzylidineamino-5,5-dimethylhydantoin (Electrolytic Preparation.)—Utilizing the set-up described in "Organic Syntheses,"[12] a mixture of 57 g. (0.33 mole) of 1-nitro-5,5-dimethylhydantoin and 1500 ml. of 20% H_2SO_4 was subjected to a current of 15 ± 1 amp. at *ca.* 6 v./8 hr. The temperature was maintained at 5–10° by stirring in an ice–salt bath. At the end of the 8-hr. period, approximately 800 ml. of electrolyte was removed under vacuum, and the residue was filtered and neutralized (to pH 7) with solid sodium hydroxide in an ice bath. A solution of 53 g. (0.5 mole) of benzaldehyde in 500 ml. of 95% ethanol was added, and the mixture was heated to boiling and put aside to cool. After standing overnight in a refrigerator, filtration yielded off-white crystals. Recrystallization from 50% aqueous ethanol resulted in colorless crystals (26.4 g., 56%), m.p. 190–192°.

(7) All melting points are corrected.

(8) British Patent 735,169 (1955).

(9) J. Shavel, Jr., F. Leonard, F. H. McMillan, and J. A. King, *J. Am. Pharm. Assoc.*, **42**, 402 (1953).

(10) A. M. Munro and F. J. Wilson, *J. Chem. Soc.*, 1257 (1928).

(11) J. R. Bailey and W. T. Read, *J. Am. Chem. Soc.*, **37**, 1884 (1915).

(12) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 485.

The Synthesis of 2-Amino-3-trifluoromethylbutyric Acid[1]

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The synthesis of amino acids containing a terminal trifluoromethyl group as possible amino acid antagonists has been reported.[3] Of several amino acids prepared, only 2-amino-5,5,5-trifluorovaleric acid greatly inhibited the growth of *Escherichia coli*. This encouraged the synthesis of the corresponding isomeric acid, 2-amino-3-trifluoromethylbutyric acid, *viz.*, 4,4,4-trifluorovaline.

Walborsky, *et al.*,[3] have shown previously that the ammonolysis of ethyl 2-bromo-4,4,4-trifluorobutyrate gave 3-amino-4,4,4-trifluorobutyramide instead of the expected 2-amino isomer. The mechanism for this transformation was postulated[3b] as an initial loss of hydrogen bromide to give ethyl 4,4,4-trifluorocrotonate followed by the addition of ammonia into the β-position. This was confirmed from the fact that addition

$$CF_3CH_2CHBrCOOC_2H_5 \xrightarrow{-HBr} CF_3CH{=}CHCOOC_2H_5 \xrightarrow{NH_3} CF_3CH(NH_2)CH_2CONH_2$$

of gaseous ammonia to ethyl 4,4,4-trifluorocrotonate and ammonolysis of ethyl 3-bromo-4,4,4-trifluorobutyrate with concentrated ammonium hydroxide gave the same 3-amino compound. The desired compound, 2-amino-4,4,4-trifluorobutyramide, was finally obtained byutilizing the less basic and more nucleophilic azide ion to decrease the tendency for elimination and favor the direct displacement of the bromine atom.[3c]

Since it was anticipated that ammonolysis of ethyl 2-bromo-3-trifluoromethylbutyrate would yield the 3-amino compound by a similar mechanism, displacement of the bromine atom with azide ion was chosen as the best possible path to the desired α-amino acid.[4]

$$CF_3CH(CH_3)CH_2COOH \xrightarrow[(2)\ C_2H_5OH]{(1)\ PCl_3\text{–}Br_2} CF_3CH(CH_3)CHBrCOOC_2H_5 \xrightarrow{NaN_3} CF_3CH(CH_3)CH(N_3)COOC_2H_5 \xrightarrow[(2)\ H_3O^+]{(1)\ Pd\text{–}H_2} CF_3(CH)CH_3CH(NH_2)COOH$$

Refluxing 3-trifluoromethylbutyric acid with bromine and phosphorus trichloride for several hours, followed by dilution with anhydrous ethyl alcohol, afforded a 32% yield of the α-bromo ester. Treatment of the bromo ester with a large excess of sodium azide gave the α-azido ester which was subsequently hydrogenated with palladium and finally hydrolyzed with concentrated hydrochloric acid. This final step afforded a 56.5% yield of practically pure amino acid.

(1) This investigation was supported by the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) Taken from a portion of the thesis submitted by D. F. Loncrini in partial fulfillment of the requirements for the Ph.D. degree in Chemistry, Florida State University, 1956; (b) General Electric Co., Insulating Materials Department, Schenectady, N. Y.

(3) (a) H. M. Walborsky and M. Schwarz, *J. Am. Chem. Soc.*, **75**, 3241 (1953); (b) H. M. Walborsky, M. Blum, and D. F. Loncrini, *ibid.*, **77**, 3637 (1955); (c) H. M. Walborsky and M. Baum, *J. Org. Chem.*, **21**, 538 (1956).

(4) It was recently demonstrated [I. L. Knunyants and Yu. A. Cheburkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (English Transl.)*, **6**, 977 (1961); *Chem. Abstr.*, **55**, 27046 (1961)] that nucleophilic reagents add at the 3-position of 3-trifluoromethylcrotonic acid as we had anticipated.