Method B.—To a warm solution of 0.02 mole of an ethyl N-arylsulfonylcarbamate in 75 ml. of toluene was added, dropwise, with stirring, a solution of 0.022 mole of the desired amine in 25 ml. of toluene. The mixture was refluxed for 3 hr. and cooled. If the product crystallized, it was isolated by filtration; otherwise, the toluene was removed under reduced pressure. The product was crystallized from dilute ethanol, with acidification with 5% hydrochloric acid just prior to cooling. Further purification was carried out as indicated in the tables.

4-Methylsulfinylbenzenesulfonamide.—To a solution of 12 g. (0.05 mole) of 4-methylmercaptobenzenesulfonamide in 200 ml. of acetic acid was added, portionwise, 5.7 g. (0.05 mole) of 30% hydrogen peroxide. After heating at about 60° for 24 hr. the mixture was taken to dryness under reduced pressure and the residue was crystallized 3 times from dilute ethanol to give 8.3 g. (75%) of product melting at 177–179°.

Anal. Calcd. for $C_7H_9NO_3S_2$: C, 38.34; H, 4.15. Found: C, 38.10; H, 4.34.

N-(4-Methylsulfinylphenylsulfonyl)urea.—Six grams (0.027 mole) of 4-methylsulfinylbenzenesulfonamide was converted to the sulfonylurea by Method A. Purification from dilute acetone gave 5 g. (54%) of product melting at 173–175°

Anal. Calcd. for $C_{14}H_{20}N_2O_4S_2$: C, 48.82; H, 5.85; N, 8.13. Found: C, 49.20; H, 5.93; N, 8.00.

N-(4-Methylsulfonylphenylsulfonyl)-N′-cyclohexylurea.—A mixture of 2 g. (0.006 mole) of N-(4-methylmercaptophenylsulfonyl)-N′-cyclohexylurea and 15 ml. of 30% hydrogen peroxide in 10 ml. of acetic acid was warmed for 30 min. on a steam bath. The crystalline material which separated on cooling weighed 1.7 g.. Crystallizations from dilute ethanol gave 1.3 g. (59%) of product melting at 196–198°.

Anal. Calcd. for $C_{14}H_{20}N_2O_5S_2$: C, 46.65; H, 5.59; N, 7.77. Found: C, 46.96; H, 5.74; N, 7.35.

N-[4-(α-Hydroxyethyl)phenylsulfonyl]-N′-cyclohexylurea.—A solution of 20.0 g. (0.616 mole) of N-(4-acetylphenylsulfonyl)-N′-cyclohexylurea, 100 ml. of absolute ethanol and 150 ml. of dioxane was reduced catalytically using initially 2.0 g. of 5% palladium on carbon under an initial hydrogen pressure of 2.8 kg./cm.^{2} As the reaction proceeded the adsorption of hydrogen became quite slow. At this point an additional 2.0 g. of catalyst was added and the reaction then proceeded to completion. The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The product, after three recrystallizations from dilute ethanol, melted at 136–137°, yield 14.7 g. (74%).

Anal. Calcd. for $C_{15}H_{22}N_2O_4S$: C, 55.19; H, 6.79; N, 8.58. S, 9.86. Found: C, 55.16; H, 6.86; N, 8.09; S, 9.16.

N-(4-Ethylphenylsulfonyl)-N′-*n*-hexylurea.—Hydrogenation of 2 g. (0.006 mole) of N-(4-acetylphenylsulfonyl)-N′-*n*-hexylurea was carried out in 200 ml. of ethanol using 1 g. of 5% palladium on carbon as a catalyst with an initial hydrogen pressure of 2.8 kg./cm.^{2}. Hydrogen uptake was complete in 15–20 min., and, after filtering, the ethanol was removed under reduced pressure. The residue crystallized on standing and two crystallizations from dilute acetone gave 5 g. (29%) of product melting at 107–109°. An analytical sample melted at 108–110°. Infrared analysis did not show the presence of an OH and was consistent for an ethyl substituent.

Anal. Calcd. for $C_{15}H_{24}N_2O_3S$: C, 57.65; H, 7.75; N, 8.96; O, 15.35. Found: C, 57.64; H, 7.57; N, 9.04; O, 15.59.

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Monoamine Oxidase Inhibitors. The Synthesis and Evaluation of a Series of Substituted Alkylhydrazines

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A series of aryloxy-, arylthio-, and arylaminoalkylhydrazines has been prepared and evaluated as *in vitro* and *in vivo* inhibitors of monoamine oxidase. Many of the compounds are powerful inhibitors, the most active being (1-methyl-2-phenoxyethyl)hydrazine.

In 1952, Zeller and co-workers[1] found iproniazid to be a powerful and specific inhibitor of the enzyme monoamine oxidase and much suggestive evidence has been subsequently presented to support the thesis that the pharmacological and clinical effects of this drug may be explained in terms of monoamine oxidase inhibition. An exhaustive study by Zeller's group of the structural features necessary for monoamine oxidase inhibition led to the discovery that simple alkylhydrazines were considerably more potent than iproniazid.[2] This, together with the reported high activity of α-methylphenethylhydrazine[3] led us to examine some related aryloxyalkylhydrazines as potential inhibitors of monoamine oxidase.

2-Phenoxyethylhydrazine and 3-phenoxypropylhydrazine were first prepared by Gabriel in 1914 by reaction of the appropriate phenoxyalkyl bromide with hydrazine.[4] 2-Phenoxyethylhydrazine was examined and found to be a potent inhibitor of monoamine oxidase whereas 3-phenoxypropylhydrazine was much less active. It was thus of interest to investigate the relationship between structure and activity in this class of compound, and this paper describes the synthesis and evaluation as monoamine oxidase inhibitors of a series of substituted hydrazines of general formula $ArX(CH_2)_nCH(Y)NHNH_2$, in which variations are made in the aryl group, the alkyl chain (n and Y varied) and the linking group X.

Experimental

Chemistry.—The substituted hydrazines were prepared by the method of Gabriel[4] from the corresponding bromide by reaction with hydrazine in boiling ethanol. In most instances they were colorless liquids which, on a small scale, could be distilled under reduced pressure in a nitrogen atmosphere with only slight decomposition. Occasionally, however, complete decomposition occurred during distillation, a hazard which appeared to be somewhat dependent upon batch size. The bases were rather

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unstable in the presence of air, even at room temperature slowly evolving nitrogen on standing. The salts, however, appeared to be stable under normal laboratory storage conditions. The intermediate bromides, many of which have been previously described were prepared by one of four general methods: (E) from a phenol and excess 1,2-dibromoethane; (F) from the appropriate alcohol with phosphorus tribromide (no solvent); (G) from the appropriate alcohol with phosphorus tribromide in chloroform; (H) from the appropriate alcohol with thionyl bromide. 1-Anilino-2-bromopropane was prepared as the hydrobromide salt by method I.

Intermediate alcohols were prepared by one of these general methods: (A) from phenoxyacetaldehyde and a Grignard reagent; (B) from a phenol and propylene oxide; (C) from a thiophenol and propylene oxide; (D) from a phenol or thiophenol and 2-chloroethanol.

Details of some typical preparations are given below.

(i) **Synthesis of Alcohols,** $ArX(CH_2)_nCH(Y)OH$.—Physical constants and analytical data for compounds not hitherto reported are given in Table I. All melting points are uncorrected.

A. 1-Phenoxy-2-pentanol.—To a solution of *n*-propylmagnesium bromide prepared from *n*-propyl bromide (86.5 g., 0.705 mole) and magnesium turnings (17.25 g., 0.72 at.) in dry ether (500 ml.) was added a solution of phenoxyacetaldehyde[5] (34 g., 0.25 mole) in dry ether (30 ml.) slowly over 90 min. The mixture was kept overnight at room temperature and finally boiled under reflux for 3 hr. After cooling, the complex was decomposed by cautious addition of iced water (500 ml.) and 2 *N* hydrochloric acid until acidic. The ethereal layer was separated and the aqueous layer extracted with ether (4 × 150 ml.). The combined extracts were dried (Na_2SO_4) and distilled to yield a colorless oil, b.p. 143–147° (18 mm.).

B. 1-(*o*-Methoxyphenoxy)-2-propanol.—Guaiacol (80 g., 0.645 mole), propylene oxide (41.2 g., 0.71 mole), and 50% sodium hydroxide solution (0.8 ml.) were placed in an autoclave and heated to 150° for 4 hr. Fractional distillation of the residue yielded 78.1 g. of a colorless oil, b.p. 96° (0.15 mm.).

C. 1-(*p*-Methoxyphenylthio)-2-propanol.—To a stirred suspension of sodium hydride (0.2 g.) in *p*-methoxythiophenol[6] (40 g., 0.286 mole), propylene oxide (18.2 g., 0.315 mole) was added dropwise. Reaction was initiated by gentle warming and the vigorous reaction was moderated by external cooling. Finally the mixture was heated at 100° for 30 min., cooled and poured into water. The oil was extracted with ether (3 × 200 ml.) and the combined extracts were washed with dilute sodium hydroxide and water. The dried (Na_2SO_4) extract was distilled to yield 41.6 g. (80%) of colorless oil, b.p. 96–100° (0.02 mm.).

D. 2-(*p*-Methoxyphenylthio)ethanol.—2-Chloroethanol (28 g.) was added to a solution of *p*-methoxythiophenol (35 g., 0.25 mole) in aqueous sodium hydroxide (13.1 g. in 175 ml.). The solution was boiled under reflux for 1 hr., cooled and extracted with ether. Distillation of the dried (Na_2SO_4) extract yielded 33.3 g. (72%) of a pale yellow solid which was recrystallized from light petroleum to give colorless plates m.p. 42–43°.

(ii) **Synthesis of Bromides,** $ArX(CH_2)_nCH(Y)Br$.—Physical constants and microanalytical data for new compounds are given in Table II.

E. 2-(3,4-Dimethylphenoxy)ethyl Bromide.—To a stirred, refluxing mixture of 3,4-xylenol (150 g.), 1,2-dibromoethane (132 ml.) and water (180 ml.), was added a solution of sodium hydroxide (53 g.) in water (100 ml.) slowly over 1 hr. After a further 6 hr. boiling the mixture was cooled and the lower organic layer separated. The aqueous layer was extracted with chloroform and the combined organic layers were washed with dilute sodium hydroxide solution, then water. Distillation yielded 128 g. (46%) of a colorless oil, b.p. 136–140° (10 mm.) which solidified and after recrystallization from methanol formed needles, m.p. 45–47°.

F. 1-Methyl-2-phenoxyethyl Bromide.—Phosphorus tribromide (100 g., 0.38 mole) was added dropwise with stirring over 1 hr. to 1-phenoxy-2-propanol[7] (101.4 g., 0.67 mole) cooled to 0°. After a further hour the mixture was heated on a steam bath for 30 min., cooled, and poured onto ice (200 g.). The oil was extracted into ether and the ether extract washed with 10% sodium hydroxide solution, followed by water. Distillation of the dried (Na_2SO_4) extract yielded a fraction of b.p. 120–130° (15 mm.), (87.3 g., 60%). After redistillation the b.p. was 119.5–122° (13.5 mm.).

G. 2-(3,4-Dichlorophenylthio)ethyl Bromide.—Phosphorus tribromide (37 g., 0.137 mole) was added dropwise with stirring over 1 hr. to a solution of 2-(3,4-dichlorophenylthio)ethanol[8] (60.1 g., 0.258 mole) in dry chloroform (125 ml.) cooled to 0°. The mixture was allowed to attain room temperature and was finally boiled under reflux for 1 hr. After cooling it was poured into iced water (300 ml.) and the chloroform layer separated. The aqueous layer was extracted with ether, and the combined organic layers were washed well with 10% sodium carbonate solution and water. The dried (Na_2SO_4) extract was distilled to yield 64.3 g. (84%) of a colorless liquid, b.p. 110–112° (0.09 mm.).

H. 2-Bromo-1-phenoxypentane.—1-Phenoxy-2-pentanol (29.3 g.) and pyridine (14.2 g.) in chloroform (100 ml.) were cooled to −30°. Thionyl bromide (37.4 g.) in chloroform (40 ml.) was added dropwise over 1 hr. with stirring and cooling. The mixture was allowed to attain room temperature and finally boiled under reflux for 15 min. After cooling, it was poured into water and the chloroform layer separated and washed with water, dilute hydrochloric acid, dilute sodium hydroxide and finally with water. Distillation of the dried (Na_2SO_4) extract yielded 23.5 g. (54%) of a colorless liquid, b.p. 74–78° (0.08 mm.).

I. 1-Anilino-2-bromopropane Hydrobromide.—Hydrobromic acid (6 g. of 47%) was added to 1-anilino-2-propanol[9] (5 g.), and water was removed at 100° under reduced pressure. To the resultant viscous oil, phosphorus tribromide (4.5 g.) was added and the mixture was cautiously heated with a flame until reaction commenced. When the initial reaction subsided, the mixture was heated at 100° for a further 30 min. The resultant red oil was dissolved in hot ethanol (75 ml.) and filtered from a small quantity of red insoluble matter. The colorless filtrate was evaporated under reduced pressure and the residual thick oil (7.4 g.) was recrystallized from 2-propanol/ethyl acetate yielding colorless crystals (2.6 g., 26%), m.p. 154–157°. Further recrystallization from 2-propanol gave colorless needles, m.p. 157–159°.

(iii) **Synthesis of Hydrazines,** $ArX(CH_2)_nCH(Y)NHNH_2$.—Physical constants and microanalytical data are given in Table III. The substituted hydrazines 1–39 in Table III were prepared by general method J, which is essentially that of Gabriel.[4] Compounds 40, 41 and 42 were prepared by the modifications of this method described below.

J. (1-Phenoxy-2-butyl)hydrazine.—2-Bromo-1-phenoxybutane[10] (23.6 g.) and hydrazine hydrate (40 ml. of 100%) in ethanol (300 ml.) were boiled under reflux for 16 hr. Solvents were removed under reduced pressure and the syrupy residue was treated with anhydrous potassium carbonate (15 g.). The mixture was extracted with chloroform, and the extract dried (Na_2SO_4) and distilled to yield 15.5 g. (76%) of a colorless oil, b.p. 85–95° (0.5 mm.).

The **hydrochloride** was prepared by adding 7 *N* ethanolic hydrogen chloride (11.2 ml.) to a solution of the base (14 g.) in ethanol (100 ml.). The solid was collected and recrystallized from ethyl acetate to yield 8 g. of colorless needles, m.p. 114–115°.

2-(*p*-Hydrophenoxy)ethylhydrazine (40).—(a) 2-(*p*-Hydroxyphenoxy)ethyl bromide[11] (26 g., 0.12 mole) and 100% hydrazine hydrate (58 ml.) in ethanol (600 ml.) were boiled under reflux for 3 hr. Removal of solvents under reduced pressure yielded a solid residue which was treated with anhydrous potassium carbonate (15 g.). The mixture was extracted with hot ethanol (2 × 100 ml.) and the combined extracts were evaporated to dryness to yield a solid which after two recrystallizations from ethyl acetate gave 4.4 g. (22%) of colorless crystals, m.p. 106°.

The **hydrochloride** was prepared by addition of ethanolic HCl (5 ml., 7 *N*) to a solution of the base (4.4 g.) in ethanol (20 ml.). The solid obtained by addition of ether was recrystallized from ethanol/ether to yield colorless crystals, m.p. 119°. Similarly prepared was the **hydrogen sulfate,** colorless crystals, m.p. 140–142° (from ethanol).

(b) The compound was also obtained in 45% yield by hydrolysis of 2-(*p*-benzyloxyphenoxy)ethylhydrazine with boiling aque-

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TABLE I

ALCOHOLS, $ArXCH_2CH(Y)OH$

Ar	X	Y	Method	Yield, %	B.p. °C.	B.p. Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	O	C_3H_7	A	65	143–147	18	$C_{11}H_{16}O_2$	73.3	8.9	73.4	9.1
o-$CH_3OC_6H_4$	O	CH_3	B	67	96	0.15	$C_{10}H_{14}O_3$	65.9	7.8	65.4	7.8
p-$CH_3OC_6H_4$	O	CH_3	B	69	86	0.04	$C_{10}H_{14}O_3$	65.9	7.8	65.8	7.9
p-$CH_3OC_6H_4$	S	H	D	72	M.p. 42–43[a]		$C_9H_{12}O_2S$	58.7	6.5	58.8	6.8
p-$CH_3OC_6H_4$	S	CH_3	C	80	96–100	0.02	$C_{10}H_{14}O_2S$	60.6	7.1	60.3	7.3
p-$CH_3SC_6H_4$	O	H	D	57	M.p. 55–56[a]		$C_9H_{12}O_2S$	58.7	6.5	59.0	6.6
p-$CH_3SC_6H_4$	O	CH_3	B	50	102	0.03	$C_{10}H_{14}O_2S$	60.6	7.1	60.4	7.2

[a] Recrystallized from petroleum ether (b.p. 40–60°).

TABLE II

BROMIDES, $ArXCH_2CH(Y)Br$

Ar	X	Y	Method	Yield, %	B.p. °C.	B.p. Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	O	CH_3	F	60	119.5–122	13.5	$C_9H_{11}BrO$	50.2	5.2	50.0	5.3
C_6H_5	O	C_3H_7	H	54	74–78	0.08	$C_{11}H_{15}BrO$[f]				
C_6H_5	NH	CH_3	I	26	m.p. 157–159[a]		$C_9H_{12}BrN \cdot HBr$	36.6	4.4	36.5	4.5
3,4-$(CH_3)_2C_6H_3$	O	H	E	46	136–140 m.p. 45–47[b]	10	$C_{10}H_{13}BrO$	52.4	5.7	52.7	5.8
3,5-$(CH_3)_2C_6H_3$	O	H	E	47	92	0.05	$C_{10}H_{13}BrO$	52.4	5.7	52.5	5.9
3,4-$Cl_2C_6H_3$	S	H	G	84	109–112	0.09	$C_8H_7Cl_2BrS$[f]				
o-$CH_3OC_6H_4$	O	CH_3	G	25	90–94	0.1	$C_{10}H_{13}BrO_2$	48.9	5.35	48.9	5.25
m-$CH_3OC_6H_4$	O	H	F	60	100–104	2	$C_9H_{11}BrO_2$	46.8	4.8	46.8	5.0
p-$CH_3OC_6H_4$	O	CH_3	G	20	98–108	0.1	$C_{10}H_{13}BrO_2$	49.0	5.4	49.4	5.4
p-$CH_3OC_6H_4$	S	H	G	87	108–120	0.2	$C_9H_{11}BrOS$[f]				
2,4-$(CH_3O)_2C_6H_3$	O	H	F	31	112–120 m.p. 63[c]	0.1	$C_{10}H_{13}BrO_3$	46.0	5.0	45.9	5.2
2,5-$(CH_3O)_2C_6H_3$	O	H	F	31	m.p. 68[d]		$C_{10}H_{13}BrO_3$	46.0	5.0	46.1	5.1
2,6-$(CH_3O)_2C_6H_3$	O	H	F	45	92	0.04	$C_{10}H_{13}BrO_3$	46.0	5.0	45.7	5.3
3,4-$(CH_3O)_2C_6H_3$	O	H	F	37	122–126 m.p. 58–59[e]	0.05	$C_{10}H_{13}BrO_3$	46.0	5.0	46.1	5.1
3,4,5-$(CH_3O)_3C_6H_2$	O	H	F	55	133	0.05	$C_{11}H_{15}BrO_4$	45.4	5.2	45.4	5.3
3,4-$(CH_2O_2)C_6H_3$	O	H	F	41	m.p. 74–75[d]		$C_9H_9BrO_3$	44.0	3.7	43.8	4.0
p-$CH_3SC_6H_4$	O	H	H	33	122	0.03	$C_9H_{11}BrOS$[f]				
p-$CH_3SC_6H_4$	O	CH_3	H	67	112–114	0.08	$C_{10}H_{13}BrOS$[f]				

[a] Recrystallized from 2-propanol. [b] Recrystallized from methanol. [c] Recrystallized from ethyl acetate. [d] Recrystallized from ethanol. [e] Recrystallized from ethyl acetate/petroleum ether. [f] These compounds underwent some decomposition during distillation and could not be obtained pure.

ous ethanolic HCl. Evaporation of the solution and recrystallization of the residue from ethanol/ether yielded the **hydrochloride,** m.p. 119–120°, undepressed on admixture with a sample prepared by method (a) above.

2-(p-Nitrophenoxy)ethylhydrazine (41).—2-(p-Nitrophenoxy)-ethyl bromide[12] (6.19 g., 0.025 mole), 100% hydrazine hydrate (6.0 ml.) and ethanol (50 ml.) were heated under reflux for 5 hr. The solution was evaporated to dryness under reduced pressure on a steam bath, and the residue extracted with hot benzene (100 ml.). On cooling the benzene extract a precipitate of the crude base was obtained, m.p. 56–59° (1.85 g., 38%). It was dissolved in boiling 3.2 N hydrochloric acid (40 ml.) and the solution filtered. On cooling the filtrate there was obtained the *hydrochloride* m.p. 203–205° dec. (1.3 g.), which after recrystallization from 1.5 N hydrochloric acid formed pale yellow needles, m.p. 205–210° dec.

2-(p-Carboxyphenoxy)ethylhydrazine (42).—4-(β-Bromoethoxy)benzoic acid[13] (22.5 g., 0.09 mole) and hydrazine hydrate (23 ml., 0.46 mole) in ethanol (250 ml.) were boiled under reflux for 3 hr. Removal of solvents under reduced pressure gave a residue which was dissolved in water (125 ml.) and acidified to pH 4.0 with acetic acid. The precipitated solid was filtered off, washed well with water, and extracted with boiling ethanol (200 ml.) to give a residue, m.p. 188–191° dec. Two further extractions with 100 ml. portions of boiling ethanol yielded a residue (7.1 g., 40%), m.p. 197–198° dec.

(b) **Determination of pK_A.**—pK_A values were measured by electrometric titration of the substituted hydrazinium salts with 0.01 N sodium hydroxide. The results were plotted using the linear, non-logarithmic method suggested by Hofstee[14] and K_A was determined from the slope of the line.

(c) **Determination of Partition Ratio.**—Partition ratios were measured by equilibrating a solution of the substituted hydrazine salt in phosphate buffer (pH 7.3) with chloroform. Estimations were carried out on the aqueous phase before and after equilibration by measuring the ultraviolet light absorption at the appropriate wave length.

(d) **Biological Evaluation.**—(i) **Monoamine Oxidase Inhibition —*in Vitro*.**—The method was essentially that of Bogdanski, Weissbach and Udenfriend[15] using rat liver homogenate (200 mg./ml.) as the enzyme source. A series of concentrations of the test compound were added 15 min. before addition of the substrate and the reaction allowed to proceed for 30 min. The 5-hydroxytryptamine remaining was extracted and measured using the method of Udenfriend, Weissbach and Clark.[16] The 50% inhibition concentration was estimated from a plot of percentage inhibition against concentration. (Concentrations are expressed as weight of the salt used—see Table III.)

(ii) **Reserpine Reversal.**—The method used was based on the reversal of reserpine sedation in mice, a phenomenon first reported for iproniazid by Chessin, Kramer and Scott.[17] Groups of 6 mice

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TABLE III

HYDRAZINES, $ArX(CH_2)_nCH(Y)NHNH_2$

No.	Ar	X	n	Y	Yield, %	B.p. °C.	B.p. Mm.	Salts $ArX(CH_2)_nCH(Y)NHNH_2 \cdot HA$ Empirical formula	M.p., °C.	Recryst from[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	O	1	H	69	138–142	9	$C_8H_{12}N_2O \cdot HCl$	142–143	E	50.9	7.0	14.8	51.2	6.8	14.5
2	C_6H_5	O	1	CH_3	76	98–102	0.2	$C_9H_{14}N_2O \cdot C_4H_4O_4$[b]	107–108	I	55.3	6.4	9.8	55.5	6.55	9.8
3	C_6H_5	O	1	C_2H_5	76	85–95	0.15	$C_{10}H_{16}N_2O \cdot HCl$	114–115	A	55.4	7.85	12.9	55.4	7.9	12.85
4	C_6H_5	O	1	C_3H_7	93	94	0.1	$C_{11}H_{18}N_2O \cdot C_4H_4O_4$	87–88	A/B	58.1	7.1	9.0	58.1	7.1	9.0
5	C_6H_5	O	2	H	71	103–108	0.1	$C_9H_{14}N_2O \cdot C_4H_4O_4$	106–107	A	55.3	6.4	9.8	55.2	6.4	9.7
6	C_6H_5	O	3	H	84	111	0.1	$C_{10}H_{16}N_2O \cdot C_4H_4O_4$	102–104	E/A	56.7	6.8	9.5	56.7	6.8	9.8
7	C_6H_5	O	4	H	62	116–122	0.1	$C_{11}H_{18}N_2O \cdot C_4H_4O_4$	96–98	A	58.1	7.1	9.0	58.4	7.2	9.2
8	C_6H_5	O	5	H	51	137–146	0.15	$C_{12}H_{20}N_2O \cdot C_4H_4O_4$	98–100	A	59.25	7.5	8.6	59.2	7.7	8.4
9	C_6H_5	S	1	H	54	120	0.05	$(C_8H_{12}N_2S)_2H_2SO_4$	212–213	W/E 1:4	44.1	6.0	12.9	44.4	6.0	12.7
10	C_6H_5	S	1	CH_3	78	96–100	0.1	$C_9H_{14}N_2S \cdot C_4H_4O_4$	95–96	A	52.35	6.05	9.4	52.3	6.25	9.6
11	C_6H_5	S	3	H	58	103–110	0.01	$C_{10}H_{16}N_2S \cdot C_4H_4O_4$	104–105	E	53.8	6.4	9.0	53.4	6.6	9.1
12	C_6H_5	NH	1	H	64	128–132	0.05	$C_9H_{13}N_3 \cdot 2HCl$	190–191	E	42.9	6.7	18.75	42.9	6.85	18.6
13	C_6H_5	NH	1	CH_3	61	118–122	0.04	$(C_{10}H_{15}N_3)_2(C_4H_4O_4)_3$	128	E/A	53.1	6.2	12.5	52.8	6.4	12.9
14	o-$CH_3C_6H_4$	O	1	H	70	93–97	0.05	$C_9H_{14}N_2O \cdot HCl$	140–141	E	53.3	7.4	13.8	53.2	7.5	13.6
15	p-$CH_3C_6H_4$	O	1	H	72	151–154	1.0	$C_9H_{14}N_2O \cdot HCl$	185–187	M	53.3	7.5	13.8	53.3	7.6	14.1
16	3,4-$(CH_3)_2C_6H_3$	O	1	H	41	117–118	0.02	$C_{10}H_{16}N_2O \cdot C_4H_4O_4$	120	E	56.7	6.8	9.5	57.0	6.8	9.7
17	3,5-$(CH_3)_2C_6H_3$	O	1	H	66	102	0.2	$C_{10}H_{16}N_2O \cdot HCl$	156	E	55.4	7.9	12.9	55.7	7.7	13.2
18	α-$C_{10}H_7$	O	1	H	65	140	0.15	$C_{12}H_{14}N_2O \cdot C_4H_4O_4$	130	E	60.4	5.7	8.8	60.3	5.9	8.5
19	β-$C_{10}H_7$	O	1	H	83	M.p. 49–51		$C_{12}H_{14}N_2O \cdot C_4H_4O_4$	139–141	A	60.4	5.7	8.8	60.3	5.6	8.8
20	m-ClC_6H_4	O	1	H	68	108–111	0.05	$C_8H_{11}ClN_2O \cdot C_4H_4O_4$	96–98	A	47.6	5.0	9.3	47.8	5.2	9.3
21	p-ClC_6H_4	O	1	H	81	128–135	0.2	$C_8H_{11}ClN_2O \cdot HCl$	170–176	M/A	43.1	5.4	12.6	43.1	5.6	12.8
22	3,4-$Cl_2C_6H_3$	S	1	H	44	160–166	0.1	$C_8H_{16}Cl_2N_2S \cdot C_4H_4O_4$	109–110	A	40.8	4.0	7.9	40.7	4.2	7.9
23	o-$CH_3OC_6H_4$	O	1	H	71	111–116	0.05	$C_9H_{14}N_2O_2 \cdot HCl$	111–113	E/A	49.4	6.9	12.8	49.6	6.7	12.8
24	o-$CH_3OC_6H_4$	O	1	CH_3	80	106–110	0.05	$C_{10}H_{16}N_2O_2 \cdot HCl$	126–129	E/A	51.6	7.4	12.0	51.9	7.6	12.2
25	m-$CH_3OC_6H_4$	O	1	H	80	118–123	0.4	$C_{12}H_{14}N_2O_2 \cdot C_4H_4O_4$	78–79	E/A	52.3	6.1	9.4	52.2	6.2	9.4
26	p-$CH_3OC_6H_4$	O	1	H	66	125–126	0.4	$C_9H_{14}N_2O_2 \cdot HCl$	169–170	E	49.4	6.9	12.8	49.4	7.0	13.2
27	p-$CH_3OC_6H_4$	O	1	CH_3	69	112–118	0.15	$C_{10}H_{16}N_2O_2 \cdot C_4H_4O_4$	102–104	A	53.8	6.5	9.0	53.8	6.5	9.3
28	p-$CH_3OC_6H_4$	S	1	H	84	120–126	0.15	$C_9H_{14}N_2OS \cdot C_4H_4O_4$	113–114	A	49.7	5.7	8.9	49.9	6.0	8.6
29	p-$CH_3OC_6H_4$	S	1	CH_3	56	140	0.2	$C_{10}H_{16}N_2OS \cdot C_4H_4O_4$	117–117.5	E/A	51.2	6.1	8.5	51.0	6.1	8.5
30	2,4-$(CH_3O)_2C_6H_3$	O	1	H	43	144–150	0.1	$C_{10}H_{15}N_2O_3 \cdot HCl$	112–113	E/A	48.3	6.9	11.3	48.4	6.75	11.2
31	2,5-$(CH_3O)_2C_6H_3$	O	1	H	40	m.p. 46		$C_{10}H_{16}N_2O_3 \cdot HCl$	120–121	E/A	48.3	6.9	11.3	48.2	6.9	11.6
32	2,6-$(CH_3O)_2C_6H_3$	O	1	H	49	138–149	0.6	$C_{10}H_{16}N_2O_3 \cdot HCl$	163–164	E/A	48.3	6.9	11.3	48.1	7.0	11.6
33	3,4-$(CH_3O)_2C_6H_3$	O	1	H	55	155–160	0.2	$C_{10}H_{16}N_2O_3 \cdot HCl$	149–151	E	48.3	6.9	11.3	48.3	6.9	11.2
34	3,4,5-$(CH_3O)_3C_6H_2$	O	1	H	59	176–184	0.1	$C_{11}H_{18}N_2O_4 \cdot HCl$	134–135	E/A	47.4	6.9	10.1	47.4	7.0	10.2
35	3,4-$(CH_2O_2)C_6H_3$	O	1	H	49	126–132	0.03	$C_9H_{12}N_2O_3 \cdot HCl$	161–163	E	46.4	5.6	12.0	46.5	5.6	12.1
36	p-$C_6H_5CH_2OC_6H_4$	O	1	H	24	C		$C_{15}H_{18}N_2O_2 \cdot HCl$	182–183	E	61.1	6.5	9.5	61.3	6.5	9.5
37	4-C_3H_5-2-$CH_3OC_6H_3$	O	1	H	43	137–143	0.1	$C_{12}H_{18}N_2O_2 \cdot C_4H_4O_4$	85–87	A	56.8	6.55	8.3	56.8	6.7	8.5
38	p-$CH_3SC_6H_4$	O	1	H	54	115–130	0.01	$C_9H_{14}N_2O_2S \cdot C_4H_4O_4$	116–118	E	49.7	5.7	8.9	50.0	5.8	9.2
39	p-$CH_3SC_6H_4$	O	1	CH_3	48	124–137	0.03	$C_{10}H_{16}N_2OS \cdot C_4H_4O_4$	108–110	A	51.2	6.1	8.5	51.2	6.4	8.9
40	p-HOC_6H_4	O	1	H	22	m.p. 106		$C_8H_{12}N_2O_2 \cdot H_2SO_4$	140–142	E	36.1	5.3	10.5	35.8	5.2	10.7
41	p-$NO_2C_6H_4$	O	1	H	38	m.p. 94–96		$C_8H_{11}N_3O_3 \cdot HCl$	205–210	H	41.1	5.2	18.0	41.1	5.5	18.0
42	p-$HO_2CC_6H_4$	O	1	H	40	—		$C_9H_{12}N_2O_3$	197–198	—	55.1	6.1	14.3	55.2	6.3	14.1

[a] E for ethanol; I, 2-propanol; A, ethyl acetate; B, benzene; W, water; M, methanol; H, 1.5 N hydrochloric acid. [b] $C_4H_4O_4$, maleic acid. [c] The hydrochloride was prepared directly from the crude base.

were injected with reserpine (5 mg./kg. i.p.) having been previously treated with graded doses of the test compounds (controls received saline) given orally in 2 doses, 24 hr. and 4 hr. prior to the injection of the reserpine. The animals were examined 45 min. after injection of reserpine. Controls were then sedated, whereas those animals receiving effective doses of test compounds showed normal or hyperactivity. The threshold dose is the lowest dose at which this effect was produced. (Doses refer to weights of salt used—see Table III.)

(iii) **Monoamine Oxidase Inhibition**—*in vivo*.—Groups of 4 rats were treated by stomach tube with graded doses of the test compounds. The animals were killed 2 hr. later, livers and brains removed, and homogenized with water to give 10 and 20% homogenates, respectively. Lubrol W.[18] (0.3 ml. of a 10% aqueous solution per ml. homogenate) was added to reduce the optical density of organ homogenates. This was found to have only slight effect on the monoamine oxidase activity of the homogenate. The monoamine oxidase activity was measured using the method of Weissbach, *et al.*[19] The 50% and 80% inhibition doses were estimated from a plot of percentage inhibition against dose.

(iv) **Acute Toxicities.**—The approximate LD_{50} values were determined by both oral and intraperitoneal routes using 5 mice per dose level.

TABLE IV

pK_A AND PARTITION RATIOS OF SUBSTITUTED HYDRAZINES

Ref. no.	Compound	pK_A	Partition ratio, $CHCl_3$ / Aqueous buffer pH 7.3
1	$C_6H_5OCH_2CH_2NHNH_2$	6.8	3.9
2	$C_6H_5OCH_2CH(CH_3)NHNH_2$	6.9	16.3
9	$C_6H_5SCH_2CH_2NHNH_2$	6.8	16.6
26	p-$CH_3OC_6H_4OCH_2CH_2NHNH_2$	7.0	6.9
40	p-$HOC_6H_4OCH_2CH_2NHNH_2$	6.9	0.08

Results and Discussion

The results of *in vitro* tests for monoamine oxidase inhibition, reversal of reserpine sedation in mice, and acute toxicities are given in Table V. It is clear that, in general, the compounds are highly active inhibitors, many of them being considerably more potent than iproniazid in the test systems used. Some of the more active members of the series approach closely the level of activity of α-methylphenethylhydrazine. The high concentration of iproniazid required to inhibit rat liver homogenate preparations of monoamine oxidase is in agreement with the results of Zeller[20] and Sjoerdsma.[21]

In general, correlation between the *in vitro* activity and the dose required for reversal of reserpine sedation is fairly good, and supports the use of this latter method as a rapid and convenient method for the screening of large numbers of compounds for *in vivo* monoamine oxidase inhibitory activity.

The effects of variations in chemical structure on activity are rather unpredictable but some points of interest do emerge. The activity of a series of homologous ω-phenoxy-n-alkylhydrazines (Table V, nos. 1, 5, 6, 7, 8) shows the effect of varying the length of the alkylene chain separating the phenoxy and hydrazine groups. Those compounds with two or four methylene groups are potent inhibitors, whereas those with three, five or six have little activity. These results are similar to the findings of Biel and co-workers[22] on a series of phenylalkylhydrazines. The effect of branching the alkylene chain is seen in compounds 1, 2, 3, 4 (Table V), from which it appears that the $-CH_2-CH(CH_3)-$ chain is the most favorable. This, however, only appears to be the case for the phenoxy compounds (X = O). Introduction of an α-methyl group into 2-anilinoethylhydrazine (12) or 2-phenylthioethylhydrazine (9) led to compounds 13 and 10 having lower activity than the parent ethyl analogs.

The effect of substitution in the phenyl ring is similarly unpredictable and is dependent on the basic structure. Thus in a series of 2-aryloxyethylhydrazines the introduction of a methoxy group in the *ortho* or *para* positions gave compounds of increased potency whereas *para* methoxylation of 2-phenylthioethylhydrazine or (1-methyl-2-phenoxy)ethylhydrazine had little effect on activity. In general, of all the substituents examined only methoxy or methylenedioxy yielded compounds of high potency. These results are dissimilar to those obtained by Biel[22] with a series of nuclear substituted α-methylphenethylhydrazines, who found *o*-methyl, *m*-chloro and 3,4-methylenedioxy to be the most active of the substituted compounds.

Although the results of the reserpine-reversal test appeared to correlate reasonably well with the *in vitro* enzyme inhibition, the method does rely on subjective assessment, and it was felt that a more precise quantitative comparison would be obtained by measuring the degree of enzyme inhibition in organs from animals which had been treated with the test compounds. Accordingly, seven of the more active compounds (2, 9, 10, 12, 13, 28, 40) were selected for such investigation. 2-(*p*-Hydroxyphenoxy)ethylhydrazine (40) was included as this had shown high activity *in vitro* but little activity in the reserpine-reversal test, and it was of interest to investigate whether low activity in the reserpine-reversal test was correlated with a low degree of inhibition of brain monoamine oxidase.

Results of these experiments are shown in Table VI. The most potent inhibitors are 2-phenylthioethylhydrazine (9) and (1-methyl-2-phenoxyethyl)-hydrazine (2) which have approximately the same activity as α-methylphenethylhydrazine. 2-(*p*-Hydroxyphenoxy)-ethylhydrazine (40) gave very little inhibition of brain monoamine oxidase at any of the doses used (up to 128 mg./kg.), and only at a dose of 128 mg./kg. was 50% inhibition of the liver enzyme obtained.

Poor absorption from the gastrointestinal tract could explain this lack of *in vivo* activity, but if this were the sole reason, a greater disparity between oral and i.p. LD_{50}'s than that found (see Table V) might be expected. A possible explanation may lie in the fact that monoamine oxidase is an intracellular enzyme and that, in order to affect this enzyme, a compound must be capable of penetration into the cell. Brodie and Hogben[23] have suggested that the transfer of foreign organic compounds across cell membranes may be considered as a process of simple partition, where the membrane behaves as an "organic solvent" layer permitting the passage of organic acids or bases in their un-ionized forms at a rate dependent upon (a) the

(18) "Lubrol W" is a fatty alcohol—ethylene oxide condensate, manufactured by Imperial Chemical Industries Limited.

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TABLE V

MONOAMINE OXIDASE INHIBITORY POTENCY AND TOXICITY OF SUBSTITUTED HYDRAZINES, $ArX(CH_2)_nCH(Y)NHNH_2$

No.	Ar	X	n	Y	MAO inhibition 50% inhib. concn. μg./ml.	Reserpine reversal, threshold dose, mg./kg. oral.	LD_{50} mg./kg. i.p.	LD_{50} mg./kg. oral
1	C_6H_5	O	1	H	1.25	10	200	200
2	C_6H_5	O	1	CH_3	0.25	4	350	500
3	C_6H_5	O	1	C_2H_5	0.6	4	200	200
4	C_6H_5	O	1	C_3H_7	1.5	4	300	500
5	C_6H_5	O	2	H	>12.5	>32	250	250
6	C_6H_5	O	3	H	1.7	4	250	375
7	C_6H_5	O	4	H	>12.5	>32	125	500
8	C_6H_5	O	5	H	>12.5	>32	375	750
9	C_6H_5	S	1	H	0.7	4	200	200
10	C_6H_5	S	1	CH_3	1.0	8	375	750
11	C_6H_5	S	3	H	4.2	16	250	200
12	C_6H_5	NH	1	H	0.7	4	175	200
13	C_6H_5	NH	1	CH_3	2.0	6	300	500
14	o-$CH_3C_6H_4$	O	1	H	3.2	16–32	200	250
15	p-$CH_3C_6H_4$	O	1	H	3.2	8	250	300
16	3,4-$(CH_3)_2C_6H_3$	O	1	H	9.0	16	375	750
17	3,5-$(CH_3)_2C_6H_3$	O	1	H	4.0	8	250	250
18	α-$C_{10}H_7$	O	1	H	3.4	8	375	625
19	β-$C_{10}H_7$	O	1	H	12.5	16–32	500	1000
20	m-ClC_6H_4	O	1	H	12	16	375	500
21	p-ClC_6H_4	O	1	H	7.2	16	300	300
22	3,4-$Cl_2C_6H_3$	S	1	H	0.9	8	200	350
23	o-$CH_3OC_6H_4$	O	1	H	1.0	4	400	700
24	o-$CH_3OC_6H_4$	O	1	CH_3	0.8	4	350	350
25	m-$CH_3OC_6H_4$	O	1	H	3.5	16	400	500
26	p-$CH_3OC_6H_4$	O	1	H	0.25	4	250	250
27	p-$CH_3OC_6H_4$	O	1	CH_3	0.4	4	400	700
28	p-$CH_3OC_6H_4$	S	1	H	0.4	4	250	250
29	p-$CH_3OC_6H_4$	S	1	CH_3	2.0	8	200	1000
30	2,4-$(CH_3O)_2C_6H_3$	O	1	H	1.5	8	150	400
31	2,5-$(CH_3O)_2C_6H_3$	O	1	H	0.8	4	125	125
32	2,6-$(CH_3O)_2C_6H_3$	O	1	H	12.0	16	200	625
33	3,4-$(CH_3O)_2C_6H_3$	O	1	H	0.8	4	90	90
34	3,4,5-$(CH_3O)_3C_6H_2$	O	1	H	3.1	8	400	400
35	3,4-$(CH_2O_2)C_6H_3$	O	1	H	0.3	4	100	250
36	p-$C_6H_2CH_2OC_6H_4$	O	1	H	2.5	64	250	1000
37	4-C_3H_5-2-$CH_3OC_6H_3$	O	1	H	4.0	8	375	625
38	p-$CH_3SC_6H_4$	O	1	H	2.5	16	400	400
39	p-$CH_3SC_6H_4$	O	1	CH_3	0.5	16	350	1000
40	p-HOC_6H_4	O	1	H	0.5	24	200	500
41	p-$NO_2C_6H_4$	O	1	H	>12.5	32	900	1000
42	p-$HO_2CC_6H_4$	O	1	H	>12.5	>32	>1000	..
	α-Methylphenethylhydrazine				0.4	2	125	250
	β-Phenethylhydrazine				1.5	4	190	90
	Iproniazid				250	36–72	750	1000

TABLE VI

MONOAMINE OXIDASE INHIBITION IN RATS. DOSE (MG./KG) REQUIRED TO PRODUCE 50% (ID_{50}) AND 80% (ID_{80}) INHIBITION OF MONOAMINE OXIDASE IN BRAIN AND LIVER

Compound		Brain		Liver	
Ref. no.	Structure	ID_{50} mg./kg. oral	ID_{80} mg./kg. oral	ID_{50} mg./kg. oral	ID_{80} mg./kg. oral
2	$C_6H_5OCH_2CH(CH_3)NHNH_2$	4	7	0.7	2
9	$C_6H_5SCH_2CH_2NHNH_2$	3.4	8	<1	2
10	$C_6H_5SCH_2CH(CH_3)NHNH_2$	13	30	3	7
12	$C_6H_5NHCH_2CH_2NHNH_2$	8	12	2	3
13	$C_6H_5NHCH_2CH(CH_3)NHNH_2$	5.5	14	2	4
28	p-$CH_3OC_6H_4SCH_2CH_2NHNH_2$	12	25	32	12
40	p-$HOC_6H_4OCH_2CH_2NHNH_2$	a	a	128	a
	$C_6H_5CH_2CH(CH_3)NHNH_2$	4	6.5	0.7	2

[a] This degree of inhibition was not achieved by the highest dose (128 mg./kg.) used.

dissociation constant of the acid or base, and (b) the partition ratio between an organic solvent and a neutral aqueous phase. Determinations of the pK_A, and partition ratio were therefore carried out with 2-(*p*-hydroxyphenoxy)ethylhydrazine, and some related compounds which had shown activity *in vivo*.

The results (Table IV) show that the pK_A values for all the compounds examined are of similar magnitude and that under physiological conditions the compounds will be approximately 25% ionized. The partition data, however, show that 2-(*p*-hydroxyphenoxy)-ethylhydrazine (40) has a very much lower chloroform/water partition ratio than the other compounds examined and thus might be expected to penetrate cell membranes only with difficulty, hence its relative inactivity as an *in vivo* inhibitor of monoamine oxidase. The structurally related phenolic bases norepinephrine, dopamine, and 5-hydroxytryptamine are known to penetrate the blood-brain barrier at a very slow rate.

The results of *in vitro* and *in vivo* tests for monoamine oxidase inhibition have shown 2-phenylthioethylhydrazine and (1-methyl-2-phenoxyethyl)hydrazine to be the most active of the series of compounds studied. (1-Methyl-2-phenoxy)ethylhydrazine (2) seemed to be a compound of particular interest in that it combines activity approximately equal to that of phenethylhydrazine and α-methylphenethylhydrazine, with an acute toxicity considerably lower than either of these two substances. Accordingly (1-methyl-2-phenoxy)-ethylhydrazine has been submitted to a more detailed pharmacological and toxicological investigation,[24] and subsequently to clinical evaluation. This product is now known in Great Britain by the B.P. Commission approved name phenoxypropazine.[25]

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(24) Ruth A. Davis, M. Horlington, R. Lazare, G. A. Poulter, Hazel Thorpe and Alicia Urbanska—unpublished results.

(25) Drazine®, phenoxypropazine hydrogen maleate.

The Synthesis of Cycloheptatriene Homologs of Some Physiologically Active Compounds[1,2]

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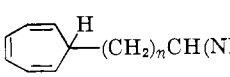
Three tropyl amino acids have been prepared and found lacking in activity against phenylalanine in *Lactobacillus*. Three tropylethylamines, however, showed analeptic activity. The preparation of ditropylindanedione is also reported.

Tropilidene (1,3,5-cycloheptatriene) bears a striking structural resemblance to benzene (6π electrons, similar molecular dimensions, and approximate planarity) and has even been called "pseudoaromatic."[4] A well-recognized device in the search for new substances of biological activity is to substitute for groups in compounds of established physiological activity new groups of similar structure to those replaced.[5] Our experience[6] in the synthesis of substituted alkyl tropilidenes led us to the synthesis and testing of a number of substances in which the tropyl group is substituted for the phenyl group of compounds of known activity.

We chose first to investigate various tropyl α-amino acids (I). Tropylglycine (Ia) is an isomer of phenyl-



I a, $n=0$; b, $n=1$; c, $n=2$

alanine; tropylalanine (Ib) is the analog (and a homolog) of phenylalanine; α-amino-γ-tropylbutyric acid (Ic) is a homolog of the analog.

These substances were prepared by the application of standard methods. Acetamido-(or phthalimido)-malonic ester was alkylated with tropylium perchlorate to give tropylacetamido-(or phthalimido)-malonic ester which was hydrolyzed to Ia in two stages. Tropylethyl bromide[6] was used to alkylate acetamidomalonic ester in the preparation of Ic. The Strecker synthesis was used starting from tropylacetaldehyde[7] for the preparation of Ib. The tendency of functionally substituted tropylalkyl compounds to undergo fragmentation reactions in acid media necessitated the use of basic hydrolysis in these preparations in place of the usual acid hydrolyses. The yields of the amino acids were 18% (three stages using ethyl acetamidomalonate; 3% using ethyl phthalimidomalonate), 29% (two stages from the aldehyde) and 24% (three stages from the bromide) for $n = 0$, 1, and 2, respectively.

A second group of substances chosen were the analogs of certain phenethylamines which are useful as sympathomimetic drugs. Along this line we have prepared β-tropylethylamine (IIa),[6] β-tropylisopropylamine (IIb) and its N-methyl derivative (IIc).

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