solved by the addition of about 20 ml. of ether. Then 2 *N* ammonia was added until the aqueous phase had pH 10–10.5. The mixture was shaken well and the aqueous layer extracted 5 times with ether. The combined ether extracts gave, after drying and evaporation at room temperature, 2.79 g. (70%) of starting material. The aqueous phase was cooled in an ice bath, acidified (congo red) with 2 *N* HCl, and then extracted 5 times with ether. After drying and evaporation at room temperature the combined ether extracts gave 0.96 g. (25% yield) of the half-ester; m.p. 139° (softens at 87°). The substance was recrystallized without heating from chloroform–isooctane. The melting point of the recrystallized material was unchanged.[15]

Anal. Calcd. for $C_{18}H_{16}I_2O_6$: C, 37.14; H, 2.77; I, 43.60. Found: C, 37.21; H, 2.90; I, 43.66.

Partial Iodination of 2-Ethoxycarbonyl-3-[4-(*p*-hydroxyphenoxy)-3,5-diiodophenyl]propionic Acid (Ie).—A partial iodination of Ie was carried out following the procedure described previously for the synthesis of Ia (R_2 = H). The triiodinated monoester Ib (R_2 = H) was contaminated with Ie and with Ib (R_2 = I). The substance could not be purified by crystallization. Purification was achieved on a small scale by descending chromatography in chloroform–formamide (lower phase) on paper that had been washed in formamide–acetone (1:3) and then dried. In this system Ie migrates slower and Ib (R_2 = I) faster than Ib (R_2 = H). The R_f values depend on how often the paper had been soaked in formamide–acetone.

2-Ethoxycarbonyl-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propionic Acid (Ib, R_2 = I).—An iodination of 815 mg. (1.40 mmoles) of 2-ethoxycarbonyl-3-[4-(*p*-hydroxyphenoxy)-3,5-diiodophenyl]propionic acid (Ie) was carried out according to the procedure described for the synthesis of Ia (R_2 = I). Crystals which formed on cooling of the reaction mixture were redissolved by the addition of water. The precipitate which formed after acidification was collected by filtration, washed with water, and dried. The crude material (theoretical yield) was recrystallized several times below 35° from ethanol containing a few drops of water and from chloroform–isooctane. The substance softened at 103–105°, decomposed with the evolution of gas (carbon dioxide) at about 115°, resolidified, and melted again at 159–160°. For elemental analysis the material was finely powdered, then dried under high vacuum at room temperature.

Anal. Calcd. for $C_{18}H_{14}I_4O_6$: C, 25.92; H, 1.69; I, 60.87. Found: C, 26.10; H, 1.86; I, 60.86.

***p*-Hydroxybenzylmalonic Acid.**—A solution of 130 g. (0.49 mole) of diethyl *p*-hydroxybenzalmalonate[5] (m.p. 90–90.5°) in 600 ml. of ethanol was hydrogenated slightly above atmospheric pressure in the presence of 10 g. of 10% palladium-on-charcoal. The catalyst was removed by filtration and the filtrate was added dropwise (1.2 hr.) to a stirred hot solution (80°) of 100 g. (1.6 moles) of potassium hydroxide (87%) in 100 ml. of water. The reaction flask was kept on a steam bath for another 2.5 hr. during which period a funnel connected to a water pump was placed over the neck of the flask in order to remove the ethanol vapors. Some precipitate which formed was redissolved by the addition of a small amount of water. The reaction mixture was cooled in an ice bath, then acidified (congo red) by the slow addition of 20% hydrochloric acid. This was followed by the addition of some water and 4 extractions with ether. The combined ether extracts were dried over calcium chloride and evaporated at room temperature. The residue weighed 100 g. (97% yield) and melted at 160–161° dec.; lit.[16] m.p 160.5° dec. The substance was recrystallized from ethyl acetate–benzene with the addition of Norit; m.p. 160.5–161.5° dec.

4-Hydroxy-3,5-diiodobenzylmalonic Acid (IIIb).—*p*-Hydroxybenzylmalonic acid (3.15 g., 15 mmoles) was iodinated according to the procedure described for the synthesis of Ia (R_2 = I). After evaporation of the ether extract 6.7 g. (97% yield) of crude product, m.p. 167.5–168.5° dec. was obtained. It was contaminated with a small amount of 3,5-diiodophloretic acid from which it was freed by fractional acidification of a solution in 0.5 *N* NaOH at 0° with small increments of dilute hydrochloric acid. The first precipitates which contained most of the contaminant were eliminated and the remaining precipitates were recrystallized from methanol below room temperature; white needles, m.p. 172–174° dec.

Anal. Calcd. for $C_{10}H_8I_2O_5 \cdot CH_3OH$: C, 26.74; H, 2.45; I, 51.38. Found: C, 26.75; H, 2.69; I, 51.82.

Incubation of 4-Hydroxy-3,5-diiodobenzylmalonic Acid.—An 0.25 *M* solution of IIIb (pH 7.5) was incubated aerobically at 37° following the procedure described previously[3] for other analogs of diiodotyrosine. After various time intervals aliquots of the incubation mixture were analyzed by paper chromatography and by high voltage electrophoresis. The solvent systems and methods used were the same as those described earlier.[3] Identification of the incubation products was made by comparison with the R_f values and mobilities of authentic samples. Starting material was present at all times. Extensive deiodination of the starting material gave rise to 4-hydroxy-3-iodobenzylmalonic acid. After 3 days 3,5-diiodophloretic acid could be detected and after 4 or 5 days also traces of 3-iodophloretic acid. After 5 days, Ia (R_2 = I) and Ia (R_2 = H) began to appear in the reaction mixture. These two acids could be detected only after extraction of the reaction mixture with 1-butanol at pH 7.5 and evaporation of the butanol extracts at room temperature.

(15) Before optimal conditions for the partial hydrolysis of diester Ic had been established, monoester Ie was frequently contaminated with dicarboxylic acid Id. These two substances were then separated as described in footnote 12.

(16) J. C. Westfall and T. S. Gresham, *J. Am. Chem. Soc.*, **76**, 1076 (1954).

Hydroxylamine Chemistry. IV. O-Aralkylhydroxylamines

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Several synthetic procedures were used to prepare a series of O-aralkylhydroxylamines. Some of the products are structurally analogous to amines of biological interest. These compounds are in general 5-hydroxytryptophan decarboxylase inhibitors and mild depressants.

Interest in hydroxylamine derivatives designed as pharmacodynamic or chemotherapeutic agents has increased in recent years.[1–6] Our efforts in this field have been directed in part to the synthesis of O-

(1) (a) R. T. Major and L. H. Peterson, *J. Org. Chem.*, **22**, 579 (1957); (b) R. T. Major, H. J. Hess, and F. Dürsch, *ibid.*, **24**, 281 (1959); (c) R. T. Major and H. J. Hess, *J. Med. Pharm. Chem.*, **1**, 381 (1959); (d) R. T. Major and H. J. Hess, *ibid.*, **2**, 461 (1960); (e) R. T. Major and K. W. Ohly, *ibid.*, **4**, 51 (1961).

(2) (a) G. Palazzo, E. F. Rogers, and G. B. Marini-Bettolo, *Gazz. Chim. Ital.*, **84**, 915 (1954); (b) E. F. Rogers, D. Bovet, V. G. Longo, and G. B. Marini-Bettolo, *Experientia*, **9**, 260 (1953).

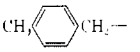
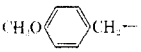
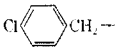
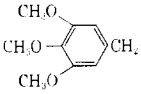
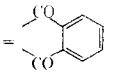
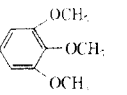
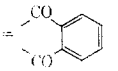
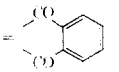
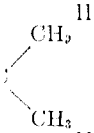
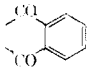
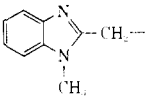
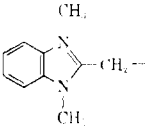
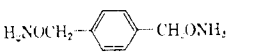
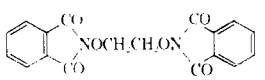
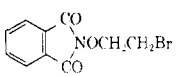
(3) (a) D. McHale, J. Green, and P. Mamalis, *J. Chem. Soc.*, 225 (1960); (b) P. Mamalis, J. Green, and D. McHale, *ibid.*, 229 (1960).

(4) A. T. Fuller and H. King, *ibid.*, 963 (1947).

(5) A. F. McKay, D. L. Garmaise, G. Y. Paris, and S. Gelblum, *Can. J. Chem.*, **38**, 343 (1960).

(6) (a) E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. DaVanzo, and M. E. Greig, *J. Med. Pharm. Chem.*, **5**, 464 (1962); (b) L. A. Paquette, *J. Org. Chem.*, **27**, 2870 (1962); (c) L. A. Paquette, *Tetrahedron Letters*, **No. 11**, 485 (1962).

TABLE I: R—O—N<A/B

No.	R	A	B	Salt	Method
I	$C_6H_5CH_2$—	H	H	HCl	A-1
II	$C_6H_5CH_2$—	$COCH_3$	$COCH_3$	...	...
III	$C_6H_5CH_2$—	A and B = isopropylidene		...	...
IV		H	H	HCl	A-1
V		H	H	HCl	C
VI		H	H	HCl	A-2
VII		H	H	HCl	C
VIII	$C_6H_5CH(CH_3)$—	H	H	HCl	C
IX	$(C_6H_5)_2CH$—	H	H	HCl	B
X	$(C_6H_5)_2CH$—	A and B = 		...	B
XI	$(C_6H_5)_2CH$—	A and B = 		...	...
XII	$(C_6H_5)_2CH$—	A and B = 		HCl	...
XIII	$(C_6H_5)_2CH$—	A and B = 		...	...
XIV	$(C_6H_5)_3C$—	A and B = 		...	B
XVa	$C_6H_5CH_2CH_2$—	H	H	maleate	B
XVb				HCl	C
XVI	$C_6H_5CH_2CH_2$—	A and B = 		...	B
XVII	$C_6H_5CHOHCH_2$—	H	H	HCl	...
XVIII	$C_6H_5CHOHCH_2$—	A and B = 		...	...
XIX	$C_6H_5CH_2CH(CH_3)$—	H	H	HCl	B
XX	$C_6H_5CH_2CH(CH_3)$—	A and B = 		...	B
XXI	$C_6H_5(CH_2)_3$—	H	H	HCl	A-2
XXII	$C_6H_5(CH_2)_3$—	—$COCH_3$	—$COCH_3$	...	...
XXIII	$C_6H_5OCH_2CH_2$—	H	H	HCl	A-2
XXIV	$(C_6H_5)_2CHCH_2CH_2$—	H	H	HCl	D
XXV	$(C_6H_5)_2CHCH_2CH_2$—	H	—CO— 	...	D
XXVI		H	H	2HCl	A
XXVII		A and B = isopropylidene		...	A
	Miscellaneous compounds				
XXVIII				2HCl	A-1
XXIX				...	B
XXX				...	B

[a] Footnotes to Table I are on p. 332.

M.p., °C.	Formula	Yield, %	Recrystn. solvent[a]	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
235 up[b,c]	$C_7H_9NO \cdot HCl$	32	A	52.67	52.66	6.32	6.25	8.78	8.91
102–103[d]	$C_{11}H_{13}NO_3$	83	B	63.75	63.49	6.32	6.45	6.76	6.82
e	$C_{10}H_{13}NO$	43	...	73.59	73.83	8.03	7.94	8.58	8.79
dec. 161 up[f]	$C_8H_{11}NO \cdot HCl$	31	A	55.33	55.17	6.97	6.96	8.07	8.00
216[g] dec.	$C_8H_{11}NO_2 \cdot HCl$	61	C	50.66	50.70	6.38	6.14	7.39	7.65
245[h] dec.	$C_7H_8ClNO \cdot HCl$	38	B	43.42	43.42	4.67	4.46	7.22	7.30
181–182 dec.	$C_{10}H_{15}NO_4 \cdot HCl$	36	D	48.10	47.86	6.46	6.43	5.61	5.94
156–157[i]	$C_8H_{11}NO \cdot HCl$	2	E	55.33	54.89	6.97	6.78	8.07	8.36
179–180 dec.	$C_{13}H_{13}NO \cdot HCl$	39	A	66.24	66.07	5.99	5.92	5.94	6.12
168–169	$C_{21}H_{15}NO_3$	26	F	76.58	76.49	4.59	4.54	4.25	4.48
78–80	$C_{19}H_{16}N_2O$	70	B	79.14	79.15	5.59	5.52	9.72	9.85
185–186	$C_{19}H_{16}N_2O \cdot HCl$	68	C	70.25	69.93	5.28	4.95	8.63	8.26
80–81	$C_{23}H_{23}NO_4$	34	A	73.19	73.04	6.14	5.75	3.71	3.80
186–187	$C_{27}H_{19}NO_3$	28	A	79.98	80.05	4.72	4.64	3.46	3.69
92–93	$C_8H_{11}NO \cdot C_4H_4O_4$	25	G	56.91	56.55	5.97	5.78	5.53	5.38
111–113[j]	$C_8H_{11}NO \cdot HCl$	6	G	55.33	55.16	6.97	6.99	8.07	8.36
67–68	$C_{16}H_{13}NO_3$	38	B	71.90	72.05	4.90	5.04	5.24	5.44
139–140[k]	$C_8H_{11}NO_2 \cdot HCl$	19	E	50.66	50.70	6.38	6.55	7.39	7.75
l	$C_{11}H_{15}NO_2$	34	...	68.37	67.69	7.82	7.92	7.25	7.03
138–140	$C_9H_{13}NO \cdot HCl$	7	C	57.60	57.61	7.52	7.12	7.47	7.26
75–77	$C_{17}H_{15}NO_3$	15	B	72.58	71.88	5.38	5.23	4.98	4.53
171[m] dec.	$C_9H_{13}NO \cdot HCl$	12	A	57.60	57.97	7.52	7.86	7.47	7.65
65–66	$C_{13}H_{17}NO_3$	42	D	66.36	66.21	7.28	7.45	5.95	6.08
181–182[n] dec.	$C_8H_{11}NO_2$	63	A	50.66	50.96	6.38	6.31	7.39	7.52
174–176 dec.	$C_{15}H_{17}NO \cdot HCl$	57	E	68.30	68.19	6.88	6.82	5.31	5.49
142–144	$C_{22}H_{21}NO_2$	35	H	79.73	79.55	6.39	6.50	4.23	4.40
127–128 dec.	$C_9H_{11}N_3O \cdot 2HCl$[o]	86[p]	I	43.22	42.95	5.24	5.43	16.80	16.80
103	$C_{12}H_{15}N_3O$	71[p]	J	66.34	66.67	6.96	6.63	19.34	19.39
263–264 dec.	$C_8H_{12}N_2O_2 \cdot 2HCl$	29	K	39.85	40.08	5.85	5.62	11.62	11.48
252–253	$C_{18}H_{12}N_2O_6$	23	L	61.36	61.62	3.43	3.20	7.95	8.17
98–100	$C_{10}H_8BrNO_3$	50	D	44.47	49.93	2.98	2.84	5.19	5.14

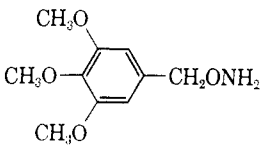
TABLE I (*Footnotes*)

[a] Legend: A, isopropyl alcohol; B, methanol; C, methanol–ether; D, absolute ethanol; E, isopropyl alcohol–anhydrous ether; F, 95% ethanol; G, ethyl acetate; H, ethyl methyl ketone; I, ethanol–ether; J, benzene–Skellysolve C; K, water; and L, dimethylformamide. [b] R. Behrend and K. Leuchs (see ref 22) reported that this product sublimed at 230–260°. [c] The free base boiled at 115–116° (30 mm.), $n^{25}D$ 1.5388. [d] Reported by D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 631 (1955). [e] B.p. 33° (0.1 mm.), $n^{25}D$ 1.5122; see ref. 22. [f] P. Mamalis, J. Green, and D. McHale (see ref. 3b) reported m.p. 233° for this compound prepared in another way and recrystallized from ethanol–water. [g] Since completion of our work the biology and the chemistry of this compound have been reported: C. R. Creveling, J. B. van der Schoot, and S. Udenfriend, *Biochem. Biophys. Res. Comm.*, **8**, 215 (1962); P. Mamalis, J. Green, D. J. Outred, and M. Rix, *J. Chem. Soc.*, 3915 (1962). The latter authors report m.p. 190–192°, considerably below that reported here. [h] A. F. McKay, *et al.*,[5] reported this substance to decompose at 243–244°; P. Mamalis, *et al.*,[3b] reported m.p. 243°. [i] See ref. 8. [j] Decomposed at 119°; unstable at room temperature (*cf.* footnotes 1c and 9); both the maleate and hydrochloride appeared to be stable at −20°. [k] Possible decomposition. [l] B.p. 110–114° (0.15 mm.), $n^{25}D$ 1.5258; G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4223 (1959), reported a 60% yield of product which boiled at 121–125° (1 mm.), $n^{20}D$ 1.5262. [m] B.p. of base, 118–120° (12 mm.), $n^{25}D$ 1.5241; P. Mamalis, J. Green, and D. McHale (see ref. 3b) reported m.p. 168–169° for this product prepared in another way. [n] P. Truitt, L. M. Long, and M. Mattison, *J. Am. Chem. Soc.*, **70**, 2829 (1948), reported a decomposition range of 172–174° for this compound prepared *via* method C. [o] The monohydrochloride decomposed at 141° after previous sintering. [p] Crude yield.

aralkylhydroxylamines, a number of which are related to amines of pharmacologic interest.

Four methods of synthesizing O-substituted hydroxylamines were utilized: (A) alkylation of acetone oxime followed by acid hydrolysis[7]; (B) alkylation of N-hydroxyphthalimide followed by hydrazinolysis[5]; (C) reaction of chloramine with a sodium alkoxide[8]; and (D) alkylation of benzohydroxamic acid followed by acid hydrolysis.[7] The choice of method, decided in most cases by trial and error, was determined by the nature of the alkylating halide and the stability of the final product. Method A was invariably tried first and the other methods were used when method A failed to give appreciable yields of the desired product.

Table I lists the compounds prepared, together with a number of derivatives and intermediates. The structures prepared included several close analogs of interesting pharmacodynamic agents (*e.g.*, VII, XVII, and XXIV) as well as the known phenelzine analog



VII.

Mescaline analog

$C_6H_5CHOHCH_2ONH_2$	$(C_6H_5)_2CHCH_2CH_2ONH_2$
XVII	XXIV
Pressor amine analog	Diphenhydramine analog

$C_6H_5CH_2CH_2ONH_2$ (XV)[1e] and the pheniprazine analog $C_6H_5CH_2CH(CH_3)ONH_2$ (XIX).[9]

Pharmacology.—The LD_{50} determinations (Table II) of these compounds, given intraperitoneally in mice, and the observation of concomitant gross behavioral changes were carried out as previously described.[10] Only compounds IV, V, VII, and VIII displayed stimulant effects expected by analogy with the related sympathomimetic amines or hydrazines, and even here the effects were slight and, in most cases, were converted to depression when the doses were raised. These four compounds showed little of the anorexigenic activity characteristic of related sympathomimetic amines. In the latter test, dogs, on a once-a-day 30 min. feeding schedule, were given the compounds orally 1 hr. prior to presentation of food. The amount of food consumed during the 30 min. feeding period was recorded. VI, VII, and XXVII were about $^1/_{35}$ as effective as amphetamine in inhibiting food consumption, while the remainder had amphetamine indices of less than $^1/_{50}$. None of the compounds had significant effects (*i.e.*, more than 50% increase) on motor activity of mice as measured in an actophotometer,[10] when given intraperitoneally at 20% of the LD_{50}.

Because of structural similarities to hydrazines which are effective inhibitors of monoamine oxidase, these compounds were subjected to a battery of *in vitro* enzyme tests. As can be seen from Table II, none of the compounds tested as monoamine oxidase inhibitors[12] caused significant inhibition of this enzyme. However, against the enzyme 5-hydroxytryptophan decarboxylase[13] these compounds were in general very effective. It is interesting that in the nine cases in which histidine decarboxylase inhibition[14] was also measured, using a bacterial enzyme, only one compound (IV) showed significant activity. These nine compounds with their per cent inhibition at 10^{-3} *M* concentration are: IV (100%), V (0%), VI (24%), VIII (36%), IX (58%), XVII (0%), XIX (23%), XXI (18%), XXIV (0%), and XXVII (12%). These results are to be contrasted with the high level of inhibition reported for *m*-hydroxy-O-benzylhydroxylamine against both nonspecific (guinea pig kidney) and specific (mast cell) histidine decarboxylase.[15]

Table II also records the effects of the more potent decarboxylase inhibitors on rat-brain serotonin levels.[12,16] Representative members of these compounds were tested also for inhibition of tryptophan

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(9) Since our work was completed this and related compound VIII have been reported, B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 1381 (1962).

(10) R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964). Table I, footnotes a and b.

(11) R. B. Moffett and P. H. Seay, *ibid.*, **2**, 229 (1960).

(12) J. B. Hester, M. E. Greig, W. C. Anthony, R. V. Heinzelman, and J. Szmuszkovicz, *ibid.*, **7**, 274 (1964).

(13) C. T. Clark, H. Weissbach, and S. Udenfriend, *J. Biol. Chem.*, **210**, 139 (1954).

(14) "Enzymes, Enzyme Reagents," Manual published by Worthington Biochemical Corp., Freehold, N. J., Section 4.1.1.22. The enzyme was purchased from Worthington and these assays were performed by Bio-Science Labs., Los Angeles, Calif.

(15) J. D. Reid and D. M. Shepherd, *Life Sciences*, **2**, 5 (1963).

(16) D. J. Drain and co-workers[17] have reported that *m*-hydroxy-O-benzylhydroxylamine, which is a potent inhibitor of dopa decarboxylase and 5-hydroxytryptophan decarboxylase, has little effect on brain serotonin levels.

(17) D. J. Drain, M. Horlington, R. Lazere, and G. A. Poulter, *Life Sciences*, **1**, 93 (1962).

TABLE II

PHARMACOLOGY

Compd. no.	LD_{50} i.p. mice	Enzyme inhibition, %: Monoamine oxidase at 10^{-3} M	5-Hydroxytryptophan decarboxylase at 10^{-2} M	5-Hydroxytryptophan decarboxylase I_{50} (M)	Elevation of rat brain serotonin: Dose (route), mg./kg.	Elevation of rat brain serotonin: %	Anorexigenic % inhibition at 5 mg./kg., p.o. (dogs)
I	650	0	100	2.3×10^{-6}	325 (s.c.)	0	13
II	>1000	15	100	2×10^{-4}	500 (i.p.)	42	
					500 (p.o.)	3	
III	533[a]	...	...	...			
IV	200[b]	−16	100	4×10^{-5}			0
V	650[c]	0	97	5×10^{-4}			0
VI	650	20	100	2×10^{-6}	325 (i.p.)	33	19
VII	1000[d]	13	100	2×10^{-6}	500 (i.p.)	10	18
VIII	533[e]	13	100	1×10^{-5}	167 (i.p.)	0	
IX	533	0	85	5×10^{-5}	266 (i.p.)	12	
X	>1000	...	...	...			0
XI	>1000	7	29	...			0
XII	650[f]	0	0				
XIII	>1000	0	10				
XIV	1000	...	...				0
XVa	650	17	100	5×10^{-7}	325 (i.p.)	19	0
XVI	>1000	...	...	...			0
XVII	650	16	0				0
XVIII	650[g]	0	20				0
XIX	650[h]	0	100	1×10^{-5}	325 (i.p.)	10	
XX	1000	...	...				0
XXI	533	20	100	2.5×10^{-6}	266 (i.p.)	29	
					266 (p.o.)	0	
XXII	>1000	10	98	5×10^{-4}	500 (i.p.)	0	
XXIII	233[i]	0	100	4×10^{-7}	116 (i.p.)	0	0
XXIV	233[j]	38	100	4×10^{-6}	117 (i.p.)	0	0
XXVI	533[k]	...					0
XXVII	650[l]	...					25
XXVIII	300	14	100	1×10^{-4}	150 (i.p.)	8	0
XXIX	>1000	...	...				14
XXX	>1000	...	...				...

[a] Depression at 100 mg./kg.; extreme depression at 300 mg./kg. [b] Stimulation and tremor at 100 mg./kg. [c] Stimulation at 100 mg./kg.; extreme depression at 300 mg./kg. [d] Stimulation at 30 mg./kg., extreme depression at 300 mg./kg. [e] Stimulation at 100 mg./kg. [f] Irritation at 10 mg./kg.; depression at 30 mg./kg., extreme depression at 300 mg./kg. [g] Depression at 100 mg./kg., sleep at 300 mg./kg. [h] Depression at 100 mg./kg., sleep at 1000 mg./kg. [i] Depression at 100 mg./kg., clonic convulsion at 300 mg./kg. [j] Depression at 100 mg./kg., extreme depression at 300 mg./kg. [k] Depression at 100 mg./kg., extreme depression at 300 mg./kg. [l] Analgesia at 100 mg./kg., sleep at 300 mg./kg.

5-hydroxylase (liver)[18] and glutamic dehydrogenase[19] and were essentially inactive.

In our toxicology studies, compounds XVII and XXIV showed none of the properties characteristic of ephedrine or diphenhydramine, respectively, and so were not studied further in this direction.

From these data it appears clear that these aminoxy compounds bear little biological resemblance to their amine or hydrazine counterparts.

Experimental[20,21]

General Procedure for Method A.—Equimolar amounts of the benzyl halide and acetoxime in an ethanolic sodium ethoxide solution (A-1) or in a solution of sodium hydroxide in 1:2 aqueous acetone (A-2) were heated under reflux. An aqueous acid suspension of the crude product was subjected to steam distillation and the hydrolysis product was isolated as described for O-benzylhydroxylamine.[22]

O-Benzhydrylhydroxylamine Hydrochloride (IX). Method B.—A stirred solution of 32.6 g. (0.2 mole) of N-hydroxyphthalimide,[23] 40.5 g. (0.2 mole) of chlorodiphenylmethane, and 44.5 g. (0.44 mole) of triethylamine in 300 ml. of dimethylformamide was slowly heated to 90° in 1 hr., maintained at 90° for 30 min., cooled, and poured into 1 l. of cold water. The precipitated oil solidified on standing. Recrystallization from ethanol gave 17.4 g. (26%) of pure N-benzhydryloxyphthalimide (X).

A solution of 18.4 g. (0.056 mole) of X in 90 ml. of dimethylformamide and 300 ml. of methanol was warmed to 60°, treated with 6.1 g. (0.12 mole) of hydrazine hydrate, and allowed to cool to room temperature for 3 hr. The stirred mixture was acidified with 2 *N* hydrochloric acid to pH 2, filtered to remove phthalylhydrazide, and the filtrate evaporated to dryness under reduced pressure. The semisolid residue was treated with 100 ml. of 2 *N* sodium hydroxide solution and extracted with ether. After washing with water, the combined ether extracts were dried over anhydrous potassium carbonate and treated with ethereal hydrogen chloride to precipitate IX.

O-4-Methoxybenzylhydroxylamine Hydrochloride (V). Method C.—Sodium, 5.7 g. (0.25 g.-atom), was dissolved in 300 g. (2.17 moles) of warm anisyl alcohol and the cooled mixture was then treated with an anhydrous solution of 0.25 mole of chloramine[24] in 250 ml. of ether. The mixture was stirred at room temperature for 1.5 hr., then poured into 3.5 l. of anhydrous ether and filtered to remove sodium chloride. Treatment of the filtrate with ethereal hydrogen chloride precipitated the product as the hydrochloride.

(18) R. A. Freedland, I. M. Wadzinski, and H. A. Waisman, *Biochem. Biophys. Res. Commun.*, **5**, 94 (1961).

(19) J. H. Copenhaver, W. H. McShan, and R. K. Meyer, *J. Biol. Chem.*, **183**, 73 (1950).

(20) All melting points are corrected.

(21) Physical constants, analyses, recrystallization solvents, and references to previous preparations are listed in Table I.

(22) R. Behrend and K. Leuchs, *Ann.*, **257**, 203 (1890).

(23) W. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

(24) Prepared by the method of G. H. Coleman and H. L. Johnson, *Inorg. Syn.*, **1**, 59 (1940).

2-Pyridinealdehyde O-Benzhydryloxime (XI).—A solution of 11.8 g. (0.05 mole) of O-benzhydrylhydroxylamine hydrochloride (IX) in 250 ml. of absolute ethanol was treated first with a solution of 5.4 g. (0.05 mole) of 2-pyridinealdehyde in ethanol, then 4.1 g. (0.05 mole) of sodium acetate in 30 ml. of water. The mixture was stirred at room temperature for 1 hr., then poured into 3 l. of cold water, and extracted with four 500-ml. portions of ether. The combined ether solutions were dried over anhydrous magnesium sulfate and evaporated to give XI. Compounds XII and XIII were prepared similarly.

N-(Triphenylmethoxy)phthalimide (XIV).—This product was prepared from N-hydroxyphthalimide and chlorotriphenylmethane *via* B, described above. However no pure O-triphenylmethylhydroxylamine could be isolated following hydrazinolysis.

O-3,3-Diphenylpropylhydroxylamine Hydrochloride (XXIV). Method D.—To a cold solution of 4 g. (0.1 mole) of sodium hydroxide in 300 ml. of 70% ethanol was added 13.7 g. (0.1 mole) of benzohydroxamic acid and 27.5 g. (0.1 mole) of 3,3-diphenylpropyl bromide.[25] The mixture was heated under reflux for 5 hr., cooled, poured into 1 l. of cold water, and extracted with three 500-ml. portions of ethyl acetate. The combined ethyl acetate solutions were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residue from ethyl methyl ketone gave 11.5 g. (35%) of pure 1,1-diphenyl-3-benzamidooxypropane (XXV).

A mixture of 11.5 g. of XXV and 35 ml. of 6% ethanolic hydrogen chloride was heated under reflux for 1 hr., then evaporated to dryness. The oily residue was triturated thoroughly with anhydrous ether and the insoluble product, O-3,3-diphenylpropylhydroxylamine hydrochloride (XXIV) was separated by filtration.

1-Methyl-2-(aminooxymethyl)benzimidazole Dihydrochloride (XXVI). Modified Method A.—A slurry of 3.8 g. (0.04 mole) of sodioacetoxime in 30 ml. of butanol was treated with 7.2 g. (0.04 mole) of 1-methyl-2-chloromethylbenzimidazole,[26] stirred 0.5 hr. at room temperature and 2.5 hr. on a steam bath, then allowed to stand at room temperature overnight. Solvent was removed under reduced pressure and the residue was mixed with 50 ml. of water and extracted with ether. The combined ether solutions were dried over anhydrous magnesium sulfate and evaporated. Recrystallization from benzene–Skellysolve C gave pure 1-methyl-2-(isopropylideneaminooxymethyl)benzimidazole (XXVII).

A solution of 11.7 g. of XXVII in 75 ml. of 6 *N* hydrochloric acid was steam distilled for 2 hr. The residual solution was evaporated to dryness under reduced pressure and the residue was treated with 50 ml. of absolute ethanol and again evaporated. Recrystallization of the residue from absolute ethanol gave a first crop, A, and addition of ether to the filtrate gave a second crop, B.

Several recrystallizations of A (the minor fraction) from 95% ethanol gave the monohydrochloride as fine white crystals. Four recrystallizations of B (the major fraction) from ethanol–ether gave the pure dihydrochloride (XXVI) as fluffy white needles.

1,2-Bis(phthalimidooxy)ethane (XXIX).—A solution of 49 g. (0.3 mole) of N-hydroxyphthalimide[23] and 56.5 g. (0.3 mole) of 1,2-dibromoethane in 750 ml. of dimethylformamide was treated with 60.5 g. (0.6 mole) of triethylamine, then stirred, warmed to 90° over a 1-hr. period, and maintained at 90° for 0.5 hr. The cooled solution was poured into 3 l. of ice–water and the precipitated solid was separated by filtration and recrystallized to give pure XXIX.

N-(2-Bromoethoxy)phthalimide (XXX).—A solution of 1128 g. (6 moles) of 1,2-dibromoethane and 98 g. (0.6 mole) of N-hydroxyphthalimide in 1.5 l. of dimethylformamide was treated with 121 g. (1.2 moles) of triethylamine, stirred, warmed slowly to 90° over a 1-hr. period, then maintained at 90° for 0.5 hr. The cooled solution was poured into 6 l. of ice–water and the precipitate, which crystallized on standing, was recrystallized to give pure XXX.

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(25) O. Exner, M. Bovička, and M. Protiva, *Collection Czech. Chem. Commun.*, **18**, 270 (1953).

(26) H. Richter, German Patent 1,078,132 (March 24, 1960).