Synthesis of 1-Methyl-1-(substituted benzyl)hydrazines

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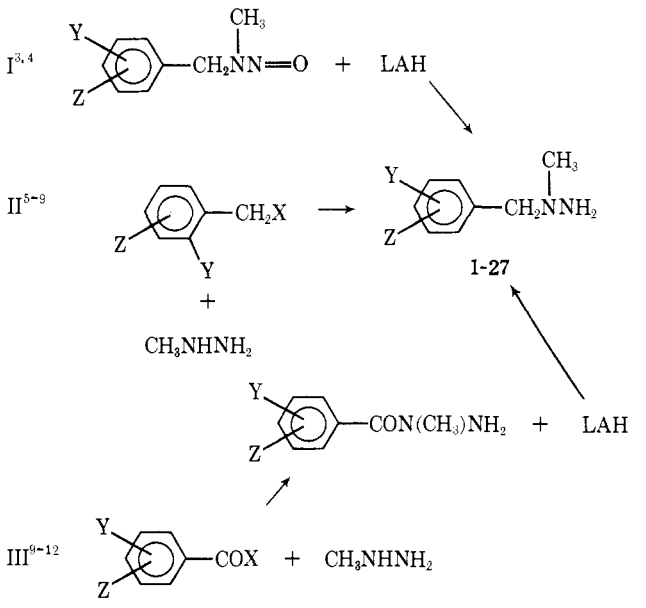
Received February 18, 1971

A series of 1-methyl-1-(substituted benzyl)hydrazines was prepared. A superior method for the preparation of 1-methyl-1-(ortho-substituted benzyl)hydrazines consists of the reaction of an ortho-substituted benzyl halide with methylhydrazine. Some of the aryl-substituted compounds possessed MAO inhibitory activity comparable to iproniazide.

In connection with other synthetic studies underway in this lab, we required a large variety of 1-methyl-1-(substituted benzyl)hydrazines in quantities of several moles. A number of the products were tested for monoamine oxidase (MAO) inhibitory activity. Methods for the synthesis of substituted hydrazines have been reviewed.[1,2] We undertook the investigation of the 3 routes shown in Scheme I for the particular hydrazines desired.

SCHEME I



If the *N*-Me-substituted benzylamine is commercially available, route I, the LAH redn of the *N*-nitrosoamine,[13] is a useful lab sequence up to a scale of 1.5 moles.[14] On a scale larger than this, the prepn is cumbersome and the work-up tedious. It has also been noted that the reaction is characterized by a long induction period followed by a rather violent initial reaction.[15,16] We recommend that 1 mole of the nitrosoamine be added to a gently refluxing, stirred, Et_2O suspension of 2 moles of LAH and that the H_2 evolution be monitored with a dry gas meter.[17] The H_2 evolution is due to the lability of the first 2 H transferred in the redn. This is also the reason a 2:1 ratio of LAH to nitrosoamine is necessary for high yields. Under these conditions no appreciable latent period has been obsd.

We investigated the second route because of the following facts: (1) a large number of investigators have alkylated hydrazine hydrate (in large excess) and obtained appreciable yields of monoalkyl hydrazines;[6-8] (2) at least one group had prepared benzylhydrazine (61%) and 1,1-dibenzylhydrazine (22%);[8] (3) the commercial availability of methylhydrazine.

A benzyl halide with an ortho substituent larger than F or H gives high yields of the desired product when treated with 3–4 equiv of methylhydrazine in anhyd EtOH (or THF) soln. In contrast, the unhindered benzyl chloride, α-chloro-*o*-fluorotoluene, and 2-(chloromethyl)pyridine gave none of the desired product due to the formation of the 1,1,1-trisubstituted hydrazinium chloride. The presence of addnl aromatic substitution did not interfere with the reaction. Some of the ortho substituents used include: Cl, Br, CF_3, CH_3, OCH_3, SCH_3. Route II is the method of choice for 1-methyl-1-(ortho-substituted benzyl)hydrazines from the standpoints of convenience, ease, time required, safety, and scale. The only limit on scale is the size of the available app. See Table I for data.

The third route can be used on the same scale as the LAH redn in route I and is convenient when the aryl acid, anhydride, or aroyl chloride are commercial. Smith and coworkers[10] have prepd benzoic acid 1-methylhydrazide from BzOH and methylhydrazine in the presence of DCI; Hinman and Fulton[9] have prepd the same using the anhydrides and we have used aroyl halides. Hinman[12] has prepd 1-benzyl-1-methylhydrazine (**1**) in 55% yield from pure benzoic acid 1-

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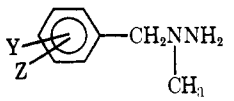
(14) The authors carried out this reaction on 1.5 moles of *N*-nitrosoamine with 3 moles of LAH in a 5-l. 3-neck flask without difficulty.
(15) C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Amer. Chem. Soc.*, **77**, 4100 (1955).
(16) H. Zimmer, L. T. Audrieth, M. Zimmer, and R. A. Rowe, *ibid.*, **77**, 790 (1955).
(17) This was a Model S110 dry gas meter calibrated in liters. It was designed for propane, butane, or natural gas and was purchased from Rockwell Manufacturing Co., Measurement and Control Division, Pittsburgh, Pa. 75208. It was fitted with hose connections after purchase.

TABLE I



Compd	Y	Z	Method	Yield, %	Empirical formula	Bp (mm) (mp of salt) of free base, °C	Analyses
1	H	H	I	85 (59)[a]	$C_8H_{12}N_2$	103–105 (15)	C, H
			III	55[b]			
2	2-CH_3	H	III[c]	84	$C_9H_{14}N_2 \cdot HCl$	99–100 (9) (112–113)	C, H
3	2-Cl	H	I	90	$C_8H_{11}ClN_2$	108–110 (3)	C, H
			II	92			
4	3-Cl	H	I	92	$C_8H_{11}ClN_2 \cdot 0.5HO_2CCO_2H$	115–120 (8) (161–163)	C, H, N
5	4-Cl	H	III[c]	60	$C_8H_{11}ClN_2$	110–112 (3)	C, H
			I	80			
6	2-Br	H	II[d]	60[e,f]	$C_8H_{11}Br_2N_2$	120–122 (4)	C, H
7	2-CF_3	H	II[d]	64[g]	$C_9H_{11}F_3N_2$	98–102 (12)	C, H
8	2-CH_3O	H	I	80	$C_9H_{14}N_2O \cdot 0.5HO_2CCO_2H$	85–87 (1) (163–165)	C, H, N
9	3-CH_3O	H	III[c]	54	$C_9H_{14}N_2O$	78–85 (0.275)	C, H
10	4-CH_3O	H	I	90	$C_9H_{14}N_2O \cdot 0.5HO_2CCO_2H$	92–94 (1.5) (159–161)	C, H, N
11	2-CH_3S	H	I	87	$C_9H_{14}N_2S \cdot 0.5HO_2CCO_2H$	101–105 (0.6) (156–158)	C, H, N
12	3-CH_3S	H	III[c]	49	$C_9H_{14}N_2S$	93–94 (0.3)	C, H
13	4-CH_3S	H	III[c]	66	$C_9H_{14}N_2S$	94–96 (0.3)	C, H
14	2-C_2H_5-S	H	II[d]	85	$C_{10}H_{16}N_2S$	93–100 (3)	C, H
15	2-*i*-C_3H_7-S	H	II[d]	87	$C_{11}H_{18}N_2S$	93–99 (0.5)	C, H
16	2-C_3H_7-S	H	II[d]	85	$C_{11}H_{18}N_2S \cdot 0.5HO_2CCO_2H$	112–113 (0.5) (130–132)	C, H, N
17	2-Allyl-S	H	II[d]	83	$C_{11}H_{16}N_2S \cdot 0.5HO_2CCO_2H$	81–83 (0.2) (137–139)	C, H, N
18	2-Cl	3-CH_3O	II[d]	80	$C_9H_{13}ClN_2O$	102–103 (0.6)	C, H, N
19	2-Cl	3-Cl	II[e]	60[h]	$C_8H_{10}Cl_2N_2$	88.5–89.5 (0.375)	C, H
20	2-Cl	4-Cl	II	95	$C_8H_{10}Cl_2N_2 \cdot HCl$	89–90 (0.2)	C, H
21	2-Cl	5-Cl	II[e]	53	$C_8H_{10}Cl_2N_2$	85–88 (0.35)	C, H
22	2-Cl	6-Cl	II	93	$C_8H_{10}Cl_2N_2$	81–84 (0.40)	C, H, N
23	2-CH_3O	4-CH_3O	II[d]	75	$C_{10}H_{16}N_2O_2 \cdot 0.5HO_2CCO_2H$	104–104.5 (0.45) (142–143)	C, H, N
24	2-CH_3O	5-CH_3O	II[d]	72	$C_{10}H_{16}N_2O_2$	103–104 (0.45)	C, H
25	3-CH_3O	4-CH_3O	I	87	$C_{10}H_{16}N_2O_2 \cdot 0.5HO_2CCO_2H$	110–111 (0.45) (141–143)	C, H, N
26	2-Cl	6-F	II[d]	83	$C_8H_{10}ClFN_2$	96–97 (4)	C, H, N
27	2-CH_3	3-CH_3O	II[d]	70	$C_{10}H_{16}N_2O$	71–72 (0.15)	C, H, N

[a] This yield was reported in ref 18. The use of insufficient LAH accounts for the poor yield. [b] Ref 12. The yield was based on pure benzoic acid 1-methylhydrazide. [c] Yield from the starting carboxylic acid. [d] Yield is from the starting benzyl alcohol. [e] Yield is from the starting toluene. [f] The *o*,α-dibromotoluene, prepd using NBS contained *o*,α,α-tribromotoluene by nmr (CCl_4) and *o*-bromobenzaldehyde (*o*-bromobenzyl)methylhydrazone (**28**) was isolated from the reaction; bp 178–181° (0.65 mm): *Anal.* ($C_{15}H_{14}Br_2N_2$) C, H. [g] The *o*-trifluoromethylbenzyl alcohol with $SOCl_2$ (uncatalyzed) in $CHCl_3$ resulted in incomplete conversion to the chloride. [h] The reaction of 2,3-dichlorotoluene with Br_2 and light gave a mixt of unreacted toluene (29%), α-bromo-2,3-dichlorotoluene (58%), and α,α-dibromo-2,3-dichlorotoluene (13%) by vpc.

methylhydrazide by this route. This route can be used with any substituents compatible with LAH and any aromatic orientation. The yields are usually considerably lower.

Yields are based on isolated, analyzed products, which were used successfully in further reactions. As noted by others,[15] hydrazines sometimes analyze with difficulty. If the free base did not analyze satisfactorily, the hydrazines were converted to the hemioxalate or hydrochloride.

Biological Results.—Biel and coworkers had found the *in vitro* inhibition of MAO activity of 1-benzyl-1-methylhydrazine (**1**) to be less than that of *N*-isopropyl-*N'*-isonicotinoylhydrazine (iproniazid) and much less active than other hydrazines included in their work.[18] In Biel's series of more active compounds, "nuclear substitution generally reduced MAO inhibitory activity." A number of the hydrazines prepd in our lab were tested for *in vitro* MAO inhibitory activity using a minor modification of the procedure described by Glowinski, *et al.*[19] In this series, some nuclear substitutions enhanced MAO inhibitory activity. Thus **3**, **4**, **5**, **6**, **10**, and **18** were as potent as iproniazide and **1**, **8**, **9**, and **11** were markedly less potent at 10^{-5} and 10^{-4} *M* concn. See Table II for data.

(18) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Amer. Chem. Soc.*, **81**, 2805 (1959).

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Experimental Section[20]

In Vitro **MAO Test Method.**—Whole mouse brain was homogenized in 6 vols of ice-cold 0.9% KCl soln containing 2 mg/ml of Versene. A 0.1-ml aliquot of the homogenate was added to a mixt of 0.3 ml of 0.9% KCl, 0.7 mg/ml of Versene, and 0.55 ml of a soln of the test compd in 0.05 *M* sodium phosphate buffer of pH 7.3. The mixt was shaken at 37° for 20 min and 0.1 μg of L-norepinephrine-*methylene*-^{14}C (169 μCi/mg) in 0.1 ml of 2 mg/ml of Versene soln was added to the mixt, and incubation was contd for 45 min. The reaction was stopped by the addn of 1 ml of 0.2 *M* NaOAc contg 2 ml/ml of ascorbic acid (pH 4.0). The mixt was centrifuged and the supernatent was passed through a column of Dowex 50 (H^+) 4 × 35 mm. A 1-ml aliquot of the effluent contg the ^{14}C deaminated products was added to 15 ml

(20) Melting and boiling points are uncorrected. The mp were detd using a Thomas-Hoover mp apparatus. Ir spectra were recorded on a Beckman Model IR-9 spectrometer. Nmr spectra were recorded on a Varian Associates A-60 spectrometer in $CDCl_3$. We wish to acknowledge the following: spectra were obtained by Dr. J. M. Vandenbelt and staff; microanalyses were performed by Mr. C. E. Childs and staff. The redns were carried out in round bottom flasks, equipped with a liquid sealed stirrer, thermometer, pressure equalized dropping funnel, and a reflux condenser connected to a dry gas meter.

TABLE II

In Vitro INHIBITION OF MOUSE BRAIN MONOAMINE OXIDASE

	Molar concn				
	10^{-5}	5×10^{-5}	10^{-4}	5×10^{-4}	I_{50}[a]
Test compd					
Iproniazide	37	88	97		1.5
1	32		75	97	2.5
3	49		92	97	1.0
4	61		90	99	0.4
5	56		95	100	0.6
6	39		87	100	1.7
8	14		51	86	7.0
9	22		72	93	3.5
10	46		87	98	1.2
11	17		70	94	4.0
18	65	87	93	100	0.3

[a] Concn $\times 10^{-5}$ *M* for 50% inhibition of MAO activity.

of scintillation fluid and the radioactivity was measured. A blank contg boiled enzyme was carried through the entire procedure. The reported results are the averages of replicates and the average variation in the same experiment was ±5%. The I_{50} was derived from a graph of the log concn/per cent inhibition.

Chemistry. I.—The *N*-nitrosoamines were prepd by the method of Hartman and Roll.[13] HCl was replaced by AcOH, the reaction was carried out under N_2 (HONO is lost by reaction with O_2), and the mixt was heated to 60–70° after the addn of the $NaNO_2$ soln. The compds were distd and anald, but can be used crude in the redns. The nmr spectra show split Me and CH_2 peaks.

Typical LAH Redn of the *N*-Nitrosoamine. 1-(*m*-Chlorobenzyl)-1-methylhydrazine (4).—A suspension of LAH (114 g, 3.0 moles) in anhyd Et_2O (2.5 l.) was heated to a gentle reflux under N_2, and a soln of *m*-chloro-*N*-methyl-*N*-nitrosobenzylamine (268 g, 1.45 moles) in THF (500 ml) was added dropwise over 3–4 hr. H_2 evoln began immediately. The mixt was refluxed overnight, cooled under N_2, and H_2O (120 ml) was added *dropwise with caution* followed by 20% NaOH (90 ml) and H_2O (420 ml). The slurry was filtered, and the filtrate concd and distd to yield **4**, 227 g (92%). See Table I for physical constants. The yields in Table I are based on starting nitroso compd.

II.—The benzyl halides were prepd by the reaction of the benzyl alcohol with excess concd HCl, HBr, or with excess $SOCl_2$ (pyridine catalysis in $CHCl_3$ or 1,2-$C_2H_4Cl_2$ soln should be used particularly for ortho-substituted examples—see **7**, Table I). If the toluene was the commercial starting material, it was treated with NBS (used crude after removal of the succinimide and CCl_4) or with Br_2 and light. The presence of the α,α-dibromotoluene in the NBS product reduces the yield.

Typical Alkylation of Methylhydrazine with an Ortho-Substituted Benzyl Halide. 1-(*o*-Chlorobenzyl)-1-methylhydrazine (3).—To a mixt of methyl hydrazine (161 g, 3.5 moles) and anhyd EtOH was added with stirring *o*,α-dichlorotoluene (161 g, 1.0 mole). The mixt was refluxed 1 hr after the temp began to fall. It was concd *in vacuo*, made alk (50% NaOH), and extd (Et_2O). The exts were washed with H_2O, dried ($MgSO_4$), concd, and distd to yield **3**, 158 g (92%). See Table I for physical characteristics. The yields in Table I are based on the starting alcohol or toluene with the exception of **3**, **20**, and **22** where the benzyl chlorides were commercial.

III.—The aroyl chlorides were prepd by the use of $SOCl_2$ on the commercial arom carboxylic acids and were used crude or were commercially available.

Typical Aroylation of Methylhydrazine and LAH Redn of the Resulting Mixt. 1-(*m*-Methoxybenzyl)-1-methylhydrazine (9).—A mixt of methylhydrazine (170 g, 3.7 moles) and H_2O (680 g) was cooled to 0° and with stirring a soln of crude *m*-methoxybenzoyl chloride (300 g, 1.76 moles) in THF (400 ml) was added. The mixt was stirred overnight and extd (Et_2O). The exts were dried ($MgSO_4$), concd, and used crude. A mixt of LAH (114 g, 3.0 moles) and THF (1.5 l.) was heated to 30–40° under N_2, and a soln of the crude *m*-methoxybenzoic acid 1-methylhydrazide in THF (300 ml) was added dropwise. The H_2 evoln was monitored,[17] and the mixt was refluxed overnight, cooled under N_2, and worked up as in I to yield **9**, 158 g (47%). See Table I for physical data. The yields in Table I are based on the starting aryl carboxylic acid or acid chloride if commercial.

Synthesis and Hypotensive Activity of Benzamidopiperidylethylindoles[1]

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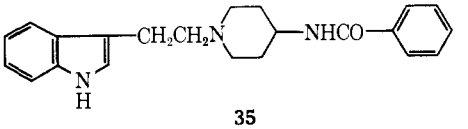
Received March 12, 1971

The synthesis and hypotensive activity of a series of indole piperidine amides are described. One member of the series—3-[2(4-benzamidopiperid-1-yl)ethyl]indole (indoramin) (**35**)—has undergone intensive pharmacological investigation. The sustained hypotensive action of **35** is believed to be due to a combination of local anesthetic and α-receptor blocking properties.

A continuing interest in indole derivatives incorporating a tryptamine residue as potential antihypertensive agents stemmed from our work with 1,4-bis(indolylethyl)piperidines.[2] In that series, the indolylethyl moiety attached to the piperidine 4 position was not an essential feature for retention of antihypertensive activity. It could, for instance, be replaced without detriment by a 3-carbethoxy-2,4-dimethylpyrrol-5-ylethyl group.[3]

We decided to retain the indolylethylpiperidine moiety of the earlier series while varying the 4 substituent of the piperidine ring, concentrating in particular on amino derivatives, which had received little attention in the past. It was soon discovered that the 4-benzamido derivative **35** (indoramin) was a potent hypotensive agent. Detailed pharmacological investigation of **35** has since revealed a combination of properties that seems likely to be advantageous in the treatment of cardiovascular disease in man.[4–6]

This compound then became the prototype for an extensive synthetic program designed to investigate structure–activity relationships and to optimize activity.



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(1) Presented in part at the IV International Congress of Medicinal Chemistry, Clermont-Ferrand, France, Sept 1968. J. L. Archibald, *Chim. Ther.*, **3**, 397 (1968).

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(3) J. L. Archibald, *J. Heterocycl. Chem.*, **3**, 409 (1966).

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(5) B. J. Alps, E. S. Johnson, and A. B. Wilson, *Brit. J. Pharmacol.*, **40**, 151P (1970).

(6) B. J. Alps, M. Hill, E. S. Johnson, and A. B. Wilson, *ibid.*, **40**, 153P (1970).