Journal of Medicinal and Pharmaceutical Chemistry

VOL. 3, No. 2 (1961)

Monoamine Oxidase Inhibitors—II. Some Amino and Dialkylaminobenzyl Hydrazines and their Acyl Derivatives

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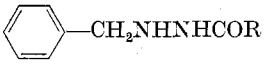
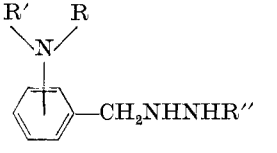
In the first paper of this series,[1] it was shown that acyl derivatives of benzylhydrazine (I) are potent monoamine oxidase (MAO) inhibitors. These compounds are characterized by a long duration of activity (more than 4 days and usually up to 30 days in the test described)[2] and are classified as irreversible MAO inhibitors.[3] Udenfriend and co-workers[3,4] have shown that some alkaloids of the Harmala group are reversible and short-acting MAO inhibitors. We have now found that by basic substitution in the phenyl ring of aralkylhydrazines and their acyl derivatives, this class of long-acting MAO inhibitors is transformed into a class of *short-acting* MAO inhibitors with activities of less than 24 hours. Other classes of synthetic MAO inhibitors have been described, as for example, the cyclopropylamine derivatives,[5] and basically substituted hydrazines prepared by a number of workers,[6] but to the best of our knowledge all of these are of the long-acting irreversible type.



(I)

R = pyridyl
isoxazolyl, etc.



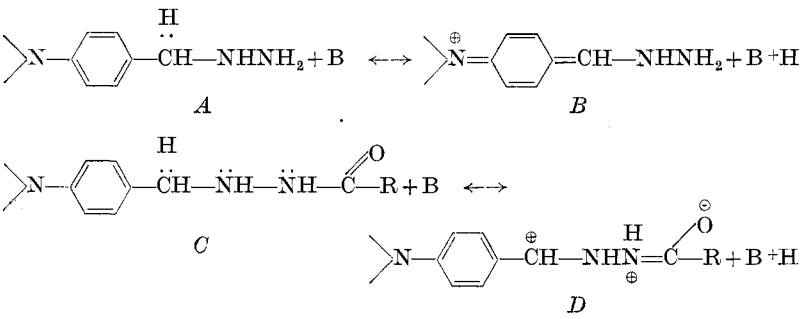
(II)

R′ = H or alkyl
R″ = H, acyl

The short duration of action of this new group of substances possibly lies in their susceptibility to oxidative attack. Benzylhydrazine itself is not a notably stable substance but N^2 substitution with a not too easily hydrolyzed acyl residue, as for example,

a pivaloyl or 5-methyl-3-isoxazolylcarbonyl, considerably stabilizes the compound.[1] The 2- and 4-amino substituted compounds are considerably less stable and acylation at N^2 again lends stability. The 3-amino compounds are somewhat more stable.

These differences in stability can be explained by the different tendencies in the direction of electron shift under basic conditions,



the basic conditions being supplied by another molecule of the compound itself. The quinonoid form *B* would be exceedingly susceptible to oxidation, whereas the hydrazonium ion *D*, not having a quinonoid form and furthermore being capable of resonance stabilization, would be less susceptible to oxidation. An electron shift of *C* in the opposite direction would give a quinonoid form but presumably the shift $C \rightarrow D$ occurs to a sufficient extent to stabilize the compound considerably. With lengthening of the alkylene bridge* between the benzene ring and the hydrazine nitrogen, these equilibria are not effective and the dialkylamino aralkylhydrazines become, as expected, more stable. This is reflected in their intermediate length of MAO inhibitor activity (more than 24 h, less than 5 days).

At present, we have no information on the metabolism of these basically substituted benzylhydrazines. It is known from metabolic studies on 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine† that the benzyl residue is oxidized to benzoic acid and eliminated as hippuric acid.[7] It would seem a fair presumption

* These compounds prepared by Dr. J. Finkelstein will be described in a subsequent publication.

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Table I. Hydrazones ($R' = NNHCOR_2''$)[a, b]

R′	R″CO	Formula	Colour	m.p., °C	% Yield	Analysis			
						Calcd.		Found	
						C	H	C	H
2-Dimethylamino-benzylidene	5-Methyl-3-isoxazolyl-carbonyl	$C_{14}H_{16}N_4O_2$	yellow	194–195	67	61·7	5·9	61·8	5·2
3-Dimethylamino-benzylidene	,,	$C_{14}H_{16}N_4O_2$	yellow	192–193	93	61·7	5·9	62·1	6·0
4-Dimethylamino-benzylidene	,,	$C_{14}H_{16}N_4O_2$	yellow	212–213	97	61·7	5·9	61·6	5·5
4-Diethylamino-benzylidene	,,	$C_{16}H_{20}N_4O_2$	pale yellow	169–170	97	64·0	6·7	64·3	6·2
3-Pyridylmethyl-idene[c]	,,	$C_{11}H_{10}N_4O_2$	colourless	228–229	60[d]	57·4	4·4	57·5	4·5
4-Nitrobenzyl-idene[e]	,,	$C_{12}H_{10}N_4O_4$	pale yellow	243–245	33	52·5	3·7	52·5	3·8
4-Dimethylamino-benzylidene	3-Methyl-5-isoxazolyl-carbonyl	$C_{14}H_{16}N_4O_2$	yellow	220–221	97	61·7	5·9	62·1	6·2
4-Diethylamino-benzylidene	Picolinoyl	$C_{17}H_{20}N_4O$	cream	129–130	96	68·9	6·8	69·0	6·6
4-Dimethylamino-benzylidene	Benzoyl	$C_{16}H_{17}N_3O$	yellow	191–192	60[d]	71·8	6·4	71·9	6·2
4-Dimethylamino-benzylidene	4-Chlorobenzoyl	$C_{16}H_{16}ClN_3O$	yellow	214–215	27[d]	63·7	5·3	63·8	5·0
4-Dimethylamino-benzylidene	2-Hydroxy-4-aminobenzoyl	$C_{16}H_{18}N_4O_2$	orange	135–136[f]	78[d, g]	64·4	6·0	64·3	6·2

[a] All the hydrazones were prepared by reacting the acid hydrazide with the aldehyde in ethanol. [b] Hydrazines were crystallized from ethanol unless otherwise noted. [c] Failed to reduce double bond using $LiAlH_4$ in ether. [d] Crystallized from methanol. [e] All attempts to reduce this compound using $NaBH_4$ failed under conditions, previously successful, described in our first paper in this series. [f] Gives a red melt. [g] Attempts to reduce this compound using $NaBH_4$ in 80% methanol–water, and in glacial acetic acid using palladium on carbon failed. It was very insoluble in most solvents.

Table II. Hydrazines (R′—NHNHCOR$_2$″)[a]

R′	R″CO	Formula Procedure[b]	Colour	m.p., °C	% Yield	Analysis Calcd. C	Calcd. H	Found C	Found H
2-Dimethylamino-benzyl	5-Methyl-3-isoxazolyl-carbonyl	$C_{14}H_{18}N_4O_2$ B	pale yellow	106–107[c]	29	61·3	6·6	61·4	6·6
3-Dimethylamino-benzyl	,,	$C_{14}H_{18}N_4O_2$ C[d]	colourless	95– 96	62	61·3	6·6	61·4	6·3
4-Dimethylamino-benzyl	,,	$C_{14}H_{18}N_4O_2$ C+B[e,f]	colourless	131–132	30–35	61·3	6·6	61·5	6·6
4-Diethylamino-benzyl	,,	$C_{16}H_{22}N_4O_2$ C	light cream	74– 75	55	63·6	7·3	63·9	7·4
4-Dimethylamino-benzyl	3-Methyl-5-isoxazolyl-carbonyl	$C_{14}H_{18}N_4O_2$ C+B	pale yellow	130–132	17	61·3	6·6	61·7	6·6
3-Aminobenzyl	Picolinoyl .3HCl[g]	$C_{13}H_{14}N_4O$ .3HCl A	cream	217–219	11	44·4	4·9	44·7	4·6
4-Aminobenzyl	Picolinoyl .2HCl	$C_{13}H_{14}N_4O$ .2HCl A	red	87– 90	5	49·4[h]	5·1	49·5	5·8

4-Dimethylamino-benzyl	Picolinoyl	$C_{15}H_{18}N_4O$ A	colourless	104–105	41	66·5	6·7	66·3	6·6
4-Diethylamino-benzyl	Picolinoyl .3HCl.$1\frac{1}{2}H_2O$	$C_{17}H_{22}N_4O$ .3HCl.$1\frac{1}{2}$.H_2O A	colourless	180–184	20	47·0	6·1	47·9	6·0[j]
4-Dimethylamino-benzyl	Nicotinoyl	$C_{15}H_{18}N_4O$ A	light red	[i]	5	66·5	6·7	66·9	7·4
4-Dimethylamino-benzyl	Isonicotinoyl	$C_{15}H_{18}N_4O$ A	pale yellow	174–176	12	66·5	6·7	66·5	6·5
4-Dimethylamino-benzyl	Benzoyl	$C_{16}H_{19}N_3O$ A	yellow	116–117	47	71·3	7·1	71·1	7·2
4-Dimethylamino-benzyl	4-Chlorobenzoy	$C_{16}H_{18}ClN_3O$ C	pale yellow	173–174	16	63·3	5·9	63·0	5·5

[a] Most compounds were crystallized from ethanol unless otherwise noted. [b] *Procedure A:* Reduction of the double bond by 10% palladium on carbon in alcohol as described in our first paper in this series. *Procedure B:* Reduction using $LiAlH_4$ in ether. *Procedure C:* Reduction using $NaBH_4$ or KBH_4 in 80% methanol–water. [c] Crystallized from ethanol and petroleum–ether (b.p. 30–60°). [d] KBH_4 gave complete reduction as shown by comparison of the ultraviolet spectra of this compound and the intermediate 'idene'. [e] KBH_4 or $NaBH_4$ gave only about 90% reduction of the double bond. A small quantity of $LiAlH_4$ in ether was used as a second step. Comparison of the ultraviolet spectra readily distinguished unreduced 'idene' in the product. [f] This compound may also be prepared by the reaction of 4-dimethylaminobenzylhydrazine on the methyl ester. [g] Reduction of the nitrobenzylidene compound. [h] *Anal.* Calcd.: Cl, 22·4. Found: Cl, 22·3, 22·2. [i] *Anal.* Calcd.: N, 12·9; Cl, 24·5. Found: N, 13·7; Cl, 24·7, 24·78. [j] Does not crystallize. An amorphous glass obtained.

Table III. Pharmacological data (R′—NHNHR″)[a]

R′	R″	MAO Inhibition in rats[b]		5-HTP[g] Potentiation in mice[h]	Duration, mg/kg[i]	Toxicity[j] 24 h i.p. LD_{50} in mice, mg/kg
		Liver *in vitro*[c]	Brain *in vivo*[d,f]			
Iproniazid[e] isopropyl	Isonicotinoyl	1·0	1·0	1·0	25 days (50)	1110 ± 50
2-Dimethylaminobenzyl[k]	5-Methyl-3-isoxazolylcarbonyl	0·25	—	8·0	—	—
3-Dimethylaminobenzyl	,,	0·08	1·25	8·0	> 5 days (20)	315 ± 17
4-Dimethylaminobenzyl	,,	0·2	1·7	8·0	< 24 h (40)	210 ± 9
4-Diethylaminobenzyl	,,	0·02	0·6	6·0	< 24 h (40)	248 ± 29
4-Dimethylaminobenzyl	3-Methyl-5-isoxazolylcarbonyl	0·7	1·5	4·0	< 24 h (30)	331 ± 10
3-Aminobenzyl	Picolinoyl .3HCl	0·5	2·0	2·0	> 5 days (60)	> 400
4-Aminobenzyl	Picolinoyl .2HCl	0·2	0·6	2·0	24 h (60)	> 500
4-Dimethylaminobenzyl	,,	0·07	0·3	4·0	< 24 h (20)	240 ± 15
4-Diethylaminobenzyl	Picolinoyl .3HCl$1\frac{1}{2}H_2O$	0·05	—	4·0	< 24 h (40)	450 ± 36

4-Dimethylaminobenzyl	Nicotinoyl	0·3	< 0·25	< 1·0	—	> 400
4-Dimethylaminobenzyl	Isonicotinoyl	0·8	—	1·0	< 24 h (120)	180 ± 162
4-Dimethylaminobenzyl	Benzoyl	0·4	0·3	< 1·0	—	305 ± 39
4-Dimethylaminobenzyl	4-Chlorobenzoyl	0·01	—	< 1·0	—	174 ± 24
3-Aminobenzyl	H 2.HCl	0·5	8·0	20	5 days (6)	92 ± 6
3-Dimethylaminobenzyl	H .HCl	[l]	—	7·5	5 days (20)	177 ± 3
4-Dimethylaminobenzyl	H ·HCl	0·4	2	30	< 24 h (4)	170 ± 8
4-Diethylaminobenzyl	H	2·2	1·0	4·0	—	202 ± 6
4-Dimethylaminobenzyl	4-Dimethylaminobenzyl	0·1	< 0·25	1·0	> 5 days (120)	192 ± 30
Benzyl	,,	0·2	1·25	2	> 5 days (40)	355 ± 11

[a] The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories. The monoamine oxidase inhibition was determined by Mrs. Carol Callahan, and the 5-hydroxytryptophan potentiation was determined by Mrs. B. H. Kappell. [b] The methods are described in detail in our first paper.[1] [c] A Warburg determination of oxygen uptake on rat liver. [d] Ran on rat brain 1 h after i.p. administration of the drug. This procedure is based on the work of A. N. Davison [*Biochem. J.*, **67**, 312 (1957)]. [e] In each test, iproniazid was used as a standard and arbitrarily assigned a value of one. Therefore, all other compounds were related to iproniazid and a compound having a MAO of 8 *in vivo* means that it is 8 times as active as iproniazid. The use of percentages has been avoided by nearly all workers in this field on the basis that such usage would be confusing. [f] On a molar basis. [g] 5-Hydroxytryptophan. [h] On a weight basis. [i] *In vivo* response to 5-HTP potentiation at different periods of time following a single dose of the compound. [L. O. Randall and R. E. Bagdon, *Ann. N.Y. Acad. Sci.*, **80**, 626 (1959)]. [j] Toxicity work was carried out by Dr. E. Keith and his associates of the Pharmacological Laboratories. [k] Due to the difficulty of making this compound, only 100 mg were prepared for this work. [l] Free base, 8·0.

that these new short-acting MAO inhibitors suffer a relatively rapid oxidative degradation after they become attached to the receptor sites.

The acyl hydrazones prepared for this programme are found in Table I, the corresponding substituted acyl hydrazines obtained by reduction are shown in Table II, and the pharmacological findings on the basic aralkyl acyl hydrazines are shown in Table III.

Pharmacological

Table III shows the activity of the compounds in the various MAO inhibition tests in comparison with iproniazid as a standard. As in the case of the corresponding unsubstituted compounds,[1] it is found that both the aralkyl group and the acyl group affect the intensity of activity. The greatest shortening of duration was obtained with the 4-amino or 4-dialkylamino derivatives, the corresponding 3-substituted compound having an intermediate period of action. Due to difficulties in preparing the 2-basically substituted compounds, only limited information on these is available. With respect to the acyl residue, it was found again that the isoxazolylcarbonyl type residue was in the balance of activity and toxicity, superior to the pyridinecarbonyl type. Some of these compounds are currently on clinical trial.

Experimental*†

The general procedure used in this work is described in the first paper of this series.[1]

3-Aminobenzylhydrazine dihydrochloride. 3-Nitrobenzaldehyde (50 g) and 85 per cent hydrazine hydrate (40 g) in isopropyl alcohol (1·2 l.) were reduced with hydrogen at 500 lb/in^2 using 10 per cent palladium on charcoal (10 g) as a catalyst at 30°. The recovered solution was concentrated to a residue and the latter treated with 10 N hydrogen chloride in ethanol (100 ml). A precipitate separated which assumed crystalline form on standing at 40° for a few days. It was recrystallized from methanol to give a light cream compound, m.p. 233–234° (40 g yield).

* All melting points are corrected.

† We are indebted to Dr. A. Steyermark and his associates for the microanalyses.

Anal. Calcd. for $C_7H_{11}N_3.2HCl$: N, 20·0. Found: N, 19·9.

3-Dimethylaminobenzylhydrazine. 3-Dimethylaminobenzaldehyde (59 g) and 85 per cent hydrazine hydrate (50 g) were reduced in isopropyl alcohol (600 ml) with hydrogen at 500 lb/in^2 at 25° using 10 per cent palladium on carbon (5 g) as a catalyst. The recovered product was fractionated through a 15-cm Vigreaux column. The fraction at 138–142°/ 2 mm was collected, n_D^{25} 1·5850 (20 g yield). The compound solidifies at 4°.

Anal. Calcd. for $C_9H_{15}N_3$: N, 25·5; Found: N, 25·2.

The monohydrochloride was prepared by treating 3-dimethylaminobenzylhydrazine with a theoretical amount of hydrogen chloride in ethanol. The monohydrochloride was precipitated with ether and recrystallized from ethanol, m.p. 157–158°.

Anal. Calcd. for $C_9H_{15}N_3.HCl$: C, 53·6; H, 8·0. Found: C, 53·9; H, 7·6.

4-Dimethlyaminobenzylhydrazine. 4-Dimethylaminobenzaldehyde (300 g) and 85 per cent hydrazine hydrate (240 g) were reduced using 10 per cent palladium on carbon (25 g) as described above for the 3-isomer. The product was distilled using a 15-cm Vigreaux column and the fraction distilling at 148–170°/6–8 mm, n_D^{25} 1·5921, was collected and refractionated at 138–141°/2 mm, n_D^{25} 1·5896 (215 g yield). A second experiment gave b.p. 140–143°/2 mm, n_D^{25} 1·5876. It solidifies at 4°.

Anal. Calcd. for $C_9H_{15}N_3$: C, 65·3; H, 9·1. Found: C, 65·6; H, 9·2.

The monohydrochloride was prepared by adding a theoretical amount of 4 N hydrogen chloride in ethanol to 4-dimethylaminobenzylhydrazine (30 g). On cooling, a colourless product separated which slowly became orange-coloured on exposure to air. The compound was recrystallized from ethanol, m.p. 149–151° (32 g yield).

Anal. Calcd. for $C_9H_{15}N_3.HCl$: Cl, 17·7. Found: Cl, 17·6.

4-Diethylaminobenzylhydrazine. Diethylaminobenzaldehyde (354 g) and 85 per cent hydrazine hydrate (240 g) in isopropyl alcohol (3 l.) was reduced using 10 per cent palladium on carbon (25 g) at 500 lb/in^2 at 25°. The recovered product was distilled using a 15-cm Vigreaux column and the fraction boiling at 163–165°/3 mm was collected. Redistillation gave a light yellow oil, b.p. 163–164°/2 mm, n_D^{25} 1·5710 (233 g yield).

Anal. Calcd. for $C_{11}H_{19}N_3$: C, 68·3; H, 9·9. Found: C, 68·7; H, 9·9.

1,2-Bis(4-dimethylaminobenzyl)hydrazine. 4-Dimethylaminobenzaldehyde (50 g) and 4-dimethylaminobenzylhydrazine (43 g) in isopropyl alcohol (1·2 l.) were reduced with hydrogen at 500 lb/in^2 at 50–55° using 10 per cent palladium on carbon (10 g). The recovered product crystallized and was recrystallized from isopropyl alcohol or ethanol, m.p. 84–86° (38 g yield).

Anal. Calcd. for $C_{18}H_{26}N_4$: C, 72·3; H, 8·8. Found: C, 72·4; H, 8·6.

1-Benzylidene-2-(4-dimethylaminobenzyl)hydrazine. 4-Dimethylaminobenzylhydrazine (41 g) was mixed with benzaldehyde (50 g) in ethanol (100 ml). On warming at 80°, the product crystallized almost immediately. Heating was continued for 15 min and the cooled semi-solid gel was filtered off. The recovered product was crystallized from ethanol, m.p. 124–134°. Recrystallization from ethanol gave a colourless material which on drying over phosphorus pentoxide *in vacuo* turned red (m.p. 124–135°) and, even with the utmost care, drying *in vacuo* gave a yellow powder, m.p. 122–133° (40 g yield).

Anal. Calcd. for $C_{16}H_{19}N_3$: C, 75·8; H, 7·5. Found: C, 75·6; H, 7·3.

The compound decomposed on prolonged heating at 75°.

1-Benzyl-2-(4-dimethylaminobenzyl)hydrazine hydrochloride. Benzaldehyde (36 g) and 4-dimethylaminobenzylhydrazine (53 g) were mixed in isopropyl alcohol (1·2 l.). The reaction solution was submitted to reduction with hydrogen at 500 lb/in^2 at 65° using 10 per cent palladium on carbon (10 g) as a catalyst. A theoretical hydrogen uptake was obtained. The recovered product was an oil. The oil in ethanol (25 ml) was treated with 10 N hydrogen chloride in ethanol (8 ml). The hydrochloride separated and was recrystallized from ethanol as a yellow-orange material, m.p. 155–158° (3·5 g yield).

Anal. Calcd. for $C_{16}H_{21}N_3$.HCl: C, 65·8; H, 7·5. Found: C, 65·9; H, 7·5.

1-(3-Pyridylmethylidene)-2-benzylhydrazine. 3-Pyridylcarboxaldehyde (25 g) and benzylhydrazine (40 g) were heated at 78° in isopropyl alcohol (300 ml) for 2 h. On cooling, the pale yellow

product crystallized. It was recrystallized from isopropyl alcohol, m.p. 91–92° (25 g yield).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73·8; H, 6·2. Found: C, 73·8; H, 6·2.

This compound failed to reduce using $LiAlH_4$ in ether.

1-(4-Dimethylaminobenzylidene)-2-trimethylacetylhydrazine. Trimethylacethydrazide (76 g), 4-dimethylaminobenzaldehyde (97 g) and *p*-toluenesulphonic acid (1·0 g) were heated at 78° in ethanol (250 ml) for 1½ h. On cooling, a yellow product crystallized which was recrystallized from ethanol, m.p. 172–173° (d.) (66 g yield).

Anal. Calcd. for $C_{14}H_{21}N_3O$: C, 68·0; H, 8·5. Found: C, 67·7; H, 8·2.

Attempts to reduce the double bond using 10 per cent palladium catalyst on charcoal in ethanol under 500 lb/in² gave a mixture which could not be separated by crystallization procedures.

Summary. In an extension of the work on 1-aralkyl-2-acyl hydrazines, the effect of substitution of a basic residue in the benzene ring on the MAO inhibition was examined. These compounds retain a moderate intensity of activity which is, however, characterized by a fairly rapid disappearance. This shortening of action is most marked in the 4-basically substituted compounds and would be expected on theoretical grounds to be pronounced also in the 2-derivatives. The 3-substituted compounds display a longer duration but this is also considerably shorter than with the unsubstituted compounds. These substitutions in the benzene nucleus, then, transform a class of typical long-acting irreversible MAO inhibitors into a class of short-acting reversible MAO inhibitors.

A number of new hydrazones, acyl hydrazones and their reduction products are described.

(*Received 23 July, 1960*)

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