$$\frac{dR_t}{di_2^0} = \frac{dR_t}{ds_2}\left(-\frac{ds_2}{di_2}\right)\frac{di_2}{di_2^0} \quad \text{(A17)}$$

But

$$R_t = f(s_2,e_2) \quad \text{(A18)}$$

so, by theorem A

$$dR_t = \left(\frac{\partial R_t}{\partial s_2}\right)_{e_2} ds_2 + \left(\frac{\partial R_t}{\partial e_2}\right)_{s_2} de_2 \quad \text{(A19)}$$

or

$$\frac{dR_t}{ds_2} = \left(\frac{\partial R_t}{\partial s_2}\right)_{e_2} + \left(\frac{\partial R_t}{\partial e_2}\right)_{s_2}\frac{de_2}{ds_2} \quad \text{(A20)}$$

The dependence of R_t on i_2 is omitted in eq. (A18)–(A20) since it has already been acknowledged in the first two terms of the right-hand side of eq. (A17).

Since $de_2/ds_2 = 1$, eq. (A20) may be simplified, giving

$$\frac{dR_t}{ds_2} = \left(\frac{\partial R_t}{\partial s_2}\right)_{e_2} + \left(\frac{\partial R_t}{\partial e_2}\right)_{s_2} \quad \text{(A21)}$$

Applied to definition (k), eq. (A21) becomes

$$\frac{dR_t}{ds_2} = k_1e_2 + k_2s_2 \quad \text{(A22)}$$

Definition (k) divided by definition (n) gives

$$-\frac{ds_2}{di_2} = -\frac{k_2e_2s_2}{k_ye_2i_2} \quad \text{(A23)}$$

Integration of definition (n) gives

$$\ln i_2 = -k_y\int e_2dt + \ln i_2^0 \quad \text{(A24)}$$

or

$$i_2 = i_2^0e^{-k_y\int e_2dt} \quad \text{(A25)}$$

and partial differentiation of eq. (A25) gives

$$\frac{di_2}{di_2^0} = e^{-k_y\int e_2dt} \quad \text{(A26)}$$

Substitution of eq. (A22), (A23) and (A26) in eq. (A17) gives

$$\frac{dR_t}{di_2^0} = (k_2e_2 + k_2s_2)\left(-\frac{k_2e_2s_2}{k_ye_2i_2}\right)e^{-k_y\int e_2dt} \quad \text{(A27)}$$

Substituting definition (k) for $k_2e_2s_2$ and eq. (A25) for i_2, cancelling identical terms, factoring and rearranging gives

$$-\frac{dR_t}{R_t} = \frac{k_2}{k_y}\left(\frac{e_2 + s_2}{e_2}\right)\frac{di_2^0}{i_2^0} \quad \text{(A28)}$$

Substitution of definition (f) in eq. (A28) gives

$$\frac{dE_t}{E_t} = \frac{k_2}{k_y}\left(\frac{e_2 + s_2}{e_2}\right)\frac{di_2^0}{i_2^0} \quad \text{(29)}$$

Derivation of Equation (30).—By the reasoning given in the 1st-order case, eq. (28) and (29) may be combined directly to give eq. (30).

Monoamine Oxidase Inhibitors. IV. Some Dialkylaminophenylalkylhydrazines and Related Compounds

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Two sequences of chemical reactions leading to several new basically substituted phenylalkylhydrazines are described. The compounds were less active and/or more toxic than the unsubstituted parent compound in limited animal tests.

Certain aralkylhydrazines and selected acyl derivatives of them are potent, long-acting monoamine oxidase inhibitors.[1] Substitution of the phenyl ring with amino or dialkylamino residues converted the length of activity from periods of the order of 25 days to less than 1 day. It was noted[2] that with increasing length of the alkylene bridge, compounds of intermediate length of activity (4–5 days) were obtained. This paper describes the preparation of these latter materials.

(4-Dimethylamino-α-methylphenethyl)hydrazine (V) was synthesized as follows

$$p\text{-}O_2NC_6H_4CH_2COCH_3 \rightarrow p\text{-}(CH_3)_2NC_6H_4CH_2COCH_3 \rightarrow p\text{-}(CH_3)_2NC_6H_4CH_2C(CH_3)=NNHCOCH_3 \rightarrow$$
$$\text{I} \qquad\qquad \text{II} \qquad\qquad \text{III}$$

$$p\text{-}(CH_3)_2NC_6H_4CH_2CH(CH_3)NHNHCOCH_3 \rightarrow p\text{-}(CH_3)_2NC_6H_{10}CH_2CH(CH_3)NHNHCOCH_3$$
$$\text{IV} \qquad\qquad \text{VI}$$

$$\downarrow \qquad\qquad \downarrow$$

$$p\text{-}(CH_3)_2NC_6H_4CH_2CH(CH_3)NHNH_2 \qquad p\text{-}(CH_3)_2NC_6H_{10}CH_2CH(CH_3)NHNH_2$$
$$\text{V} \qquad\qquad \text{VII}$$

1-(4-Nitrophenyl)-2-propanone (I) was prepared by treating 4-nitrophenylacetyl chloride with diethyl ethoxymagnesium malonate.[3] It was reduced readily in the presence of formalin to produce 1-(4-dimethylaminophenyl)-2-propanone (II) in 91% yield as a yellow distillable oil, which was treated with acetyl hydrazine to form the corresponding acetylhydrazone (III) which was reduced to IV in acetic acid by H_2/PtO_2, stopping the absorption of one equivalent of hydrogen. If the reduction was permitted to continue, the cyclohexyl compound VI was formed which, on deacetylation, gave VII. Deacetylation of IV gave V.

The synthesis of the higher homolog, 1-(4-dimethylaminophenyl)-3-hydrazinobutane and related products, is shown in the scheme at the top of the next page.

(1) T. S. Gardner, E. Wenis, and J. Lee, *J. Med. Pharm. Chem.*, **2**, 133 (1960).

(2) T. S. Gardner, E. Wenis, and J. Lee, *ibid.*, **3**, 241 (1961).

(3) C. G. Overberger and H. Biletch, *J. Am. Chem. Soc.*, **73**, 4881 (1951).

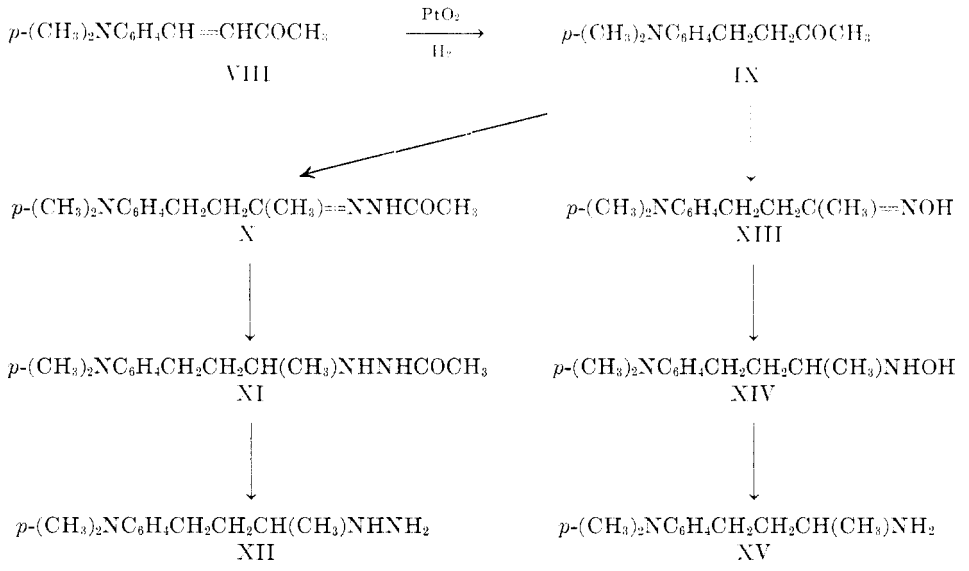

TABLE I

PHARMACOLOGICAL DATA (R'NHNHR")[a]

Cpd.	R'	R"	MAO inhibition in rats[b] — Liver *in vitro*[c]	Brain *in vivo*[d,f]	Heart *in vivo*[d,f]	5-HTP[g] poten. in mice[h]	Duration mg./kg.[i]	Toxicity 24 hr. i.p. LD_{50} in mice mg./kg.
[e,j]	Isopropyl	Isonicotinoyl	1.0	1.0	1.0	1.0	25 days (50)	1150 ± 50
[k]	2-Phenylisopropyl	H	8.0	43	40	60	...	...
VII	4-Dimethyl-amino-α-methyl-phenethylhydrazine	H	0.5	2.5	2.0	<1	5 days (4)	>400
XIII	3-(4-Dimethylaminophenyl)-1-methylpropyl	H	3.3	8.3	...	30	5 days (4)	16.6 ± 1

[a] The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories. [b] The methods are described in detail.[1] [c] Warburg determination of oxygen uptake on rat liver. [d] Ran on rat brain 1 hr. 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. [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] Iproniazid. [k] Catron®.

The 4-(*p*-dimethylaminophenyl)-2-butanone (IX) was obtained by reducing 4-dimethylaminobenzylidene acetone (VIII)[4] in ethyl acetate with hydrogen and platinum oxide. This reduction proceeded until one equivalent of hydrogen was absorbed, whereas in the Raney nickel reduction reported,[5] the reduction had to be stopped to prevent more than the olefinic group from being reduced. The ketone was then allowed to react with acetylhydrazine in refluxing benzene to give a very high yield of the acetylhydrazone X. The most satisfactory method for reducing this hydrazone to the corresponding acetylhydrazine (XI) was in ethanolic hydrogen chloride with platinum oxide. The reduction was terminated at the uptake of one equivalent of hydrogen when the solution had become colorless. Hydrolysis of XI with dilute hydrochloric acid gave 1-(4-dimethylaminophenyl)-3-hydrazinobutane dihydrochloride XII. The oxime XIII, hydroxylamine XIV, and amine XV, related to the above ketone, were obtained in the sequence shown.

Pharmacological.—The techniques previously described[1,2] were employed for determination of the monoamine oxidase inhibiting activity, iproniazid being used as a standard. The results are given in Table I. The compounds have lower activity and/or higher toxicity than the reference compounds in the single species (mice) tested.

Experimental[6,7]

1-(4-Dimethylaminophenyl)-2-propanone (II).—A solution of 39.5 g. of I[3] and 57 ml. of formalin in 1 l. of ethanol was hydrogenated at room temperature under 200 lb. (14.4 kg./cm.^{2}) of hydrogen pressure in the presence of Raney nickel. The uptake was completed in 2 hr. After filtering, it was concentrated *in vacuo* from a water bath and the residual liquid fractionated; yield 36.4 g. of yellow liquid, b.p. 120–125° (2–3 mm.).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.58; H, 8.47; N, 7.9[illegible]. Found: C, 74.05; H, 8.67; N, 8.07.

The base formed a yellow crystalline *picrate* in ethanol, m.p. 134–136°.

Anal. Calcd. for $C_{17}H_{18}N_4O_8$: C, 50.25; H, 4.43; N, 13.79. Found: C, 50.34; H, 4.32; N, 13.78.

1-(4-Dimethylaminophenyl)-2-propanoneacetylhydrazone (III).—A solution of 4.8 g. of II and 2.4 g. of acetylhydrazine in 50 ml. of dry benzene was refluxed, collecting the water produced by the azeotropic distillation in a trap. After 3 hr., the benzene solution was concentrated *in vacuo* to give a yellow solid which was purified readily by recrystallization from methanol; m.p. 152–154°.

Anal. Calcd. for $C_{13}H_{19}N_3O$: C, 67.00; H, 8.17; N, 18.04. Found: C, 66.98; H, 7.84; N, 18.10.

(4) L. C. Reifor and M. M. Cooper, *J. Org. Chem.*, **3,** 13 (1939).

(5) H. Rupe, A. Collin, and L. Schmiderer, *Helv. Chim. Acta*, **14,** 1340 (1931).

(6) All melting points are corrected.

(7) We are indebted to Dr. A. Steyermark and his associates for the microanalyses.

1-Acetyl-2(4-dimethylamino-α-methylphenethyl)hydrazine IV.—A solution of 2.7 g. of III in 40 ml. of acetic acid was reduced at 50 lb. (3.6 kg./cm.^{2}) pressure of hydrogen in the presence of PtO_2. The reduction was rapid and was stopped at the absorption of 1 equiv. of hydrogen. The catalyst was filtered off, the filtrate concentrated *in vacuo* from a water bath, and the residual syrup dissolved in water. The solution was made alkaline with dilute NaOH solution and repeatedly extracted with ether. After the ether extract was dried and evaporated *in vacuo*, a yellow syrup was obtained which crystallized upon scratching. The product was recrystallized from cyclohexane to be isolated as yellow crystals; m.p. 82–84°.

Anal. Calcd. for $C_{13}H_{21}N_3O$: C, 66.40; H, 8.93; N, 17.86. Found: C, 66.22; H, 9.01; N, 17.77.

(4-Dimethylamino-α-methylphenethyl)hydrazine Dihydrochloride V.—A solution of 0.72 g. of IV was dissolved in 10 ml. of 3 *N* HCl refluxed for 3 hr. and concentrated to dryness *in vacuo*. The concentration was repeated twice after the addition of 10 ml. of water each time and then once with 15 ml. of ethanol. The residue was then dissolved in a minimum amount of hot ethanol, filtered, and kept at room temperature to crystallize. For analysis, the compound was recrystallized from ethanol; tan needles, m.p. 179–180°.

Anal. Calcd. for $C_{11}H_{19}N_3 \cdot 2HCl$: C, 49.60; H, 7.90; N, 15.80. Found: C, 49.43; H, 8.01; N, 15.29.

1-(4-Dimethylaminocyclohexyl)-2-hydrazinopropane Dihydrochloride (VII).—A solution of 22 g. of the acetylhydrazone III in 100 ml. of acetic acid was reduced under 50 lb. (3.6 kg./cm.^{2}) pressure of hydrogen in the presence of 1 g. of PtO_2. The reduction was permitted to continue to completion which required the absorption of 4 equiv. of hydrogen. After filtering, the solution was concentrated *in vacuo*, the residue diluted with water, made alkaline with aqueous sodium hydroxide and extracted with ether. The ether was evaporated and the crude acetylhydrazine was hydrolyzed by refluxing with 75 ml. of 6 *N* HCl for 6 hr. The solution was concentrated *in vacuo* under nitrogen and the resultant syrup was dissolved in hot ethanol from which white crystals were isolated. The salt was recrystallized from 96% ethanol; m.p. 242–244°.

Anal. Calcd. for $C_{11}H_{25}N_3 \cdot 2HCl$: C, 48.49; H, 9.94; N, 15.44. Found: C, 48.56; H, 9.85; N, 15.05.

The absence of aromaticity was confirmed by the infrared spectrum.

4-(4-Dimethylaminophenyl)-2-butanone (IX).—A solution of 154 g. of 4-dimethylaminobenzylideneacetone (VIII)[4] in 3.5 l. of ethyl acetate at 24° was reduced at a pressure of 147 lb. (10.8 kg./cm.^{2}) pressure of hydrogen in the presence of 4 g. of PtO_2. At the end of 80 min., the reduction was completed. After filtering and concentrating *in vacuo*, a crystalline product was obtained. After recrystallizing from ethanol, it consisted of white platelets; m.p. 47–48°; lit.[5] m.p. 50.5–51.5°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 7.33. Found: C, 74.90; H, 8.78; N, 7.07.

4-(4-Dimethylaminophenyl)-2-butanone Acetylhydrazone (X).—A solution of 96 g. of ketone and 41 g. of acetylhydrazine in 1 l. of benzene was refluxed for 18 hr. collecting 8.5 ml. of water in a trap. The benzene then was removed *in vacuo* and the resulting solid recrystallized from ligroin (b.p. 90–120°), m.p. 109–111°, yellow crystals.

Anal. Calcd. for $C_{14}H_{21}N_3O$: C, 68.00; H, 8.50; N, 17.00. Found: C, 67.67; H, 8.65; N, 16.28.

2-[1-Acetyl-2-(4-dimethylaminophenyl)hydrazino]butane (XI).—A solution of 7.5 g. of the acetylhydrazone X was prepared in 250 ml. of absolute methanol, and 2 ml. of 6.7 *N* ethanolic hydrogen chloride was added causing the yellow solution to turn red. In the presence of 100 mg. of PtO_2, the solution was reduced under 50 lb. (3.6 kg./cm.^{2}) pressure of hydrogen until the theoretical uptake was achieved. The filtered solution was brought to pH 8 with dilute sodium hydroxide solution and concentrated *in vacuo* from a water bath under nitrogen. The residue was treated with 50 ml. of water and extracted 3 times with 50 ml. of ether. The combined ether extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to an oily product which turned solid after trituration with ligroin at 0°. After recrystallization from ligroin (60–90°), a white crystalline product was obtained; m.p. 74–76°.

Anal. Calcd. for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.37; H, 8.97; N, 16.86.

1-(4-Dimethylaminophenyl)-3-hydrazinobutane Dihydrochloride (XII).—A solution of 3 g. of the above acetylhydrazine XI was dissolved in 120 ml. of 3 *N* HCl and refluxed for 2 hr. under nitrogen. The solution was then concentrated *in vacuo* from a water bath, and this was repeated after the addition of 20 ml. of water. The solid residue was dissolved in 50 ml. of hot ethanol, and after permitting to cool slowly, the product was obtained crystalline. The white compound was recrystallized from ethanol; m.p. 169–171°.

Anal. Calcd. for $C_{12}H_{21}N_3 \cdot 2HCl$: C, 51.42; H, 8.27; N, 14.99. Found: C, 51.34; H, 8.18; N, 15.45.

4-(4-Dimethylaminophenyl)-2-butanone Oxime (XIII).—This derivative was prepared in the usual manner. After 3 recrystallizations from isopropyl alcohol–cyclohexane, the product was obtained pure; m.p. 113–115°.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.57 Found: C, 70.11; H, 8.59; N, 13.64.

4-(4-Dimethylaminophenyl)-2-hydroxylaminobutane (XIV).—A solution of 6.2 g. of the oxime XIII dissolved in 250 ml. of methanol containing 2.5 ml. of ethanolic hydrogen chloride and 200 mg. of PtO_2 was reduced under 50 lb. (3.6 kg./cm.^{2}) pressure of hydrogen. The reaction was terminated when 1 equiv. of hydrogen was absorbed. The solution was filtered and evaporated to yield a product which could not be crystallized directly. It was dissolved in water, neutralized with dilute aqueous sodium hydroxide solution and extracted with ether. The dried ethereal extract was evaporated to yield a solid which was recrystallized from cyclohexane, m.p. 86–88°. The compound gave a positive test with Fehling solution in water. The *oxalate* was prepared and recrystallized from 95% ethanol; m.p. 130–133°.

Anal. Calcd. for $C_{12}H_{20}N_2O \cdot 2C_2H_2O_4$: C, 49.48; H, 6.19; N, 7.22. Found: C, 49.63; H, 6.36; N, 6.94.

4-(4-Dimethylaminophenyl)-2-aminobutane Dihydrochloride (XV).—A solution of 10.3 g. of the oxime XIII dissolved in 250 ml. of methanol was reduced at 50 lb. (3.6 kg./cm.^{2}) pressure of hydrogen in the presence of Raney nickel. When the theoretical amount of hydrogen was absorbed, the reduction stopped. After filtration, the methanol solution was distilled *in vacuo*, and the residue dissolved in ether and converted to its hydrochloride. The salt was recrystallized from methanol–isopropyl alcohol; m.p. 208–210°.

Anal. Calcd. for $C_{12}H_{20}N_2 \cdot 2HCl$: C, 54.35; H, 8.36; N, 10.56. Found: C, 54.60; H, 8.35; N, 10.13.