cooled and filtered to give 5.6 g. of colorless material of m.p. 150-154° (84.5% yield).

Anal. Calcd. for $C_{12}H_{28}NCl$: Cl^-, 16.0. Found: Cl^-, 15.9.

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Reaction of Hydrazine with Acetic Acid at 25°[1]

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While studying the oxidation of hydrazine in glacial acetic acid, it was noted that the basicity of the solution of hydrazine in acetic acid decreased with time. No record was found for the rate of reaction of hydrazine with acetic acid at room temperatures. The following work was undertaken to determine if a standard solution of hydrazine in acetic acid was stable.

Hydrazine can effectively disappear from solution in acetic acid by the following scheme:

$$NH_2NH_2 + CH_3COOH \longrightarrow CH_3CONHNH_2 + H_2O \quad (1)$$

$$CH_3CONHNH_2 + CH_3COOH \longrightarrow CH_3CONHNHCOCH_3 + H_2O \quad (2)$$

The acethydrazide formed initially can disproportionate[2] as indicated, regenerating hydrazine and forming symmetrical diacethydrazide. The disappearance of hydrazine function measured in the present work does not correspond to reaction 1

$$2CH_3CONHNH_2 \longrightarrow NH_2NH_2 + CH_3CONHNHCOCH_3 \quad (3)$$

alone, but to Reaction 1 counterbalanced somewhat by the hydrazine regeneration *via* step 3. It is thus necessary to follow the disappearance of both hydrazine and acethydrazide.

A review of the literature yielded no methods for the determination of hydrazine in the presence of acethydrazide and diacethydrazide in acetic acid as the solvent. Grammaticakis[3] reported the formation of disalicylalhydrazine on treatment of hydrazine with freshly distilled salicylaldehyde. This reaction was found to occur rapidly in acetic acid at room temperature and to yield a yellow solution or precipitate. The spectrum for a solution containing 0.2 mg. per ml. of hydrazinium acetate is shown in Fig. 1. An analytical procedure based on this color formation is decribed below.

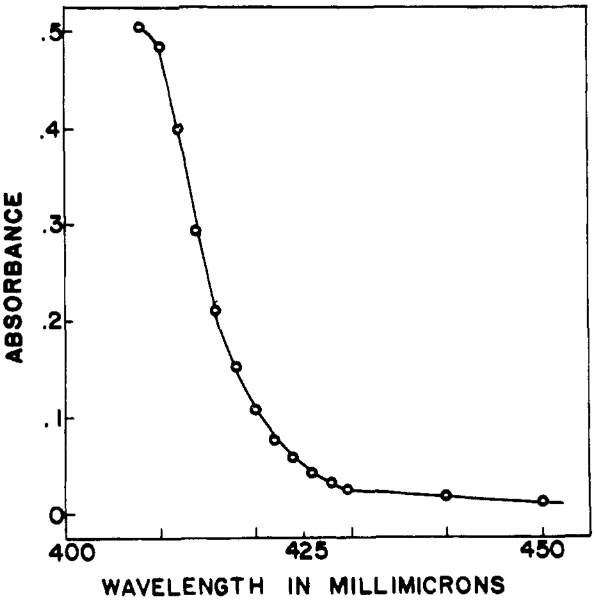

Fig. 1. Visible spectrum for disalicylalhydrazine

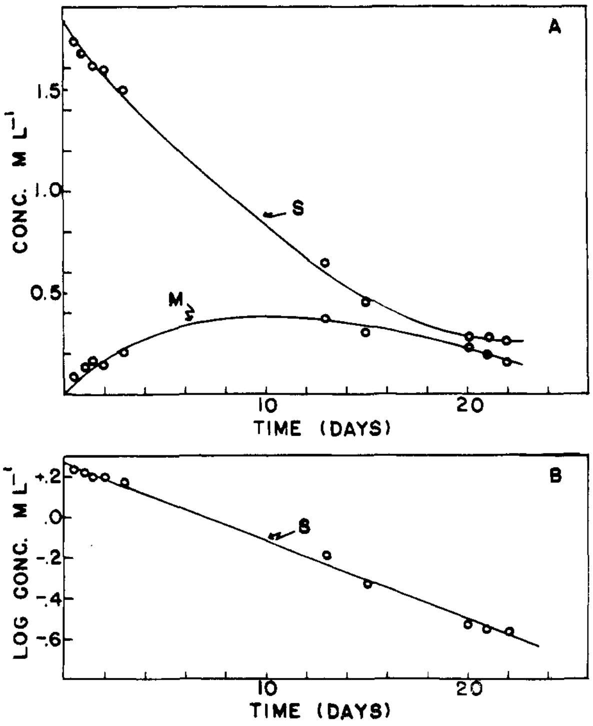

Fig. 2. A. Hydrazine-acetic acid reaction. S—salt concentration, M—acethydrazide concentration. B. First order plot for hydrazine acetate

The analytical results for the reaction of acetic acid with hydrazine are summarized in Fig. 2A and those for the disproportionation of acethydrazide in Fig. 3A.[4] In both cases the concentration unit is moles per liter. From these results it appears that both reactions must be considered as occurring but that the rates are very different so pseudo rate constants are not too much in error.

The disproportionation of acethydrazide (Equation 3) is a moderately fast reaction which is second

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(1) Abstracted from the Ph.D. thesis submitted by William C. Harris to the School for Advanced Graduate Studies, Michigan State University.

(2) W. Autenrieth and P. Spiess, *Ber.*, **34**, 187 (1901).

(3) P. Grammaticakis, *Bull. soc. chim., France*, 690 (1950).

(4) Detailed experimental data are available on request.

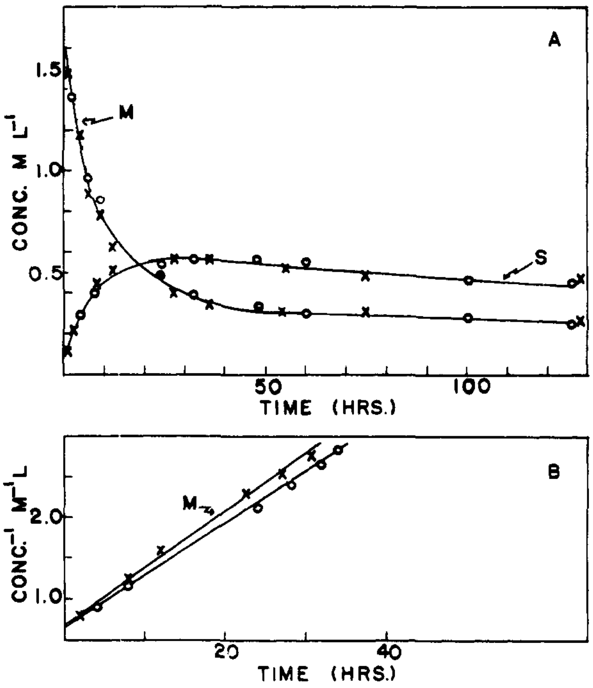

Fig. 3. A. Disproportionation of acethydrazide. M—acethydrazide, S—salt, x—$2M$ H_2O, o—$4M$ H_2O. B. Second order plot for acethydrazide

order in acethydrazide. During the first 20 hr. the specific rate constant is 0.074 l. per mole per hour. After about 20 hr. the concentration of hydrazinium acetate is enough so that the formation of acethydrazide (Equation 1) becomes important and calculations become difficult. The presence of additional water beyond that equal to the water produced by the formation of acethydrazide has a slight effect.

The formation of acethydrazide is a very slow reaction at 25°. The disproportionation of acethydrazide is so fast by comparison that the pseudo first order plot for hydrazinium acetate is not seriously in error in the regions where experimental values are shown. The pseudo first order rate constant is 0.0036 per day. The disappearance of hydrazine which is observed essentially corresponds to the reaction:

$$NH_2NH_2 + 2CH_3COOH \longrightarrow CH_3CONHNHCOCH_3 + 2H_2O \quad (4)$$

The addition of water equal to the hydrazine concentration produced no detectable changes.

It was found that the disproportion of acethydrazide is appreciable after 30 min., but that a solution of hydrazine acetate in acetic acid can be kept for about 24 hr. with no detectable change.

EXPERIMENTAL

All chemicals used were reagent grade unless otherwise specified. Glacial acetic acid was found to contain 0.16% water by the Karl Fischer method. Hydrazine hydrate was analyzed by the iodate method of Bray and Cuy.[5] Hydrazinium acetate was prepared by neutralizing hydrazine hydrate with acetic acid and recrystallizing from 1:1 chloroform ethanol. The product melted at 96–97° (lit.[6] 87.5°) and had a neutral equivalent of 92.0 ± 0.4 (theor. 92.1) by titration either with sodium hydroxide or with perchloric acid in acetic acid to a blue-green color of crystal violet. Acethydrazide was prepared by the method of Curtius and Hofmann[7] and melted at 66.7° (lit.[5] 67°) after precipitation by ethyl ether from chloroform. The product had a neutral equivalent of 74.2 ± 0.5 (theor. 74.1) by titration with perchloric acid in acetic acid.

The disappearance of hydrazine was studied by keeping a $2M$ *solution of hydrazinium acetate in glacial acetic acid* in a flask in a water bath at 25 ± 0.5° and removing aliquots for analysis periodically. Addition of ethyl ether precipitated hydrazinium acetate from early samples and diacethydrazide from later samples. The diacethydrazide was identified by comparison with a known sample prepared by the method of Stolle.[8] The isolated material melted at 138–140° (lit. 138°,[8] 140°[9]) and a mixture of isolated and prepared material melted at 138–140°. Another set of observations was obtained in the same way using hydrazine hydrate to test the effect of a small amount of water.

The disproportionation of acethydrazide in acetic acid was studied by keeping a solution which was $2M$ both in acethydrazide and water (to approximate the reaction mixture from hydrazine and acetic acid) in a flask in a water bath at 25 ± 0.5° and removing aliquots for analysis periodically. A second mixture $4M$ in water to approximate the hydrazine hydrate reaction mixture was also followed.

All analyses were done by removing 1 ml. aliquots from the reaction mixtures. The sum of hydrazine and acethydrazide was determined by titration with perchloric acid in acetic acid to the blue-green of crystal violet indicator.

For quantitative measurement of hydrazine it was found that the sample solution should contain 50% by volume of salicylaldehyde for rapid color development. The wave length for measurement was a compromise since the blank was opaque below 410 mμ and the sensitivity decreased as the wave length increased. The best compromise was 418 mμ. For the determination an aliquot of less than 5 ml. containing less than 1.2 mg. hydrazine was put in a 10 ml. volumetric flask, 5 ml. of freshly distilled salicylaldehyde was added and the flask was filled to the mark with acetic acid. After mixing and standing for 10 min. to allow the color to develop, the absorbance was determined at 418 mμ using 1:1 acetic acid–salicylaldehyde as the blank. The color is stable for at least 2 hr. Some results with known samples are given in Table I.

A series of samples was run to test the effect of acethydrazide, diacethydrazide, and water on the determination of

TABLE I

ABSORBANCE *vs.* CONCENTRATION OF HYDRAZINIUM ACETATE

$N_2H_4 \cdot HOAc$, Mg./Ml.	Absorbance	A./Mg./Ml.
0.20	0.157	0.78
0.40	0.318	0.79
0.60	0.469	0.78
0.80	0.611	0.76
1.20	0.930	0.77

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[5] W. C. Bray and E. S. Cuy, *J. Am. Chem. Soc.*, **46**, 858–75 (1924).

[6] V. I. Semishin, *J. Gen. Chem. USSR*, **13**, 632–42 (1943).

[7] Th. Curtius and T. S. Hofmann, *J. prakt. Chem.*, (2) **53**, 524 (1896).

[8] R. Stolle, *Ber.*, **32**, 796 (1899).

[9] G. Pellizzari, *Gazz. Chim. ital.*, **39I**, 536 (1909).

hydrazine. From the results in Table II it is seen that only acethydrazide has an effect. This effect is thought to be the result of disproportionation of acethydrazide yielding hydrazine and diacethydrazide.

TABLE II

EFFECT OF IMPURITIES

System	Absorbance A	Absorbance B
a. $N_2H_4\cdot HOAc$	0.318	0.612
b. a + 5.4 mM. $AcNHNH_2$	0.322	0.618
c. b + 5.2 mM. AcNHNHAc	0.314	0.610
d. a + 1% water	0.316	0.611

A. $N_2H_4\cdot HOAc$ = 0.40 mg./ml., 4.35 mM.
B. $N_2H_4\cdot HOAc$ = 0.80 mg./ml., 8.70 mM.

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Mescaline Analogs IX. Tetra- and Pentamethyl-β-phenethylamines

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As part of a continuing study of the relationship between chemical structure and psychotomimetic activity, the effect of replacing the methoxyl groups in the hallucinogen mescaline with methyl groups has been examined.[3] This series of ring-substituted polymethyl-β-phenethylamines has been extended to include all three possible tetramethyl-β-phenethylamines and pentamethyl-β-phenethylamine. The psychopharmacological properties of these compounds are to be compared with those of the corresponding tetra- and pentamethoxy-β-phenethylamines, which were described previously.[4]

The ring-substituted tetra- and pentamethyl-β-phenethylamines were all prepared by the same synthesis scheme as outlined by the following general equation, where Ar represents the appropriately polymethyl-substituted phenyl group: $ArH \rightarrow ArCH_2Cl \rightarrow ArCH_2CN \rightarrow ArCH_2CH_2NH_2$. This synthetic route was particularly well suited to this series of compounds, since all of the starting tetra- and pentamethylbenzenes are commercially available or are readily accessible, and the chloromethylation reaction can give only one monochloromethyl product in each case. Treatment of the substituted benzyl chlorides so obtained with sodium cyanide and reduction of the resulting substituted phenylacetonitriles with lithium aluminum hydride proceeded smoothly and afforded the desired ring-substituted polymethyl-β-phenethylamines, which were isolated as their hydrochlorides.

Results of psychopharmacological studies will be published elsewhere.

EXPERIMENTAL[5]

Preparation of polymethylbenzyl chlorides. All of the polymethylbenzyl chlorides were prepared by chloromethylation of the appropriate hydrocarbon by a procedure similar to that described by Aitken *et al.*[6] In a typical run, a mixture of 25 g. (0.183 mole) of 1,2,3,4-tetramethylbenzene, 57 ml. of glacial acetic acid, 105 ml. of concentrated HCl, and 13 g. of 37% aqueous formaldehyde was stirred and heated at 60–70° for 6 hr., adding an additional 5.4 g. of formaldehyde solution at the end of the first 3 hr. When cool, the aqueous layer was decanted from the insoluble white solid reaction product, which was dissolved in benzene. The resulting solution was washed with aqueous Na_2CO_3, dried over anhydrous $MgSO_4$, and the solvent was removed by distillation under reduced pressure. Distillation of the residue gave 18.0 g. (52%) of pure 2,3,4,5-tetramethylbenzyl chloride; b.p. 140–150°/7–10 mm.; m.p. 44–45° (literature,[7] m.p. 44–45°). By employing this procedure with other polymethylbenzenes, the following benzyl chlorides were prepared: pentamethylbenzyl chloride, m.p. 81–82° (literature,[6] m.p. 82–84°), from pentamethylbenzene; 2,3,4,6-tetramethylbenzyl chloride, b.p. 133–137°/10 mm. (literature,[8] b.p., 113–115°/5 mm.), from isodurene[9]; 2,3,5,6-tetramethylbenzyl chloride, b.p. 122–125°/5 mm. (literature,[6] b.p. 140–148°/15 mm.), m.p. 70–71° (literature,[9] m.p. 67–68°), from durene.

Preparation of polymethylphenylacetonitriles. All of the intermediate polymethylphenylacetonitriles were prepared by treatment of the benzyl chlorides with NaCN in an aqueous alcohol solution and refluxing the mixture for a period of 3 hr. The phenylacetonitriles were isolated and purified by the procedure outlined by Adams and Thal.[10] The following polymethylphenylacetonitriles were obtained by this procedure: 2,3,5,6-tetramethylphenylacetonitrile, m.p. 85–87° (literature,[6] m.p. 84–85°); 2,3,4,6-tetramethylphenylacetonitrile, b.p. 148–164°/7 mm.; m.p. 49–50°[11]; *2,3,4,5,6-pentamethylphenylacetonitrile,* b.p. 143–146°/1.2 mm., m.p. 103–104°.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 82.6; H, 9.0; N, 8.0.

Polymethyl-β-phenethylamines. The intermediate nitriles were reduced by means of lithium aluminum hydride using a procedure previously described for the preparation of pentamethoxy-β-phenethylamine by reduction of the corresponding nitrile.[4] The β-phenethylamines were isolated by hydrolyzing the final reduction mixture with a limited quantity of water, filtering the ether solution of the product from inorganic matter, and drying the filtrate over anhydrous magnesium sulfate. In each instance, the product was

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[3] F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 22, 332 (1957).

[4] F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 20, 102 (1955).

[5] All melting and boiling points are uncorrected.

[6] R. R. Aitken, G. M. Badger, and J. W. Cook, *J. Chem. Soc.*, 331 (1950).

[7] L. I. Smith and C. L. Agre, *J. Am. Chem. Soc.*, **60**, 648 (1938).

[8] R. C. Fuson and C. A. Sperati, *J. Am. Chem. Soc.*, **63**, 2643 (1941).

[9] Prepared from mesitylene as described by L. I. Smith, *Org. Syntheses*, **Coll. Vol. II**, 1st ed., 360 (1943).

[10] R. Adams and A. F. Thal, *Org. Syntheses*, **Coll. Vol. I**, 2nd ed., 107 (1948).

[11] Product was not further purified prior to use in next step. L. I. Smith, *J. Am. Chem. Soc.*, **60**, 648 (1938), reported a melting point of 57–58° for this nitrile.