bromide. After working up the reaction mixture in the usual way, the infrared spectrum indicated the presence of unreacted ester by an absorption peak at 5.82 μ. The unreacted ester was saponified by refluxing with methanolic potassium hydroxide. Water then was added to the reaction mixture and the *o*-dibenzoylbenzene was extracted with benzene and ether. The benzene-ether solution was dried over magnesium sulfate and then removed at reduced pressure to give an orange-green oil. Upon addition of a small amount of ether, *o*-dibenzoylbenzene precipitated as a fine white powder. The product after recrystallization from absolute ethanol weighed 11.5 g. (8% yield) m.p. 146–146.5°, lit.[9] m.p. 146–147°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA 4, PENNSYLVANIA.

Mescaline Analogs. VI. Mescaline Homologs[1]

F. BENINGTON,[2] R. D. MORIN,[2] AND L. C. CLARK, JR.[3]

Received August 15, 1956

To examine the effect of structural variations on the unique physiological action of mescaline, 3,4,5-trimethoxy-β-phenethylamine, a number of closely related phenethylamines have been synthesized, and their effect on certain enzyme systems vital to brain function has been examined.[4]

All of the compounds previously reported[5] were β-phenethylamines with nuclear substituents which varied in type, number and position. A series of compounds related to mescaline now has been synthesized in which a 3,4,5-trimethoxybenzene nucleus is attached to aminoalkyl groups both longer and shorter than the aminoethyl side-chain of mescaline. These include 3,4,5-trimethoxybenzylamine and γ-(3,4,5-trimethoxyphenyl)propylamine. A sidechain isomer of mescaline, N-methyl-3,4,5-trimethoxybenzylamine, was also prepared. γ-(3,4-Dimethoxyphenyl)propylamine is a mescaline analog lacking one of the nuclear methoxyl groups and having an extra methylene group in the aminoalkyl side-chain. The physiological properties of these compounds are being examined to determine the influence of the nature of the aminoalkyl side-chain on the unique hallucinating properties of mescaline; the results of these studies will be reported elsewhere.

All of the compounds reported here were obtained by reduction of the corresponding amides with lithium aluminum hydride. 3,4,5-Trimethoxybenzylamine has been prepared previously[6] by reduction of 3,4,5-trimethoxybenzaldoxime with sodium amalgam. Reduction of the more readily available 3,4,5-trimethoxybenzamide with lithium aluminum hydride was convenient and proceeded in high yield. N-Methyl-3,4,5-trimethoxybenzylamine has been obtained by catalytic hydrogenation of the Schiff base obtained from 3,4,5-trimethoxybenzaldehyde and methylamine.[7] Lithium aluminum hydride reduction of N-methyl-3,4,5-trimethoxybenzamide resulted in an excellent yield of the corresponding amine. γ-(3,4,5-Trimethoxyphenyl)propylamine does not appear to have been synthesized previously; it was formed by lithium aluminum hydride reduction of β-(3,4,5-trimethoxyphenyl)propionamide, which was obtained from 3,4,5-trimethoxybenzaldehyde by the method of Slotta and Heller.[8] Similarly, γ-(3,4-dimethoxyphenyl)propylamine, also a new compound, was obtained from β-(3,4-dimethoxyphenyl)propionamide.

EXPERIMENTAL[9]

3,4,5-Trimethoxybenzylamine. To a solution of 2 g. of lithium aluminum hydride in 50 ml. of absolute ether was added 4.3 g. of 3,4,5-trimethoxybenzamide, m.p. 178–179°, obtained in quantitative yield from redistilled 3,4,5-trimethoxybenzoyl chloride and aqueous ammonia, by the Soxhlet extraction technique. Because of the low solubility of the amide in ether, transfer by extraction required over 100 hours. Using the procedure of Ramirez and Burger,[10] the reaction mixture was treated cautiously with water and then with 10% sulfuric acid to obtain two clear layers. The aqueous layer was neutralized to about *p*H 6 with solid lithium carbonate while stirring and heating on the steam-bath. The precipitated alumina was removed by filtration and the clear filtrate was treated at about 70° with a hot alcoholic solution of 8 g. of picric acid; on cooling, the picrate of 3,4,5-trimethoxybenzylamine crystallized; yield, 7.6 g. (89%); m.p. 195–196° after recrystallization from ethanol.

Anal. Calc'd for $C_{16}H_{18}N_4O_{10}$: C, 45.1; H, 4.2. Found: C, 45.2; H, 4.1.

The *hydrochloride* of 3,4,5-trimethoxybenzylamine was obtained by treatment of a solution of 7.5 g. of the picrate in 125 ml. of boiling water with 20 ml. of hydrochloric acid, removal of picric acid by filtration, and extraction with nitrobenzene, and evaporation of the resulting aqueous solution under reduced pressure; yield, 3.6 g. (91%); m.p. 205–206° (dec.), after recrystallization from methanol-ethyl acetate. The only salt of this amine recorded in the literature[6] is the *chloroplatinate*, m.p. 197°.

Anal. Calc'd for $C_{10}H_{16}ClNO_3$: Cl, 15.2; N, 6.0. Found: Cl, 15.0; N, 5.9.

N-Methyl-3,4,5-trimethoxybenzylamine. A hot solution of 8.1 g. of N-methyl-3,4,5-trimethoxybenzamide,[11] m.p. 136–137°, in 150 ml. of boiling reagent benzene was added to a stirred and refluxing solution of 7 g. of lithium aluminum

---

[1] This research was supported by Battelle Memorial Institute funds and in part by Public Health Service Grant No. M-600(R).

[2] Battelle Memorial Institute.

[3] Fels Research Institute.

[4] Clark, Fox, Benington, and Morin, *Federation Proc.*, **13,** 27 (1954).

[5] Benington, Morin, and Clark, *J. Org. Chem.*, **19,** 11 (1954); **20,** 102 (1955); **20,** 1292 (1955).

[6] Heffter and Capellmann, *Ber.*, **38,** 3634 (1905).

[7] Sonn, Müller, Bülow, and Meyer, *Ber.*, **58,** 1103 (1925).

[8] Slotta and Heller, *Ber.*, **63,** 3029 (1930).

[9] Melting points are uncorrected.

[10] Ramirez and Burger, *J. Am. Chem. Soc.*, **72,** 2781 (1950).

[11] Sonn and Meyer, *Ber.*, **58,** 1096 (1925).

hydride in 300 ml. of absolute ether during one hour. After refluxing overnight, the reaction mixture was cooled and hydrolyzed with water and 10% sulfuric acid. Alumina was precipitated with lithium carbonate as described previously, and the picrate of N-methyl-3,4,5-trimethoxybenzylamine crystallized from the filtrate after addition of a hot alcoholic solution of 10 g. of picric acid; yield, 15.0 g. (95%); m.p. 181–182°, after recrystallization from ethanol.

Anal. Calc'd for $C_{17}H_{20}N_4O_{10}$: C, 45.9; H, 4.5. Found: C, 46.0; H, 4.6.

The *hydrochloride* of N-methyl-3,4,5-trimethoxybenzylamine, obtained in 89% yield by decomposition of the picrate with HCl, melted at 178–179° (reported[7] m.p. 178°).

γ-(3,4,5-Trimethoxyphenyl)propylamine. Following the route of Slotta and Heller,[8] 3,4,5-trimethoxybenzaldehyde was condensed with malonic acid in the presence of pyridine and piperidine to obtain 3,4,5-trimethoxycinnamic acid, m.p. 124–125°, (reported[8] m.p. 124°) in 76% yield. Reduction with 2% sodium amalgam resulted in a 75% yield of β-(3,4,5-trimethoxyphenyl)propionic acid, m.p. 100–101°, after recrystallization from benzene-ligroin (reported[8] m.p. 98°). Conversion to the amide by refluxing a chloroform solution of the acid with purified thionyl chloride, removal of solvent under reduced pressure, and treatment of the residue with excess ammonium hydroxide gave a product melting at 108–109°, unchanged after several recrystallizations from benzene-ligroin. Slotta and Heller report a melting point of 171° for this compound.[8] Analysis of a specimen of the substance melting at 108–109° verified the structure assigned.

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.3; H, 7.1; N, 5.9. Found: C, 60.1; H, 7.3; N, 5.9. Reduction of 8.4 g. of β-(3,4,5-trimethoxyphenyl)propionamide with a solution of 3 g. of lithium aluminum hydride in 250 ml. of absolute ether was carried out by the Soxhlet addition method. Treatment of the reaction mixture as previously described gave 12.7 g. (80%) of the picrate of γ-(3,4,5-trimethoxyphenyl)propylamine, m.p. 216–217°, after recrystallization from ethanol-acetic acid.

Anal. Calc'd for $C_{18}H_{22}N_4O_{10}$: C, 47.6; H, 4.9. Found: C, 47.8; H, 5.0.

Decomposition of the picrate with boiling dilute hydrochloric acid, removal of picric acid, and evaporation gave 5.8 g. (89%) of *γ-(3,4,5-trimethoxyphenyl)propylamine hydrochloride*, m.p. 180–181°, after recrystallization from methanol-ethyl acetate.

Anal. Calc'd for $C_{12}H_{20}ClNO_3$: Cl, 13.6; N, 5.4. Found: Cl, 13.4; N, 5.4.

γ-(3,4-Dimethoxyphenyl)propylamine. β-(3,4-Dimethoxyphenyl)propionamide,[12] m.p. 121–122°, (10.5 g.) was added by the Soxhlet extraction method to a solution of 3.8 g. of lithium aluminum hydride in 250 ml. of absolute ether. Treatment of the reaction mixture as described above resulted in a yield of 18.1 g. (85%) of γ-(3,4-dimethoxyphenyl)-propylamine picrate, m.p. 145–146°, after recrystallization from ethanol.

Anal. Calc'd for $C_{17}H_{20}N_4O_9$: C, 48.1; H, 4.7. Found: C, 47.9; H, 4.6.

The *hydrochloride* of γ-(3,4-dimethoxyphenyl)propylamine was obtained in 83% yield by decomposition of the picrate with HCl; m.p. 166–167°, after recrystallization from methanol-ethyl acetate-ether.

Anal. Calc'd for $C_{11}H_{18}ClNO_2$: Cl, 15.3; N, 6.1. Found: Cl, 15.1; N, 6.0.

BATTELLE MEMORIAL INSTITUTE
COLUMBUS 1, OHIO
FELS RESEARCH INSTITUTE
YELLOW SPRINGS, OHIO

---

[12] Pictet and Finkelstein, *Ber.*, **42**, 1979 (1909).

The Peroxide Induced Reaction of Amines with Carbonyl Sulfide

FRED BAIOCCHI,[1a] RAY A. FRANZ,[2] AND LESTER HORWITZ[1a, 1b]

Received August 20, 1956

Carbonyl sulfide and a strongly basic aliphatic amine react in the cold easily to form the amine thiocarbamate salt, which on heating gives a 1,3-disubstituted symmetrical urea. Apparently the urea formation arises from the reaction of the isocyanate and amine which are formed, in addition to H_2S, by the thermal decomposition of the alkylammonium thiocarbamate.[3,4]

Weakly basic aromatic amines with carbonyl sulfide, at elevated temperatures or under the influence of ultraviolet irradiation, gave exceedingly poor yields of 1,3-diarylureas.[3] Aromatic amines are similarly sluggish in their reactions with carbon disulfide and it was found convenient to speed up the reaction in this case by the addition of dilute aqueous hydrogen peroxide.[5]

This study has extended the effect of peroxides to the reaction of amines with carbonyl sulfide and the results are listed in Table I.

Some findings are worthy of mention. As expected, by analogy to the reaction of amines with carbon disulfide, elemental sulfur was produced. In the case of the 1,3-dialkylureas the products had to be purified by recrystallization until they were sulfur free. With the 1,3-diarylureas the sulfur could be conveniently removed by boiling the mixture in an alkaline solution of sodium sulfide, in which the urea was stable and the sulfur soluble. The sulfur produced corresponded approximately to the molar quantity of urea formed. In experiments where aniline was omitted only a trace amount of sulfur was produced by the action of hydrogen peroxide on carbonyl sulfide, but adding bases increased sulfur formation.

If the hydrogen peroxide was doubled or halved with respect to the aniline concentration the yield of 1,3-diphenylurea was lowered by some 10%, with no appreciable difference in the amount of elemental sulfur isolated. When the hydrogen peroxide concentration was lowered even further, the yields then began to drop sharply.

Where the amines used had a vicinal hydroxy or amino group, there formed the corresponding cyclic products.

When aniline and carbonyl sulfide in methanol are treated either with zinc peroxide, di-*tert*-butyl

---

[1] (a) Midwest Research Institute; (1) (b) To whom inquiries may be addressed.

[2] Lion Oil Company.

[3] Hagelloch, *Ber.*, **83**, 258 (1950).

[4] Freund and Asbrand, *Ann.*, **285**, 173 (1895).

[5] Hünig, Lehmann, and Grimmer, *Ann.*, **579**, 77 (1953).