

Sulfur Analogs of Psychotomimetic Amines

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Abstract □ The syntheses and physical properties are described for 2,5-dimethoxy-4-methylthiophenylethylamine and 2,5-dimethoxy-4-methylthiophenylisopropylamine. The latter compound is the sulfur analog of the psychotomimetic phenylisopropylamines 2,4,5-trimethoxyphenylisopropylamine and 2,5-dimethoxy-4-methylphenylisopropylamine wherein the methylthio group replaces a methoxy group or a methyl group, respectively. This compound is predicted to be about 30 times as active as mescaline.

Keyphrases □ Amines, phenylalkyl, substituted—sulfur analogs of psychotomimetic agents synthesized □ Sulfur analogs—psychotomimetic substituted phenylalkylamines synthesized □ Psychotomimetic agents, potential—sulfur analogs of substituted phenylalkylamines synthesized

The 2,4,5-substituent orientation provides maximum potency in the trisubstituted psychotomimetic phenylisopropylamines (1), and recent studies focused attention upon the pharmacological importance of the chemical nature of specific 4-substituents (2, 3). 2,5-Dimethoxy-4-methylphenylisopropylamine¹ (I) is a potent compound which produces severe sensory disturbances and hallucinations. Increasing the length of the alkyl chain at the 4-position results in an increase in activity. Optimum activity is realized when the alkyl chain is three carbons (2, 3), and this result may be related to lipid partitioning (4).

The qualitative nature of intoxication induced also varies with the 4-substituent. For example, 2,5-dimethoxy-4-ethylphenylisopropylamine (II) and 2,5-dimethoxy-4-bromophenylisopropylamine (III) are about two and 10 times more potent, respectively, than I (5–7) in producing threshold central nervous system effects. In contrast, neither elicits the severe visual disturbances characteristic of I. Both the quantitative and the qualitative nature of the drug's action apparently are determined by the 4-substituent, although these relationships have not been defined clearly.

DISCUSSION

One route for the metabolism of I is through oxidation of the 4-methyl group (8, 9). It might be anticipated that such oxidation would be less favored in the higher alkyl homologs and that it could not occur with the 4-bromo compound. It was shown recently that II is metabolized in rats at the 4-ethyl position, but more slowly than with I (10), and that III generates no detectable inorganic bromide in humans (11).

The ability of a compound to produce hallucinatory disturbances may be lost when the 4-substituent is resistant to oxidation. The concept that facile oxidation of the 4-function might be involved in the production of hallucinations by psychotomimetic amphetamine derivatives may receive support through study of an amphetamine derivative with a 4-substituent that is unusually susceptible to oxidative metabolism.

The sulfur atom would appear to be an excellent choice for such a substituent. Metabolically, it should retain the chemical properties of oxygen in reactions such as S-demethylation but should allow the formation of sulfoxides and sulfones as products of oxidative me-

tabolism (12). The lipophilicity, electronic character, and size of sulfur also seem ideal. A comparison of the σ_p and π values for methoxy, methyl, methylthio, and bromo shows that the methylthio group lies intermediate between methyl and bromo (13–15). Barfknecht *et al.* (4) correlated human activity with octanol–water partition coefficients; by using the principles of additivity (16), one can predict that the methylthio analog should be some 30 times as potent as mescaline.

This paper describes the syntheses and properties of 2,5-dimethoxy-4-methylthiophenylisopropylamine (IV) and 2,5-dimethoxy-4-methylthiophenylethylamine (V). Compounds IV and V, as well as the intermediates IX, Xa, and Xb, have not been reported previously.

EXPERIMENTAL²

2,5-Dihydroxyphenylthiosulfuric Acid, Sodium Salt (VI)—The method of Alcalay (17) was modified as follows (Scheme I). A solution of 43.2 g of benzoquinone (0.4 mole) in 200 ml of acetic acid was added over 10 min to a solution of 149 g of sodium thiosulfate in 300 ml of water. The mixture was stirred for 1 hr and then reduced under vacuum to a thick syrup. The residue crystallized on standing and was slurried in a saturated salt solution and filtered. The solids were washed with small portions of a saturated salt solution, sucked dry, and finally dissolved in methanol and filtered through diatomaceous earth³. The methanol filtrate was concentrated *in vacuo*, yielding 67 g (68%) of VI as a yellow powder. This powder was used directly in the next step.

2,5-Dihydroxythiophenol (VII)—Fifty grams of VI (0.205 mole) was dissolved in a mixture of 200 ml of water and 400 ml of concentrated hydrochloric acid. Zinc dust (250 g) was added slowly over 1.5 hr, with external ice bath cooling applied as needed to keep the temperature at 50–60°. Adequate ventilation was needed because a large quantity of hydrogen sulfide was generated. Near the end of the reduction, the reaction mixture changed to a semisolid gray mass.

An additional 50 ml of concentrated hydrochloric acid was added to the mixture, and the solution was decanted from unreacted zinc metal. The aqueous acid solution was extracted with ether (6 × 100 ml), and the pooled extracts were washed with saturated sodium chloride solution (3 × 75 ml), dried (sodium sulfate), and concentrated *in vacuo*. The resulting yellow solid was recrystallized from ether to yield 24.7 g (85%) of pale-yellow needles, mp 118–119° [lit. (17) mp 118°].

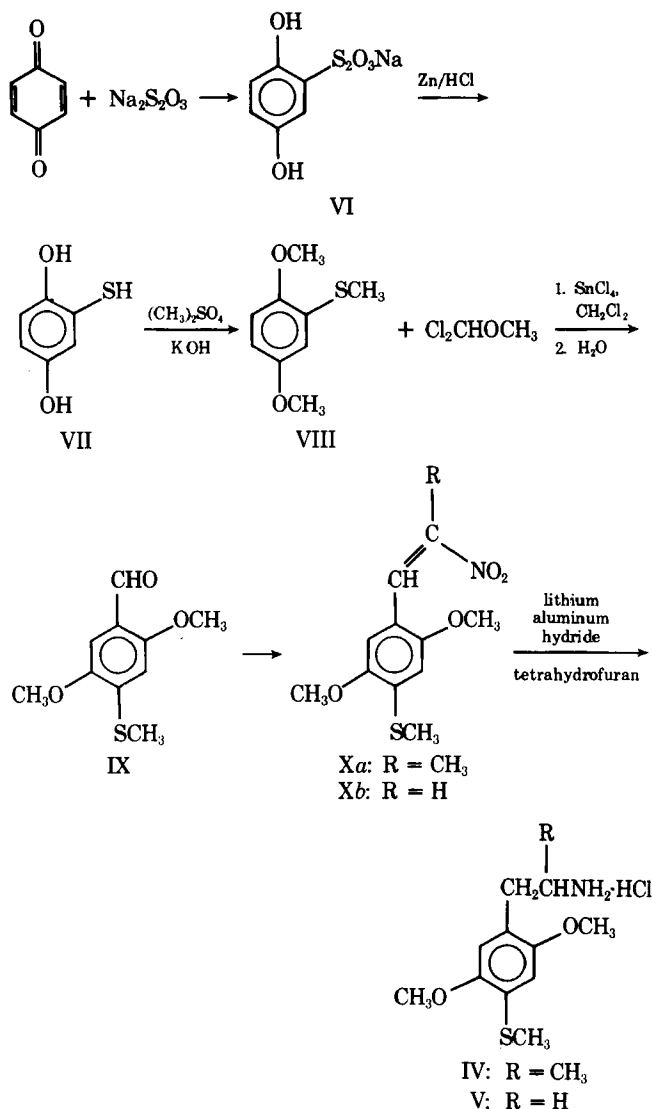
2,5-Dimethoxymethylthiophenol (VIII)—The method of Butenandt *et al.* (18) was modified as follows. To 200 ml of 9 N KOH (1.8 M) stirred under nitrogen was added 24 g (0.169 mole) of VII. Methyl sulfate (160 g, 1.27 mole) was added, with vigorous stirring, over 2 hr. The temperature (50–60°) was maintained by the rate of addition. The mixture was then heated to reflux for 3 hr, stirred overnight at room temperature, and filtered. The filtrate was extracted with 6 × 100 ml of ether, and the combined ether extracts were washed with 2 × 50 ml of saturated sodium chloride solution, dried (sodium sulfate), and concentrated *in vacuo*. The residue was vacuum distilled to give 25.9 g (83%) of product, bp 86–88°/0.04 mm [lit. (18) bp 96–97°/0.07 mm] and mp 33–34° [lit. (18) mp 35°].

2,5-Dimethoxy-4-methylthiobenzaldehyde (IX)—The aldehyde was prepared using the method of Rieche *et al.* (19). A solution of 6.07 g (0.033 mole) of VIII in 40 ml of dry dichloromethane under nitrogen was cooled in an ice bath. To the solution was added 13.02 g (0.05 mole) of stannic chloride over 2 min. Dichloromethyl methyl ether, 3.45 g (0.03 mole), was then added dropwise over 5 min, and stirring was continued with ice bath cooling for 15 min. The reaction was allowed to warm to room temperature over 30 min and was stirred for

² NMR spectra were obtained on a Varian A-60 or EM-360 spectrometer. IR spectra were obtained using a Beckman IR-18. Melting points were determined in open glass capillaries and are uncorrected.

³ Celite.

¹ Also referred to as DOM and STP.



Scheme I

an additional 1 hr, at which time hydrogen chloride evolution had ceased.

Then the mixture was slowly poured onto 15 g of ice in a separator, and the aqueous layer was separated and discarded. The organic phase was washed with 3×25 ml of 3 *N* HCl and 3×25 ml of saturated sodium chloride solution and dried (sodium sulfate), and the solvent was removed *in vacuo*. The solid residue was dissolved in methanol, filtered, and recrystallized from methanol–water to give 5.86 g (92%) of yellow needles. TLC (silica gel, chloroform) showed only one product. An analytical sample was further purified *via* the sodium bisulfite adduct and recrystallized from methanol–water, mp 99–100°; NMR (CDCl_3): δ 2.48 (s, 3H, SCH_3), 3.92, 3.97 (2s, 6H, OCH_3), 6.74, 7.29 (2s, 2H, ArH), and 10.45 (s, 1H, CHO).

Anal.—Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_3\text{S}$: C, 56.58; H, 5.70; S, 15.11. Found: C, 56.85; H, 5.51; S, 14.72.

The ylidinemalononitrile derivative of IX was prepared from equal weights of the benzaldehyde and malononitrile in ethanol with triethylamine catalysis, mp 185–186° after recrystallization from ethanol.

Anal.—Calc. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 59.98; H, 4.62; N, 10.76; S, 12.32. Found: C, 59.78; H, 4.83; N, 10.80; S, 11.96.

1-(2,5-Dimethoxy-4-methylthiophenyl)-2-nitropropene (Xa)—A solution of 2.3 g (0.011 mole) of IX in 7.5 ml of nitroethane containing 0.45 g of ammonium acetate was heated on the steam bath for 6 hr. Removal of most of the nitroethane *in vacuo*, followed by the addition of 10 ml of methanol, gave crystals. After filtering and washing with cold methanol, the product was recrystallized from 140 ml of boiling ethanol, yielding 1.8 g (62%) of bright-orange crystals,

mp 137–138°; NMR (CDCl_3): δ 2.42 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 3.88 (s, 6H, OCH_3), 8.29 (broad s, 1H, $=\text{CH}$), 6.79, and 6.83 (2s, 2H, ArH).

Anal.—Calc. for $\text{C}_{12}\text{H}_{15}\text{NO}_4\text{S}$: C, 53.51; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.47; H, 5.71; N, 5.27; S, 11.99.

1-(2,5-Dimethoxy-4-methylthiophenyl)-2-nitroethylene (Xb)—Essentially the same procedure as for Xa was used, but use of nitromethane instead of nitroethane gave the homologous nitrostyrene. Recrystallization from ethanol gave rust-orange crystals (yield 68%), mp 165.5–166°.

Anal.—Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_4\text{S}$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 50.81; H, 5.12; N, 5.57; S, 11.96.

2,5-Dimethoxy-4-methylthiophenylisopropylamine (IV)—To a gently refluxing suspension of 1.4 g of lithium aluminum hydride in 40 ml of tetrahydrofuran was added dropwise a saturated solution of 1.7 g (0.006 mole) of Xa in tetrahydrofuran. Reflux with stirring was continued for 7 hr. The reaction mixture was then cooled externally with ice water; 1.6 ml of water, 1.6 ml of 15% NaOH, and finally 4.8 ml of water were added dropwise. Stirring was continued until no gray-colored solids remained. The mixture was filtered, the filter cake was washed with tetrahydrofuran, and the mother liquor and washings were combined and evaporated to dryness *in vacuo*.

The free base was a white solid; an analytical sample, after recrystallization from hexane, had a melting point of 91–93°. The product was dissolved in 25 ml of 2-propanol, titrated with concentrated hydrochloric acid to a persistent pink color (0.57 ml), and diluted with 100 ml of anhydrous ether. After a few moments, there was spontaneous formation of white crystals, 1.2 g (68% yield), mp 204–205°.

Anal.—Calc. for $\text{C}_{12}\text{H}_{20}\text{NO}_2\text{S}$: C, 51.87; H, 7.25; N, 5.04. Found: C, 51.40; H, 7.07; N, 5.52.

2,5-Dimethoxy-4-methylthiophenylethylamine (V)—The same procedure as was used for IV but with Xb instead of Xa gave the corresponding phenethylamine hydrochloride (V) as white crystals from 2-propanol–ether (57% yield). Recrystallization from ethanol gave melting point of 240–241° with prior darkening.

Anal.—Calc. for $\text{C}_{11}\text{H}_{18}\text{ClNO}_2\text{S}$: C, 50.08; H, 6.87; N, 5.31; S, 12.15. Found: C, 50.03; H, 6.83; N, 5.54; S, 12.10.

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Rapid Procedure for Assessment of Compounds that Modify Uptake and Release of Tritiated Norepinephrine

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Abstract □ A rapid procedure to estimate tritiated norepinephrine (levarterenol) in a single mouse heart is described. The method is based upon oxidation of the tritium in the tissue to tritiated water, which is then determined by liquid scintillation spectroscopy. Large numbers of samples can be assayed with great facility. The effects of standard compounds that modify the uptake and release of ^3H -norepinephrine in heart tissue were determined with this system, and a procedure for studying their interactions is described.

Keyphrases □ Norepinephrine, tritiated—liquid scintillation spectroscopic analysis, effects of various compounds on uptake and release, mouse heart □ Spectroscopy, liquid scintillation—analysis, tritiated norepinephrine, mouse heart □ Radiolabeled compounds—tritiated norepinephrine, liquid scintillation spectroscopic analysis, mouse heart □ Adrenergic agents—norepinephrine, liquid scintillation spectroscopic analysis, mouse heart

Compounds that modify norepinephrine (levarterenol) uptake, release, storage, or turnover are frequently used in clinical medicine and in many procedures for the investigation, development, and characterization of new therapeutic agents (1–4). Norepinephrine metabolism has been studied by measuring changes in tritiated norepinephrine concentrations in the hearts of several species (5–7). Since some of these procedures are tedious and time consuming, only small numbers of individual or pooled samples can be conveniently assayed in a single experiment.

Introduction of instrumentation for the oxidation of small tissue samples allowed the development of a rapid and sensitive assay of ^3H -norepinephrine. This report describes a rapid screening procedure for studying compounds that affect the uptake and release of ^3H -norepinephrine in individual mouse hearts. The interactions of several test compounds with tyramine, reserpine, metaraminol, amphetamine, and tetrabenazine determined with this procedure are presented.

EXPERIMENTAL

Materials—The radiochemical purity (>95%) of 7- ^3H -*l*-norepinephrine¹, specific activity of 4.1 Ci/mmol, was verified by ascending paper chromatography in 1-butanol-acetic acid-water (4:1:1). The following compounds were used: *l*-norepinephrine bitartrate², *l*-

metaraminol bitartrate², tyramine hydrochloride³, reserpine hydrochloride⁴, dextroamphetamine sulfate⁵, tetrabenazine methanesulfonate⁶, chlorpromazine hydrochloride⁷, guanethidine sulfate⁸, bretylium *p*-toluenesulfonate⁹, desipramine hydrochloride¹⁰, and cocaine hydrochloride¹⁰.

Animals and Dosage—Swiss Webster mice, 20 ± 2 g, were used. All compounds were administered as a solution in 0.2 ml of distilled water. ^3H -Norepinephrine ($1 \mu\text{Ci}$) was administered intravenously in the tail vein. Test compounds were administered subcutaneously.

^3H -Norepinephrine Assay—Mice were killed by cervical dislocation. Hearts were removed, blotted, and weighed on tared low ash filter paper disks¹¹ and dried overnight in a refrigerator (4°). The tissue sample was compressed in a tablet press and oxidized in a sample oxidizer¹². The resulting tritiated water was collected in counting vials, and 15 ml of scintillation fluid¹³ was added. Radioactivity was measured in a liquid scintillation spectrometer¹². The counting efficiency was determined by the channels ratio method.

Heart tritium concentrations were proportional to dose over the range studied, 0.25–5.0 μCi of tritiated norepinephrine. The dose used in these studies, 1 μCi , yielded about 10,000 cpm/mouse heart (220 nCi/g) after 2 hr.

Uptake and Release Study—Effects on the uptake of ^3H -norepinephrine by the heart were determined by administering the test compounds subcutaneously 15 min before the intravenous administration of 1 μCi of ^3H -norepinephrine. The animals were sacrificed 2 hr after the administration of the radiotracer. Release of ^3H -norepinephrine was determined by administering the test compound subcutaneously 15 min after the administration of ^3H -norepinephrine. After 2 hr, the animals were sacrificed, hearts were removed, and radioactivity was determined.

Interaction Study—The interactions of desipramine, chlorpromazine, and cocaine with tyramine, reserpine, metaraminol, amphetamine, and tetrabenazine were estimated by their effects in combination on the release of ^3H -norepinephrine from the heart. ^3H -Norepinephrine (1 μCi) was administered intravenously to 11 groups of mice, and the test compound was administered to five groups after 15 min. Then 15 min later, the releasing agents were administered to the pretreated animals and to additional control groups. One group served as unmedicated controls. The animals were sacrificed 2 hr after administration of ^3H -norepinephrine.

³ Eastman Organic Chemicals.

⁴ Knoll Pharmaceutical.

⁵ Mann Research Labs.

⁶ Hoffmann-La Roche.

⁷ Smith Kline and French Labs.

⁸ Ciba-Geigy Pharmaceuticals.

⁹ Burroughs Wellcome Co.

¹⁰ Merck & Co.

¹¹ Carl Schleicher and Scheull.

¹² Packard Tri-Carb.

¹³ Consisting of 5 g of 2,5-diphenyloxazole, 0.75 g of 1,4-bis[2-(5-phenyloxazolyl)]benzene, 100 g of naphthalene, 150 ml of toluene, 40 ml of ethyl alcohol, and dioxane to make 1 liter.

¹ Amersham/Searle.

² Sterling-Winthrop Research Institute.