[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

# Chlorinated *o*-Dimethylaminopropylaminodiphenyl Sulfide Derivatives[1]

ALFRED BURGER AND JOSEPH L. STANMYER, JR.

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The synthesis of several 2'-, 4-, and 5-chloro- and 3',4-, 4',5-, and 4,4'-dichloro-2-(γ-dimethylaminopropylamino)diphenyl sulfide derivatives for biological evaluation is described.

In view of the varied and useful physiological activities of 10-dialkylaminoalkylphenothiazine derivatives, analogs derived from systems in which the hetero-ring has been "opened" have been prepared in recent years. Among them were 2-dialkylaminoalkylamino- and 2-dialkylaminoacyl-diphenyl sulfides.[2,3] It has been reported[3] that 2-(2-dimethylaminopropylamino)diphenyl sulfide prevents nicotine tremors to the same degree as 10-(2-diethylaminopropylamino)phenothiazine but lacks the antihistaminic properties of this drug. The dimethylaminopropionamido analog showed similar effects, while 2 - (2 - dimethylaminoethylamino)diphenyl sulfide was somewhat antihistaminic. One may conclude that opening of the phenothiazine ring at position 10 decreases antihistaminic effects without modifying parasympatholytic activity. Earlier, several diethylaminoalkylaminodiphenyl sulfides had been prepared[4] in a systematic variation of plasmodicidal structures, and had been reported to possess anesthetic and amebacidal properties. Since chlorpromazine and other nuclear substituted dialkylaminoalkylphenothiazine derivatives exhibit antiemetic properties which aid in the symptomatic treatment of irradiation damage, a series of nuclear chlorinated 2-dimethylaminopropylaminodiphenyl sulfide derivatives have now been synthesized for tests in this condition.

Benzenethiol, its *m*- and *p*-chloro derivatives, or 2-aminobenzenethiol were condensed with 2-chloronitrobenzene or appropriate 2,x-dichloronitrobenzenes in ethanolic alkaline solution. This method was superior to others previously recommended for the synthesis of 2-nitrodiphenyl sulfide derivatives. For example, benzenethiol and 2-chloronitrobenzene gave nitrodiphenyl sulfide in 77% yield while attempts to work by an older method[5] in the absence of a solvent furnished only intractable tars. Where 2-aminobenzenethiol was used in the condensation, the resulting 2'-amino-2-nitrodiphenyl sulfide derivatives were subjected to a Sandmeyer reaction to replace the amino group by chlorine. 2-Nitro-5-chlorodiphenyl sulfide was obtained by condensing 1,2-dinitro-4-chlorobenzene with benzenethiol, and 2-nitro-4',5-dichlorodiphenyl

TABLE I

DERIVATIVES OF 2-NITRODIPHENYL SULFIDE

| Starting Materials: Benzene Derivative | Starting Materials: Benzene Derivative | Derivative of 2-Nitrodiphenyl Sulfide | M.p., °C. (corr.) | Yield, % |
|---|---|---|---|---|
| 1-SH-2-$NH_2$ | 1-$NO_2$-2-Cl | 2'-$NH_2$[6] | 85–86 | 50 |
| 1-SH-3-Cl | 1-$NO_2$-2-Cl | 3'-Cl[7] | 105–107 | 41 |
| 1-SH-4-Cl | 1-$NO_2$-2-Cl | 4'-Cl[7] | 95–97 | 48 |
| -SH | 1,4-$Cl_2$-2-$NO_2$ | 4-Cl[8] | 81.5–84.5 | 90 |
| 1-SH-2-$NH_2$ | 1,4-$Cl_2$-2-$NO_2$ | 2'-$NH_2$-4-Cl[9] | 128–130 | 91 |
| 1-SH-3-Cl | 1,4-$Cl_2$-2-$NO_2$ | 3',4-$Cl_2$[a] | 81–83 | 85 |
| 1-SH-4-Cl | 1,4-$Cl_2$-2-$NO_2$ | 4,4'-$Cl_2$[8] | 159.5–162.5 | 99 |
| -SH | 1,2-($NO_2$)$_2$-4-Cl | 5-Cl[10] | 125 | 50[d] |
| 1-SH-4-Cl | 1,2-($NO_2$)$_2$-4-Cl | 4',5-$Cl_2$[b] | 119–126 | 47[d] |
| 2-Nitro-2'-aminodiphenyl sulfide | | 2'-Cl[6] | 121–122 | 36 |
| 2-Nitro-2'-amino-4-chlorodiphenyl sulfide | | 2',4-$Cl_2$[c] | 70–71.5 | 28 |

[a] Crystallized from acetic acid. Calc'd for $C_{12}H_7Cl_2NO_2S$: C, 48.01; H, 2.35. Found: C, 48.25; H, 2.69. [b] Yellow needles from acetic acid. Calc'd for $C_{12}H_7Cl_2NO_2S$: C, 48.01; H, 2.35. Found: C, 48.27; H, 2.41. [c] Yellow, from dilute ethanol. Calc'd for $C_{12}H_7Cl_2NO_2S$: C, 48.01; H, 2.35. Found: C, 48.12; H, 2.34. [d] The other products found in the reaction mixtures by Loudon[10] in unspecified yields have not been elaborated in these experiments.

(1) This research was supported by the USAF under Contract No. AF18(600)-929, monitored by the School of Aviation Medicine, USAF, Randolph Field, Texas.

(2) E. Knüsli, *Experientia*, **8**, 262 (1952).

(3) G. L. Gatti, *Rend. ist. super. sanità*, **16**, 140 (1953).

(4) B. Pützer and F. Schönhöfer, German Patent 550,327 (1930); *Chem. Abstr.*, **26**, 4062 (1932).

(5) N. M. Cullinane and C. G. Davies, *Rec. trav. chim.*, **55**, 881 (1936).

(6) T. Mazónski, *Roczniki Chem.*, **23**, 318 (1949); *Chem. Abstr.*, **45**, 5647 (1951).

(7) R. Passerini, *Boll. sci. facoltà chim. ind. Bologna*, **8**, 122 (1950); *Chem. Abstr.*, **45**, 7975 (1951).

(8) J. D. Loudon and N. Shulman, *J. Chem. Soc.*, 1618 (1938).

(9) A. Levi, L. A. Warren, and S. Smiles, *J. Chem. Soc.*, 1490 (1933).

(10) J. D. Loudon, *J. Chem. Soc.*, 902 (1939).

sulfide was formed in a similar manner by using *p*-chlorobenzenethiol. The starting materials and products from these reactions are listed in Table I.

Of several chemical and catalytic methods tried to reduce the chloro-2-nitrodiphenyl sulfide derivatives to the corresponding amines, the procedure of Balcom and Furst[11] proved most applicable, yields of 43% to 76% being obtained. The *N*-alkylation of the resulting chloro-2-aminodiphenyl sulfides with 3-dimethylaminopropyl chloride under the influence of sodium hydride, sodamide or potassium amide in toluene medium was successful only with 2-amino-4′-chlorodiphenyl sulfide; isomeric chloro compounds, and even aniline could not be dimethylaminopropylated this way. It became necessary to treat the aminodiphenyl sulfides with β-chloropropionyl chloride and replace the aliphatic chlorine atom of the resulting β-chloropropionamides with the dimethylamino group by heating with a dry benzene solution of dimethylamine for 24 hours at 100°. The average yields in this amination lay between 36 and 45%; without autoclaving they ranged from 4 to 19% only. One of the reactions with dimethylamine took a different course; 2-(3-chloropropionamido)-4-chlorodiphenyl sulfide gave an unsaturated amide which from its composition and behavior towards bromine and potassium permanganate appeared to be 2-acrylamido-4-chlorodiphenyl sulfide.

The β-dimethylaminopropionamides were reduced with lithium aluminum hydride. In this manner, 4,4′-dichloro- and 4′,5-dichloro-2-(3-dimethylaminopropylamino)-diphenyl sulfide were obtained.

The lengthy approach to the chlorinated 2-aminodiphenyl sulfide derivatives needed as intermediates in these syntheses prompted us to study the possibility of reductive chlorination of some of the corresponding chlorine-free 2-aminodiphenyl sulfoxides. The procedure of reductive halogenation had been particularly rewarding in the series of phenothiazine-5-oxides.[12,13] Therefore, 2-acetamidodiphenyl sulfoxide was prepared by oxidizing the corresponding sulfide with hydrogen peroxide in acetone solution in the presence of a small amount of acetic acid without which oxidation could not be effected. Treatment of the sulfoxide with either concentrated hydrochloric or hydrobromic acid merely reduced and deacylated the compound to 2-aminodiphenyl sulfide without halogenating the benzene rings.

## EXPERIMENTAL[14]

*Materials.* 4-Chlorobenzenethiol was purchased from Evans Chemetics, Inc., New York 17, N. Y. One batch of 3-chlorobenzenethiol was supplied by Dr. George Connitt of Smith, Kline & French Laboratories, Philadelphia, Pa., who also donated 3-dimethylaminopropyl chloride hydrochloride. The main amount of 3-chlorobenzenethiol was prepared by heating 1 mole of dry sodium 3-chlorobenzenesulfonate, 1 mole of phosphorus oxychloride, and 0.5 mole of phosphorus pentachloride at 170–180° for 15 hours, decomposing with 1500 g. of ice-water, and working up the oily 3-chlorobenzenesulfonyl chloride. It had b.p. 142–145° (16 mm.),[15] yield, 56 to 69%. It was reduced by the standard method with tin and hydrochloric acid. The yield of colorless 3-chlorobenzenethiol, b.p. 90–92° (13 mm.) was 31.5%. The literature[16] reports b.p. 205–207°.

*General directions.* (*a*) *Chloro-2-nitrodiphenyl sulfides.* One mole of 2-chloronitrobenzene was added to a solution of 0.8 mole of the respective thiol (thiophenol, chlorothiophenol, or 2-aminothiophenol) in a 5% aqueous or ethanolic solution of 1 mole of sodium hydroxide. The mixture was refluxed for 2.5 hours and filtered hot. The inorganic precipitate was washed with hot ethanol and the filtrate was steam-distilled to remove unreacted 2-chloronitrobenzene. The residue was recrystallized from ethanol with the aid of charcoal. If 1,4-dichloronitrobenzene or 1,2-dinitro-4-chlorobenzene was used, molar proportions were reacted throughout, the heating time was one hour, and the solid residue which separated on cooling was recrystallized from glacial acetic acid or ethanol.

(*b*) *Sandmeyer reactions.* 2′-Chloro- and 2′,4-dichloro-2-nitrodiphenyl sulfide were prepared from the corresponding 2′-amines. A stirred solution of 1 mole of the nitro amine in 365 ml. of 37% hydrochloric acid and 625 ml. of hot water was cooled to below 1°, and a solution of one mole of sodium nitrite in 160 ml. of water was added at a rate to keep the temperature below 1°. The suspension of the resulting diazonium salt was stirred into a solution of 1 mole of cuprous chloride in 800 ml. of 37% hydrochloric acid at 60–70° over a period of 30 minutes, and the reaction mixture was heated on a steam-bath for 1.5 hours. The brown solid precipitate was filtered, washed with water, dissolved in 500 ml. of benzene, washed well with 5% sodium hydroxide solution, dried, and either chromatographed over alumina, or evaporated. The residue was recrystallized repeatedly from dilute ethanol.

(*c*) *Reduction of 2-nitro- to 2-aminodiphenyl sulfides.* A solution of 1 mole of the nitro compound and 5 moles of 100% hydrazine hydrate in 4.5 l. of ethanol was warmed to 50°, and 1 to 3 spatula-fulls of Raney nickel was added. When the initial frothing had subsided after about one hour, another 7–20 g. of Raney nickel was added, the mixture was boiled for one hour, the catalyst filtered, the filtrate cleared with charcoal, and the solvent evaporated under reduced pressure. If crystalline, the residue was recrystallized, or if oily, it was distilled through a short Vigreux column and converted to a salt.

(*d*) *N-Acetylation* of the 2-aminodiphenyl sulfide derivatives was done by refluxing the amine (0.02 mole) with about five volumes of acetic anhydride and five drops of concentrated sulfuric acid for two hours, pouring the mixture into ice-water, making the solution alkaline with sodium carbonate, and recrystallizing the acetamide derivative.

(*e*) *N-β-Chloropropionylation* of the amines was carried out according to the procedure given by Mayer, *et al.*[17] for β-chloropropionanilide. A solution of 0.1 mole of β-chloropropionyl chloride in 20 ml. of dry acetone was added dropwise to a refluxing solution of 0.2 mole of the amine in 10–200 ml. of acetone. After refluxing for one hour, the mixture was poured into 300 ml. of 12% hydrochloric acid, and the precipitated solid recrystallized from methanol.

(11) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

(12) A. C. Schmalz and A. Burger, *J. Am. Chem. Soc.*, **76**, 5455 (1954).

(13) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **77**, 3862 (1955).

(14) All melting points are corrected. Microanalyses by Miss Barbara J. Williamson.

(15) E. Kieselinsky, *Ann.*, **180**, 108 (1876) did not report any data for this compound.

(16) C. Daccomo, *Jahresber. Fortschr. Chem.*, 1375 (1891).

(17) F. Mayer, L. van Zütphen, and H. Phillips, *Ber.*, **60**, 858 (1927).

TABLE II

DERIVATIVES OF DIPHENYL SULFIDE

| Substituents and Position | | | | | | Yield, | M.p., | B.p., | | | Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Calc'd | | Found | |
| 2 | 4 | 5 | 2′ | 3′ | 4′ | % | °C. | °C. | Mm. | Composition | C | H | C | H |
| $NH_2$ | | | | | | 65[c] | | 167–168 | 1 | | | | | |
| $NH_2$ | | | Cl | | | 57 | 76–77.5 | | | $C_{12}H_{10}ClNS$ | 61.14 | 4.28 | 61.02 | 4.06 |
| $NH_2$ | | | | Cl | | 76 | | 169–172 | 1.9 | | | | | |
| $NH_2$·HCl | | | | Cl | | | 173–177 | | | $C_{12}H_{10}ClNS$·HCl | 52.95 | 4.07 | 52.74 | 4.09 |
| $NH_2$ | | | | | Cl | 74 | | 164–166 | 0.45 | | | | | |
| $NH_2$·HCl | | | | | Cl | | 172–174 | | | $C_{12}H_{10}ClNS$·HCl | 52.95 | 4.07 | 52.99 | 3.93 |
| $NH_2$ | Cl | | | | | 74 | 63–65 | | | $C_{12}H_{10}ClNS$ | 61.14 | 4.28 | 61.11 | 4.45 |
| $NH_2$ | Cl | | | Cl | | 43 | 41.5–44 | 194 | 0.65 | | | | | |
| $NH_2$·HCl | Cl | | | Cl | | | 158.5–163 | | | $C_{12}H_9Cl_2NS$·HCl | 47.00 | 3.29 | 46.71 | 3.30 |
| $NH_2$ | Cl | | | | Cl | 47 | 71.5–72.5 | 183–189 | 0.7 | $C_{12}H_9Cl_2NS$ | 53.34 | 3.36 | 53.45 | 3.47 |
| $NH_2$ | | Cl | | | | 46 | | 172–174 | 1 | | | | | |
| $NH_2$·HCl·$H_2O$ | | Cl | | | | | 184.5–189.5[a] | | | $C_{12}H_{10}ClNS$·HCl·$H_2O$ | 49.66 | 4.52 | 49.28 | 4.13 |
| $NH_2$ | | Cl | | | Cl | 57 | [b] | 196 | 2.5 | | | | | |
| $NH_2$·HCl | | Cl | | | Cl | | 169–174 | | | $C_{12}H_9Cl_2NS$·HCl | 47.00 | 3.29 | 46.98 | 3.15 |
| $NHCOCH_3$ | | | | Cl | | 10 | 104–105 | | | $C_{14}H_{12}ClNOS$ | 60.53 | 4.35 | 60.35 | 4.52 |
| $NHCOCH_3$ | | | | | Cl | 40 | 118–119 | | | $C_{14}H_{12}ClNOS$ | 60.53 | 4.35 | 60.61 | 4.39 |
| $NHCOCH_3$ | Cl | | | | Cl | | 69.5–71.5 | | | $C_{14}H_{11}Cl_2NOS$ | 53.85 | 3.55 | 53.52 | 3.55 |
| $NHCOCH_3$ | | Cl | | | | | 68–70 | | | $C_{14}H_{12}ClNOS$ | 60.53 | 4.35 | 60.11 | 4.17 |
| $NHCOCH_3$ | | Cl | | | Cl | 58 | 117–118 | | | $C_{14}H_{11}Cl_2NOS$ | 53.85 | 3.55 | 53.96 | 3.48 |
| $NHCOCH_2CH_2Cl$ | Cl | | | | | 97 | 87–89 | | | $C_{15}H_{13}Cl_2NOS$·$^1/_2H_2O$ | 53.74 | 4.18 | 53.55 | 4.01 |
| $NHCOCH_2CH_2Cl$ | Cl | | | | Cl | 86 | 142–143 | | | $C_{15}H_{12}Cl_3NOS$ | 49.95 | 3.35 | 50.09 | 3.59 |
| $NHCOCH_2CH_2Cl$ | | Cl | | | Cl | 79 | 129–130.5 | | | $C_{15}H_{12}Cl_3NOS$ | 49.95 | 3.35 | 49.99 | 3.31 |
| $NHCOCH_2CH_2N(CH_3)_2$ | Cl | | | | Cl | 45 | 78–80 | | | $C_{17}H_{18}Cl_2N_2OS$ | 55.28 | 4.91 | 54.99 | 4.89 |
| $NHCOCH_2CH_2N(CH_3)_2$ | | Cl | | | Cl | 36 | 81.5–83.5 | | | $C_{17}H_{18}Cl_2N_2OS$ | 55.28 | 4.91 | 55.34 | 4.79 |
| $NH(CH_2)_3N(CH_3)_2$ | Cl | | | | Cl | 44 | | 196–198 | 0.6 | | | | | |
| $NH(CH_2)_3N(CH_3)_2$·HCl | Cl | | | | Cl | | 157.5–159.5 | | | $C_{17}H_{20}Cl_2N_2S$·HCl | 52.11 | 5.40 | 51.99 | 5.61 |
| $NH(CH_2)_3N(CH_3)_2$ | | Cl | | | Cl | 31.5 | | 227–229 | 2.9 | | | | | |
| $NH(CH_2)_3N(CH_3)_2$·2HCl | | Cl | | | Cl | | 128–135 | | | $C_{17}H_{20}Cl_2N_2S$·2HCl·-$^1/_2H_2O$ | 46.69 | 5.30 | 46.55 | 5.47 |
| $NH(CH_2)_3N(CH_3)_2$ | | | | | Cl | 38 | | 198–199.5 | 1.5 | | | | | |
| $NH(CH_2)_3N(CH_3)_2$·HCl | | | | | Cl | | 171–172 dec. | | | $C_{17}H_{21}ClN_2S$·HCl | 57.14 | 6.21 | 57.20 | 6.09 |
| $NHCOCH{=}CH_2$ | Cl | | | | | 40 | 72.5–74 | 211 | 2.3 | $C_{15}H_{12}ClNOS$ | 62.17 | 4.17 | 61.71 | 3.94 |

[a] Softens at 150°. [b] Solidifies to a low-melting solid. [c] E. Bourgeois and P. Huber, *Rec. trav. chim.*, **31**, 30 (1912).

(*f*) *Conversion of β-chloropropionamides to β-dimethylaminopropionamides.* In a typical reaction, 1 mole of β-chloropropionanilide and a 20% solution of 10 moles of dimethylamine in dry benzene were heated in a glass-lined steel autoclave at 100° for 24 hours, the solvent was distilled, and the tan residue was treated with 10% sodium hydroxide solution and extracted with ether. The oily residue was fractionated. Solid products from analogous diphenyl sulfide compounds were recrystallized from hexane or isoöctane. Hydrochloride salts were prepared in dry ether, and recrystallized from ethanol–ether.

(*g*) *Reduction of β-dimethylaminopropionamides to γ-dimethylaminopropylamines.* As an example for these reductions, a solution of 9.73 g. (26 mmoles) of 4,4′-dichloro-2-(β-dimethylaminopropionamido)diphenyl sulfide in 200 ml. of dry ether was added to a solution of 1.2 g. (32.5 mmoles) of lithium aluminum hydride in 200 ml. of dry ether at a rate sufficient to maintain reflux. Stirring and refluxing was continued for 20 hours, the complex was decomposed with excess ice-water, and the mixture was made strongly alkaline and repeatedly extracted with ether. The oily residue was fractionated and converted to a hydrochloride in ether solution.

*4′-Chloro-2-(3-dimethylaminopropylamino)diphenyl sulfide.* A stirred solution of 20.4 g. (86 mmoles) of freshly distilled 2-amino-4′-chlorodiphenyl sulfide in 250 ml. of dry toluene was treated with 2.1 g. (86 mmoles) of sodium hydride, and the pale yellow mixture was refluxed for four hours when it turned dark red. To it was added 5.2 g. (43 mmoles) of freshly distilled 3-dimethylaminopropyl chloride (b.p. 60–61°/57 mm.) and refluxing and stirring was continued for another 13 hours. Sodium chloride was filtered from the cooled mixture, and the filtrate was washed with two small portions of water, dried over potassium carbonate, and the dark red residue from the ether solution was fractionated through a short Vigreux column.

*N-β-Dimethylaminopropionanilide.* This compound was prepared by the general procedure described above. The yield of oily material of b.p. 149° (1.4 mm.), or 136° (0.25 mm.) was 37%. The *hydrochloride* crystallized as plates, m.p. 197–199°.

*Anal.* Calc'd for $C_{11}H_{16}N_2O_2 \cdot HCl$: C, 57.76; H, 7.49. Found: C, 57.79; H, 7.37.

*N-γ-Dimethylaminopropyl aniline.* This derivative was prepared from the amide above by reduction with lithium aluminum hydride. The yield of pale yellow oil of b.p. 83–84° (0.4 mm.) was 32.4%. The colorless dihydrochloride melted at 174.5–178.5° dec.

*Anal.* Calc'd for $C_{11}H_{18}N_2 \cdot 2HCl$: C, 52.59; H, 8.02. Found: C, 52.59; H, 7.78.

*2-Acetamidodiphenyl sulfoxide.* A mixture of 7.38 g. (0.303 mole) of 2-acetamidodiphenyl sulfide, 3.4 g. (0.303 mole) of 30% hydrogen peroxide, 50 ml. of ethanol, and 10 ml. of acetic acid was refluxed for 12 hours. The yellow solution was poured into 150 ml. of water and concentrated to about 100 ml. The tan solid which deposited on standing was recrystallized from isopropyl ether, m.p. 99–101°. The yield was 3.33 g. (42.4%).

*Anal.* Calc'd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05. Found: C, 64.86; H, 5.05.

*Reductive hydrolysis of 2-acetamidodiphenyl sulfoxide with hydrohalic acids.* (a). A mixture of 3.2 g. of 2-acetamidodiphenyl sulfoxide and 75 ml. of 37% hydrochloric acid was refluxed for two hours, and the clear solution was decanted from a very small amount of brown oil and neutralized. The precipitated red oil was extracted into ether, dried, and fractionated. The clear yellow distillate (0.3 g.) boiled at 135–140° (0.7 mm.). 2-Aminodiphenyl sulfide *hydrochloride*, formed in dry ether solution and recrystallized from ethanol-ether, melted at 211–214° dec.

*Anal.* Calc'd for $C_{12}H_{12}ClNS$: C, 60.62; H, 5.09. Found: C, 60.06; H, 4.93.

(*b*). When 4.46 g. of 2-acetamidodiphenyl sulfoxide, and 17 ml. of 24% hydrobromic acid were agitated for 0.5 hour and then refluxed for one hour, a clear solution resulted which was separated from traces of insoluble oil. It deposited, on cooling, tan crystals of 2-aminodiphenyl sulfide hydrobromide which became colorless on recrystallization from ethanol-ether, m.p. 213–215°.

*Anal.* Calc'd for $C_{12}H_{12}BrNS \cdot 2H_2O$: C, 45.29; H, 5.07. Found: C, 45.79; H, 4.78.

*Biological results.* 4′,5-Dichloro-2-(3-dimethylaminopropionamido)diphenyl sulfide markedly prolonged the survival time of mice which had received a lethal dose of Roentgen rays. 4,4′- and 4′,5-Dichloro-2-(3-dimethylaminopropylamino)diphenyl sulfide were active against a considerable number of pathogenic fungi *in vitro*. Details of these tests will be published by the staff of the USAF School of Aviation Medicine, Randolph Air Force Base, Texas.

CHARLOTTESVILLE, VA.