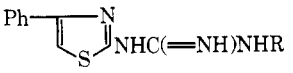
Similarly, various aryl-substituted N-aryl-N′-2-thiazolylguanidines and their hydrochlorides were prepared (see Table II).

TABLE II

N-ARYL-N′-2-(4-PHENYLTHIAZOLYL)GUANIDINES



No.	R	Mp, °C	Formula[a]	HCl Mp, °C	HCl formula[a]
1	*o*-MeC_6H_4	146	$C_{17}H_{16}N_4S$	193	$C_{17}H_{17}ClN_4S$
2	*m*-MeC_6H_4	142	$C_{17}H_{16}N_4S$	130–131	$C_{17}H_{17}ClN_4S$
3	*p*-MeC_6H_4	142	$C_{17}H_{16}N_4S$	187	$C_{17}H_{17}ClN_4S$
4	*o*-$OMeC_6H_4$	142	$C_{17}H_{16}N_4OS$	185–186	$C_{17}H_{17}ClN_4OS$
5	*m*-$OMeC_6H_4$	143	$C_{17}H_{16}N_4OS$	179–180	$C_{17}H_{17}ClN_4OS$
6	*p*-$OMeC_6H_4$	144	$C_{17}H_{16}N_4OS$	183	$C_{17}H_{17}ClN_4OS$
7	*p*-$OEtC_6H_4$	145	$C_{18}H_{18}N_4OS$	125	$C_{18}H_{19}ClN_4OS$
8	*p*-ClC_6H_4	147	$C_{16}H_{13}ClN_4S$	134–135	$C_{16}H_{14}Cl_2N_4S$

[a] See footnote *a*, Table I.

Polyiodo Derivatives of Anisidine Isomers

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Iodinated aromatic compounds are useful diagnostic agents because of their X-ray absorbtivity and their stability which minimizes generation of iodide ion.[1] We have prepared some tri- and tetraiodoanisidine derivatives for use as intermediates in the synthesis of potential radiopaque agents by treating potassium iodide with polyacetoxymercuri-N-acetylanisidines.[2] These polyiodo compounds are 70–80% in iodine, a level comparing favorably to that in currently used radiodiagnostic agents.[3]

Experimental Section[4]

Acetoxymercuration of the N-Acetylanisidines.—A ground mixture of 4.1 g (0.025 mole) N-acetyl-*p*-anisidine[5] and 32.0 g (0.100 mole) of $Hg(OAc)_2$ was heated in an open glass vessel in a 115–130° oil bath for 40 min. A shield was used. The resulting pink viscous liquid was treated at 80° with 50 ml of H_2O to yield 0.9 g (3.0%) of a white powder, mp 250–260° dec (from AcOH–H_2O). On the basis of subsequent iodination reactions, the product was tetraacetoxymercuri-N-acetyl-*p*-anisidine. Evaporation of the filtrate to 10 ml gave 3.0 g of a second white powder, mp 180–200° dec (from AcOH–H_2O). On the basis of subsequent iodination reactions, the product was a triacetoxymercuri-N-acetyl-*p*-anisidine.

It was possible to prepare the tetraacetoxymercuri derivative in 83% yield (crude) by heating for 1 hr at 130° a molar ratio of 5:1 $Hg(OAc)_2$–N-acetyl-*p*-anisidine.

The tetraacetoxymercuri derivatives of N-acetyl-*o*- and -*m*-anisidine were prepared similarly with the 5:1 molar ratio and the more severe reaction conditions. Table I (footnotes *d* and *e*) give properties.

Polyiodo-N-acetylanisidines.—Over a period of 45 min, a solution of 0.91 g (0.0040 mole) of I_2 and 1.72 g (0.012 mole) of KI in 25 ml of H_2O was added dropwise to a refluxing, stirred suspension of 0.85 g (0.00071 mole) of tetraacetoxymercuri-N-acetyl-*p*-anisidine in 100 ml of H_2O. Reaction was continued for 30 min after addition. On cooling, the product precipitated. It was filtered and washed with dilute KI solution and then H_2O to give 0.38 g (80%) of tetraiodo-N-acetyl-*p*-anisidine, mp 271° dec (from 95% EtOH). *Anal.* ($C_9H_7I_4NO_2$) I.

Tetraiodo-N-acetyl-*o*-anisidine, tetraiodo-N-acetyl-*m*-anisidine, and a triiodo-N-acetyl-*p*-anisidine were prepared essentially as above. See Table I.

Tetraiodo-*o*-anisidine and a Triiodo-*o*-anisidine.—To a solution of 4.0 g (0.0060 mole) of tetraiodo-N-acetyl-*o*-anisidine in 400 ml of 96% H_2SO_4, 164 ml of H_2O was added dropwise with stirring and cooling to keep the temperature below 60°. After addition, the solution was heated rapidly to 125° and at once was cooled to room temperature when 1.32 g (35%) of tetraiodo-*o*-anisidine separated. It was filtered on glass wool and washed (dilute $NaHCO_3$, H_2O), mp 149–151° (from MeOH). *Anal.* ($C_7H_5I_4NO$) I.

The filtrate was poured onto crushed ice and 0.38 g of a triiodo-*o*-anisidine separated, the structure of which was not determined; mp 132–133° (from MeOH). *Anal.* ($C_7H_6I_3NO$) I: calcd, 75.94; found, 76.28.

TABLE I

POLYIODO ANISIDINES

Isomer	Acetylated	Mp, °C	Yield,[a] %	Formula[g]
p	Yes	271	80	$C_9H_7I_4NO_2$
p[c]	Yes	258–259[b]	88	$C_9H_8I_3NO_2$
m[d]	Yes	266[b]	75	$C_9H_7I_4NO_2$
o[e]	Yes	278–279[b]	74	$C_9H_7I_4NO_2$
o	No	149–151	35[f]	$C_7H_5I_4NO$
o[e]	No	132–133	...	$C_7H_6I_3NO$[h]

[a] Crude yields based on acetoxymercuri precursor except where noted. [b] Melts with decomposition. [c] Particular triiodo isomer not determined. [d] Acetoxymercuri precursor obtained in 53% yield, mp 224–233° dec (from AcOH–H_2O). [e] Acetoxymercuri precursor obtained in 83% yield, mp 238–240° dec (from AcOH–H_2O). [f] Yield based on N-acetyl precusor. [g] All compounds were analyzed for I. [h] I: calcd, 75.94; found, 76.28.

Some Sulfonamide Derivatives of Cyclohexane[1]

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In continuation of our studies on reactions of N-halosulfonamides,[2] the reaction of N,N-dibromo-4-nitrobenzenesulfonamide with cyclohexene was investigated; *trans*-2-bromo-1-(4-nitrobenzenesulfonamido)cyclohexane (I) was the major product. Some compounds (III–V) having substituents other than bromine were synthesized starting from I *via* N-(4-nitrobenzenesulfonyl)-cyclohexenimine (II) and reduced catalytically to corresponding sulfanilamide derivatives (VI–IX).

Experimental Section[3]

N,N-Dibromo-4-nitrobenzenesulfonamide.—4-Nitrobenzenesulfonamide (20.2 g) was dissolved in a solution of NaOH (8 g) in H_2O (200 ml) and Br_2 (36 g) was added dropwise with stirring. The crystals that separated were filtered off, washed with H_2O, and dried, mp 163–164° dec. The yield was 34 g (94.5%). A

(1) V. H. Wallingford, *J. Am. Pharm. Assoc.*, **42**, 721 (1953).

(2) M. Ragno, *Gazz. Chim. Ital.*, **70**, 420 (1940); *Chem. Abstr.*, **35**, 3242 (1941).

(3) P. K. Knoefel in "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 1429.

(4) Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of theoretical values. Analyses were performed by Micro Tech Laboratories, Skokie, Ill. Melting points were taken in capillary tubes and are uncorrected.

(5) N. D. Cheronis and J. B. Entriken, "Semimicro Qualitative Organic Analysis," Thomas Crowell Co., New York, N. Y., 1947, p 404.

(1) Part IX of a series entitled Reaction of N-Haloamide. Part VIII: *Chem. Pharm. Bull.* (Tokyo), in press.

(2) Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *ibid.*, **15**, 1198, 1322, 1328 (1967).

(3) All melting points were uncorrected and determined using a W. Büchi melting point determination apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

part of this substance was recrystallized from EtOAc; the pure orange crystals melted at 166° dec. *Anal.* ($C_6H_3Br_2N_2S$) C, H, N.

***trans*-2-Bromo(4-nitrobenzenesulfonamido)cyclohexane (I).**—N,N-Dibromo-4-nitrobenzenesulfonamide (10 g) was added to a mixture of cyclohexene (30 ml) and CCl_4 (15 ml). A white precipitate appeared with slight evolution of heat. After the exothermic reaction subsided, the mixture was refluxed for 2.5 hr, and the precipitate was filtered with suction. Recrystallization (EtOH) gave colorless needles, mp 170–171°, yield 8.8 g (87.3%). *Anal.* ($C_{12}H_{15}BrN_2O_4S$) C, H, N.

***trans*-2-Ethoxy-1-(4-nitrobenzenesulfonamido)cyclohexane (III).**—2-Bromo-1-(4-nitrobenzenesulfonamido)cyclohexane (I) (3 g) was added to a solution of Na (0.2 g) in absolute EtOH (30 ml). The mixture was refluxed on a steam bath for 2 hr. After the solution was cooled, 3.5% HCl (9.1 ml) was added and allowed to stand to yield 2.1 g (75%) of pale yellow needles, mp 140–141° (from MeOH). *Anal.* ($C_{14}H_{20}N_2O_5S$) C, H, N.

N-(4-Nitrobenzenesulfonyl)cyclohexenimine (II).—Dried Ag_2O (prepared from 3 g of $AgNO_3$), I (2 g), and Me_2CO (25 ml) were mixed and refluxed for 6 hr. The precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized (C_6H_6) giving pale yellow needles, mp 133–136°, yield 1.25 g (80.7%). This compound was also obtained by the treatment of I with AgOAc in C_6H_6. *Anal.* ($C_{12}H_{14}N_2O_4S$) C, H, N.

***trans*-2-Acetoxy-1-(4-nitrobenzenesulfonamido)cyclohexane (IV).**—A mixture of II (0.5 g) and AcOH (3 ml) was refluxed for 3 hr. After cooling, H_2O (2 ml) was added; the white precipitate was recrystallized (EtOH) yielding yellow granules, 0.55 g (90%), mp 157–158°. *Anal.* ($C_{14}H_{18}N_2O_6S$) C, H, N.

***trans*-2-Chloro-1-(4-nitrobenzenesulfonamido)cyclohexane (V).**—A mixture of II (0.564 g) and 13% HCl (4.2 ml) was refluxed for 3 hr. After cooling, the precipitate was collected and recrystallized (EtOH), mp 150–151°, yield 0.574 g (89%). *Anal.* ($C_{12}H_{15}ClN_2O_4S$) C, H, N.

Catalytic Reduction of Nitro Compounds I, III–V.—These compounds were reduced catalytically in EtOH (PtO_2) to the corresponding amino compounds (VI–IX, respectively) in good yields as follows: VI, mp 174–175° [*Anal.* ($C_{12}H_{17}BrN_2O_2S$) C, H, N]; VII, mp 105–106° [*Anal.* ($C_{14}H_{22}N_2O_3S$) C, H, N]; VIII, mp 157–158° [*Anal.* ($C_{14}H_{20}N_2O_4S$) C, H, N]; IX, mp 159–160° [*Anal.* ($C_{12}H_{17}ClN_2O_2S$) C, H, N]. VI was treated with Ac_2O to give *trans*-2-bromo-1-(4-acetamidobenzenesulfonamido)cyclohexane (X), mp 179–180° [*Anal.* ($C_{14}H_{19}BrN_2O_3S$) C, H, N].

Studies in Cinnoline Chemistry. I. The Synthesis of Substituted Phenyl Cinnolyl Sulfides

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Cinnoline compounds have been recommended as drugs in the chemotherapy of trypanosomiasis,[1] as bactericides and antiparasites,[2] and in antitumor screening.[3] The antileukemic activity of various 4-substituted benzylthiocinnolines reported by Castle and his coworkers[4] aroused our interest in preparing a series of substituted phenyl cinnolyl sulfides and subjecting them for pharmacological screening. This paper describes the preparation of some new substituted-phenyl cinnolyl sulfides.

(1) J. R. Keneford, E. M. Lonrie, J. S. Morley, J. C. E. Simpson, J. Williamson, and P. H. Wright, *J. Chem. Soc.*, 2595 (1952).

(2) E. P. Taylor, M. D. Potter, H. O. J. Collier, and W. C. Austin, British Patent 812,994 (May 6, 1959); *Chem. Abstr.*, **53**, 18971 (1959).

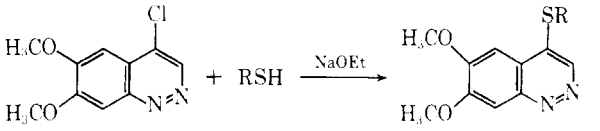
(3) R. N. Castle, H. Ward, N. White, and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960).

(4) R. N. Castle, K. Adachi, and W. D. Guither, *J. Heterocyclic Chem.*, **2**, 459 (1965).

Experimental Section[5]

General Procedure.—The method is illustrated with the preparation of 2-chlorophenyl 4-(6,7-dimethoxycinnolyl) sulfide. To a dry solution of NaOEt from Na (0.02 g-atom) in absolute EtOH (20 ml) under N_2 was added with shaking *o*-chlorothiophenol (0.02 mole) followed by addition of 0.02 mole of 4-chloro-6,7-dimethoxycinnoline.[6] The reaction mixture was refluxed for 2 hr under N_2, diluted with sufficient H_2O, and made alkaline to dissolve the unreacted thiophenol. The solid material was filtered and recrystallized from dilute EtOH: mp 164–165°, yield 1.5 g. Compounds prepared in this way are listed in Table I.

TABLE I



No.	R	Yield,[a] %	Mp, °C	Formula[b]
1	C_6H_5	72	165	$C_{16}H_{14}N_2O_2S$
2	*p*-$CH_3C_6H_4$	94	181–182	$C_{17}H_{16}N_2O_2S$
3	*o*-ClC_6H_4	75	152	$C_{16}H_{13}ClN_2O_2S$
4	*m*-ClC_6H_4	34	176–177	$C_{16}H_{13}ClN_2O_2S$
5	*p*-ClC_6H_4	47	199	$C_{16}H_{13}ClN_2O_2S$
6	2,5-$Cl_2C_6H_3$	67	200–201	$C_{16}H_{12}Cl_2N_2O_2S$
7	3,5-$Cl_2C_6H_3$	58	177–178	$C_{16}H_{12}Cl_2N_2O_2S$
8	3,4-$Cl_2C_6H_3$	68	192	$C_{16}H_{12}Cl_2N_2O_2S$[c]

[a] All compounds were recrystallized from EtOH–H_2O. [b] All compounds were analyzed satisfactorily for C, H, N. [c] This compound was analyzed satisfactorily for C, H.

Acknowledgment.—Thanks are due to Professor S. Siddappa for his interest in the work. One of us (S. M. Y.) is grateful to the University Grants Commission, New Delhi, India, for a Research Training Scholarship. We thank Mr. V. A. Desai and Mr. R. S. Inamdar for the analytical data recorded.

(5) Melting points were taken in capillary tubes and are uncorrected.

(6) R. N. Castle and F. H. Kruse, *J. Org. Chem.*, **17**, 1571 (1952).

N,N,N′,N′-Tetraalkylhomopiperazinium Salts[1]

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The availability of homopiperazine (1,4-diazacycloheptane) by a novel and simple synthesis[2] has made it possible to prepare a series of symmetrical N,N′-dialkylhomopiperazines and their quaternary ammonium salts. The bis-quaternary dimethosulfates were prepared for the purpose of determining their bactericidal properties in comparison with homologous compounds derived from N,N′-dialkylpiperazines and with N-alkyl-N-methylpyrrolidinium methosulfates and N-alkyl-N-methylmorpholinium and -thiamorpholinium methosulfates previously described.[3]

Experimental Section[4]

Symmetrical N,N′-dialkylhomopiperazines (Table I) were prepared by refluxing 5 g (0.05 mole) of homopiperazine with

(1) Abstracted in part from the thesis of K. E. Jones presented to Lafayette College in partial fulfillment of the requirements for the degree of B.S. in Chemistry, June 1964.

(2) F. Poppelsdorf and R. C. Myerly, *J. Org. Chem.*, **26**, 131 (1961).

(3) (a) D. R. Smith, J. W. Curry, and R. L. Eiffert, *J. Am. Chem. Soc.*, **72**, 2969 (1950); (b) W. F. Hart and M. E. McGreal, *J. Org. Chem.*, **22**, 81 (1957); (c) *ibid.*, **22**, 87 (1957), and references cited therein.

(4) Melting points were taken in capillary tubes and are corrected. Elemental analyses were determined by Drs. Weiler and Strauss, Oxford, England. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical value.