

lency of these materials. Such a property is a composite of volatility and intrinsic potency. The latter is presumably dependent upon structure⁶ and independent of volatility. In the case of the present compounds minor differences in intrinsic potency are minimized by the dominant importance of volatility. Nonetheless, it is apparent that gross differences in intrinsic potency do exist. Notable is the lack of repellency in II-1 and III-1, whose volatility is comparable to other members of these series. It is also apparent (Table II) that the simple aromatic diethylbenzamidines (I) are more potent than the II and III compounds of similar volatility (compare I-2,5,10, bp 96–114° (0.5 mm), with II-5,8, bp 111° (0.6 mm), and III-6, bp 107° (0.6 mm)). Similarly, within series I the relatively low intrinsic repellency of **12** may be cited.

It is of interest that the similarity of MEQ and MEC values (Table II) in series I indicates that differences in duration on skin are not significantly related to differential absorption rates in this series. The present results further emphasize the importance of structure and volatility in determining both repellency and duration of effectiveness of topical repellents. In addition, they indicate that volatility must be considered in both the design and interpretation of results of methods for testing repellency.

(6) J. T. Davies and F. H. Taylor, *Biol. Bull.*, **117**, 222 (1959); T. P. McGovern, M. Beroza, and H. Gouck, *J. Econ. Entomol.*, **60**, 1591 (1967).

Experimental Section

Synthesis.—The compounds (II and III) were synthesized by reaction of the acid chloride of the appropriate substituted benzoic acid with the N,N,N'-trisubstituted diamine in the presence of excess amine. Products were purified and boiling points (uncorrected) were determined by vacuum distillation through a 10-cm Vigreux column. Physical constants are given in Table I. Compounds I-2 and -17-19 were obtained from Eastman Organic Chemicals Co., and before use were distilled as described above.

Biological Evaluation.—Olfactometer determinations of MEQ values were performed by a modification of the method previously described.¹ Sample vapors were delivered to the olfactometer cage by passing air through a 100-ml sample flask to which had been added a known weight of test compound. The test compound was prepared for evaluation by dissolving it in a standard amount of Et₂O; it was then deposited in the flask by spin evaporation of the ether *in vacuo* for a period of 2–3 min. Remaining ether vapors were removed with a brief flushing with N₂. For each compound a series of quantities was tested in order to bracket a weight range which produced a minimum response in terms of mosquito distribution. Female *Aedes aegypti* mosquitoes (5–7 days old) were used exclusively in all tests. Similarly, MEC tests were conducted by uniform application of various amounts of repellent in EtOH to an exposed area of the arm of a human subject. In this manner, a minimum concentration range for prevention of biting was determined by exposure of the treated area to a 0.3 m² cage of 100 mosquitoes. Exposure was delayed for 15 min following application in order to allow dissipation of the solvent. Such a procedure was repeated once with each compound and in the repeated tests all compounds were run on the same day. Duration testing was conducted in a similar manner except that application was at the rates of 0.2 and 0.4 mg/cm². The treated area was exposed to mosquitoes every 0.5 hr until biting was noted and confirmed during the subsequent exposure. The same test subject was used in all determinations.

New Compounds

Synthesis of N-Aryl-N'-2-thiazolylguanidines

WAHID U. MALIK, P. K. SRIVASTAVA, AND S. C. MEHRA

Department of Chemistry, University of Roorkee,
Roorkee, India

Received July 29, 1968

Rose and Swain¹ prepared and studied the biological activities of a series of bisdiguanydes; Ram² reported some arylguanidines in which one group was substituted benzothiazole and another was a phenyl or substituted-phenyl group and studied their antibacterial properties. Recently some benzothiazolylguanidines were also reported³ to possess algacidal properties. It was therefore thought worthwhile to synthesize some additional thiazolylguanidines.

Experimental Section

N-Phenyl-N'-2-(4-phenylthiazolyl)thiocarbamide.—Phenyl isothiocyanate (3 ml) and 2-amino-4-phenylthiazole (5 g) were refluxed for 2 hr. Excess phenyl isothiocyanate and 2-amino-4-phenylthiazole were removed by washing several times (petroleum ether (bp 40–60°), Et₂O). The thiocarbamide thus obtained

was crystallized from EtOH, mp 176°, yield 95%. *Anal.* (C₁₆H₁₃N₃S₂) N, S.

Similarly, various substituted N-aryl-N'-2-(4-phenylthiazolyl)thiocarbamides were prepared (see Table I).

TABLE I
N-ARYL-N'-2-(4-PHENYLTHIAZOLYL)THIOCARBAMIDES

No.	R	Mp, °C	Formula ^a
1	<i>o</i> -MeC ₆ H ₄	192	C ₁₇ H ₁₃ N ₃ S ₂
2	<i>m</i> -MeC ₆ H ₄	199	C ₁₇ H ₁₃ N ₃ S ₂
3	<i>p</i> -MeC ₆ H ₄	195	C ₁₇ H ₁₃ N ₃ S ₂
4	<i>o</i> -OMeC ₆ H ₄	200	C ₁₇ H ₁₃ N ₃ OS ₂
5	<i>m</i> -OMeC ₆ H ₄	170	C ₁₇ H ₁₃ N ₃ OS ₂
6	<i>p</i> -OMeC ₆ H ₄	190	C ₁₇ H ₁₃ N ₃ OS ₂
7	<i>p</i> -OEtC ₆ H ₄	225	C ₁₈ H ₁₇ N ₃ OS ₂
8	<i>p</i> -ClC ₆ H ₄	136	C ₁₆ H ₁₂ ClN ₃ S ₂

^a All compounds analyzed satisfactorily for N, S.

N-Phenyl-N'-2-thiazolylguanidine.—N-Phenyl-N'-2-thiazolylthiocarbamide quantitatively formed N-phenyl-N'-2-thiazolylguanidine when heated with yellow PbO and ethanolic NH₃ in a sealed tube at 110°. The product was crystallized from 50% EtOH, mp 136°. *Anal.* (C₁₆H₁₄N₄S) N, S.

(1) F. L. Rose and G. Swain, *J. Chem. Soc.*, 4422 (1956).

(2) P. Ram, Ph.D. Thesis, Banaras Hindu University, 1963.

(3) G. C. Singh, *J. Indian Chem. Soc.*, **45**, 27 (1968).

Similarly, various aryl-substituted N-aryl-N'-2-thiazolyl-guanidines 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	formula ^a
1	<i>o</i> -MeC ₆ H ₄	146	C ₁₇ H ₁₆ N ₄ S	193	C ₁₇ H ₁₇ ClN ₄ S
2	<i>m</i> -MeC ₆ H ₄	142	C ₁₇ H ₁₆ N ₄ S	130-131	C ₁₇ H ₁₇ ClN ₄ S
3	<i>p</i> -MeC ₆ H ₄	142	C ₁₇ H ₁₆ N ₄ S	187	C ₁₇ H ₁₇ ClN ₄ S
4	<i>o</i> -OMeC ₆ H ₄	142	C ₁₇ H ₁₆ N ₄ OS	185-186	C ₁₇ H ₁₇ ClN ₄ OS
5	<i>m</i> -OMeC ₆ H ₄	143	C ₁₇ H ₁₆ N ₄ OS	179-180	C ₁₇ H ₁₇ ClN ₄ OS
6	<i>p</i> -OMeC ₆ H ₄	144	C ₁₇ H ₁₆ N ₄ OS	183	C ₁₇ H ₁₇ ClN ₄ OS
7	<i>p</i> -OEtC ₆ H ₄	145	C ₁₈ H ₁₈ N ₄ OS	125	C ₁₈ H ₁₉ ClN ₄ OS
8	<i>p</i> -ClC ₆ H ₄	147	C ₁₆ H ₁₃ ClN ₄ S	134-135	C ₁₆ H ₁₄ Cl ₂ N ₄ S

^a See footnote a, Table I.

Polyiodo Derivatives of Anisidine Isomers

FRANCIS B. ALVEY AND CHARLES H. JARBOE

Medicinal Chemistry Section, Department of Pharmacology,
University of Louisville, School of Medicine,
Louisville, Kentucky 40202

Received July 11, 1968

Iodinated aromatic compounds are useful diagnostic agents because of their X-ray absorptivity 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 Section⁴

Acetoxymercuration of the N-Acetylanisidines.—A ground mixture of 4.1 g (0.025 mole) N-acetyl-*p*-anisidine⁵ 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 H₂O to yield 0.9 g (3.0%) of a white powder, mp 250-260° dec (from AcOH-H₂O). 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-H₂O). 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 I₂ and 1.72 g (0.012 mole) of KI in 25 ml of H₂O was added dropwise to a refluxing, stirred suspension of 0.85 g (0.00071 mole) of tetraacetoxymercuri-N-

(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 $\pm 0.4\%$ 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.

TABLE I
POLYIODO ANISIDINES

Isomer	Acetylated	Mp, °C	Yield, %	Formula ^a
<i>p</i>	Yes	271	80	C ₉ H ₇ I ₄ NO ₂
<i>p</i> ^c	Yes	258-259 ^b	88	C ₉ H ₅ I ₃ NO ₂
<i>m</i> ^d	Yes	266 ^b	75	C ₉ H ₇ I ₄ NO ₂
<i>o</i> ^e	Yes	278-279 ^b	74	C ₉ H ₇ I ₄ NO ₂
<i>o</i>	No	149-151	35 ^f	C ₇ H ₅ I ₄ NO
<i>o</i> ^g	No	132-133	...	C ₇ H ₆ I ₃ NO ^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-H₂O). ^e Acetoxymercuri precursor obtained in 83% yield, mp 238-240° dec (from AcOH-H₂O). ^f Yield based on N-acetyl precursor. ^g All compounds were analyzed for I. ^h I: calcd, 75.94; found, 76.28.

acetyl-*p*-anisidine in 100 ml of H₂O. Reaction was continued for 30 min after addition. On cooling, the product precipitated. It was filtered and washed with dilute KI solution and then H₂O to give 0.38 g (80%) of tetraiodo-N-acetyl-*p*-anisidine, mp 271° dec (from 95% EtOH). *Anal.* (C₉H₇I₄NO₂) 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% H₂SO₄, 164 ml of H₂O 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 NaHCO₃, H₂O), mp 149-151° (from MeOH). *Anal.* (C₇H₅I₄NO) 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.* (C₇H₅I₃NO) I: calcd, 75.94; found, 76.28.

Some Sulfonamide Derivatives of Cyclohexane¹

YOSHIO UENO, SHOJI TAKEMURA, KENJI OZAWA,
AND SHIGEO KOMATSU

Faculty of Pharmacy, Kinki University,
Kowakae, Higashi-Osaka, Osaka-fu, Japan

Received June 17, 1968

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 Section³

N,N-Dibromo-4-nitrobenzenesulfonamide.—4-Nitrobenzenesulfonamide (20.2 g) was dissolved in a solution of NaOH (8 g) in H₂O (200 ml) and Br₂ (36 g) was added dropwise with stirring. The crystals that separated were filtered off, washed with H₂O, and dried, mp 163-164° dec. The yield was 34 g (94.5%). A

(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 $\pm 0.4\%$ of the theoretical values.