lency of these materials. Such a property is a composite of volatility and intrinsic potency. The latter is presumably dependent upon structure[6] 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 diethylbenzamides (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.[4] 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 Et_2O; 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 N_2. 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 m^3 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/cm^2. 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

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Rose and Swain[1] prepared and studied the biological activities of a series of bisdiguanides; Ram[2] 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 reported[3] to possess algaecidal properties. It was therefore thought worthwhile to synthesize some additional thiazolylguanidines.

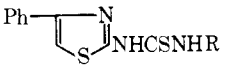
Experimental Section

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°), Et_2O). The thiocarbamide thus obtained was crystallized from EtOH, mp 176°, yield 95%. *Anal.* ($C_{16}H_{13}N_3S_2$) 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	*o*-MeC_6H_4	192	$C_{17}H_{15}N_3S_2$
2	*m*-MeC_6H_4	199	$C_{17}H_{15}N_3S_2$
3	*p*-MeC_6H_4	195	$C_{17}H_{15}N_3S_2$
4	*o*-$OMeC_6H_4$	200	$C_{17}H_{15}N_3OS_2$
5	*m*-$OMeC_6H_4$	170	$C_{17}H_{15}N_3OS_2$
6	*p*-$OMeC_6H_4$	190	$C_{17}H_{15}N_3OS_2$
7	*p*-$OEtC_6H_4$	225	$C_{18}H_{17}N_3OS_2$
8	*p*-ClC_6H_4	136	$C_{16}H_{12}ClNS_2$

[a] All compounds analyzed satisfactorily for N, S.

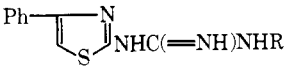
N-Phenyl-N′-2-thiazolylguanidine.—N-Phenyl-N′-2-thiazolylthiocarbamide quantitatively formed N-phenyl-N′-2-thiazolylguanidine when heated with yellow PbO and ethanolic NH_3 in a sealed tube at 110°. The product was crystallized from 50% EtOH, mp 136°. *Anal.* ($C_{16}H_{14}N_4S$) N, S.

(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-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[c]	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 precursor. [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.