with 4.4 g (0.02 mole) of PCl_5 at room temperature. The dioxime gradually went into solution, and the reaction mixture, after being allowed to stand at room temperature for 1 day, was poured into 400 ml of cold water; tetrahydrofuran was removed by a stream of air. The crude product was collected by filtration, washed with water, and dried in air. On recrystallization from acetone–methanol there was obtained 1.5 g (50%) of 2,8-diacetamidophenothiazine 5,5-dioxide (Vb) as white crystals, mp 382–384°.

Anal. Calcd for $C_{16}H_{13}N_3O_4S$ (345.4): C, 55.6; H, 4.38; N, 12.2; S, 9.28. Found: C, 55.5; H, 4.40; N, 12.2; S, 9.20.

Beckmann rearrangement of the dioxime (VIII) was carried out by a similar procedure to give a 73% yield of 2,8-diacetamido-10-acetylphenothiazine (IX), mp 297–299° (lit.[18] mp 301–302°).

2,8-Diaminophenothiazine 5,5-Dioxide (Va).—The diacetamide Vb (0.85 g, 0.0025 mole) was boiled with 100 ml of 18% HCl for 1.5 hr. The reaction mixture was filtered, and the cooled filtrate was neutralized with NH_4OH. The precipitate was collected by filtration, washed with water, and dried in air to give 0.62 g (95%) of the crude Va, mp 342–345° dec. On recrystallization from methanol, the pure amine was obtained as pale yellow needles, mp 348–350° dec (lit. 355–356°,[6] 339–342°[9]).

Anal. Calcd for $C_{12}H_{11}N_3O_2S$ (261.3): C, 55.1; H, 4.25; N, 16.1. Found: C, 54.9; H, 4.32; N, 15.7.

2,8-Bis(ethylamino)phenothiazine 5,5-Dioxide (Vc).—A suspension of 4.5 g (0.013 mole) of the diacetamide Vb in 120 ml of anhydrous tetrahydrofuran was treated with 65 ml of a 1 *M* solution of borane in the same solvent. The reaction mixture was heated under reflux for 1 hr in a hood, and water was cautiously introduced to decompose the excess borane. After dilution with 100 ml of water, the tetrahydrofuran was distilled, and an additional 300 ml of water was added. The precipitated solid was filtered by suction, washed with water, and allowed to dry in air to give 3.9 g (90%) of Vc, mp 270–273° dec. On recrystallization from methanol, analytically pure Vc was obtained as white needles: mp 276–278° dec; $\lambda_{max}^{ethanol}$ 268 mμ (ε 89,000), 312 mμ (ε 11,000). The infrared spectrum has maxima at 2.9, 6.2, 6.3, 6.7, 6.9, 8.2, and 8.8 μ.

Anal. Calcd for $C_{16}H_{19}N_3O_2S$ (317.4): C, 60.5; H, 6.03; N, 13.2. Found: C, 60.6; H, 5.98; N, 13.0.

2,8-Bis(methylamino)phenothiazine 5,5-Dioxide (Ve).—To an acetic formic anhydride solution (prepared by mixing 55 ml of 98–100% formic acid and 35 ml of acetic anhydride, and allowing the mixture to stand for 20 min before use) was added in small portions, 1.7 g (0.006 mole) of 2,8-diaminophenothiazine 5,5-dioxide (Va). The formylation mixture was stirred at room temperature for 4 hr, then diluted with 800 ml of water. The product was collected by filtration, washed with water, and dried in air to give 1.85 g of Vd, mp 392–395° dec. Compound Vd is a white solid, extremely insoluble in methanol and other common organic solvents. Its infrared spectrum showed the expected amide absorption bands at 6.0, 6.5, and 8.0 μ. The product thus obtained was used for the following reduction without purification.

The reduction of Vd was carried out in 100 ml of anhydrous tetrahydrofuran with 40 ml of 1 *M* borane in the same solvent. The reaction mixture was heated under reflux for 1.5 hr and worked up as described for its ethyl analog (Ve) to afford 1.5 g of Ve, mp 272–274° dec. The over-all yield from Va was 81%. On recrystallization from methanol, pure Ve was obtained as white needles: mp 275–277° dec; $\lambda_{max}^{ethanol}$ 267 mμ (ε 93,000), 311 mμ (ε 10,000); maxima in the infrared spectrum were at 2.9, 3.0, 6.2, 6.3, 6.7, 7.0, 8.2, and 8.9 μ.

Anal. Calcd for $C_{14}H_{15}N_3O_2S$ (289.4): C, 58.2; H, 5.23; N, 14.5. Found: C, 58.2; H, 5.30; N, 14.5.

2,8-Bis(dimethylamino)phenothiazine 5,5-Dioxide (Vg).—To a solution of 1.3 g (0.0045 mole) of Ve in 20 ml of 98% formic acid was slowly added 45 ml of mixed anhydride, prepared from 30 ml of formic acid and 15 ml of acetic acid as described above. After being stirred overnight at room temperature, the reaction mixture was poured slowly into 700 ml of water. The solid was collected by filtration, washed with water, and dried in the air to give 1.5 g of the diformamido intermediate Vf, mp 345–348° dec. It was extremely insoluble in methanol and was reduced without further purification in 50 ml of tetrahydrofuran by addition, in several portions, of 50 ml of 1 *M* borane in the same solvent. After being heated under reflux for 1 hr the reaction mixture was worked up in the same manner as for the preceding products to give 1.3 g (93%) of Vg, mp 361–364° dec. One recrystallization from dimethylformamide gave an analytically pure sample which melted at 363–367° dec: $\lambda_{max}^{ethanol}$ 272 mμ (ε 77,000), 315 mμ (ε 12,000).

Anal. Calcd for $C_{16}H_{19}N_3O_2S$ (317.4): C, 60.5; H, 6.03; N, 13.2. Found: C, 60.4; H, 6.18; N, 13.2.

Acknowledgments.—The authors wish to express their appreciation to Mrs. Margaret L. Rounds, Mr. John R. Cravatt, and Mr. Leland R. Lewis for their valuable assistance in performing analytical and instrumental measurements.

1,3-Diethyleneguanidines

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As part of a program dealing with the chlorination of isothiocyanates,[1] we have synthesized various 1,3-diethyleneguanidines, a new class of potent insect chemosterilants.

1,3-Diethyleneguanidines (I, $n = 1$) as well as bis-(1,3-diethyleneguanidines) (I, $n = 2$) were synthesized from isocyanide dichlorides (II) and 1,2-alkylenimines (aziridines) in the presence of triethylamine as hydrogen chloride scavenger.[2] The reaction proceeded particularly smoothly in the aromatic series and afforded compounds I in high purity. The infrared absorption spectra of I show as dominant features a very strong >C=N– absorption at approximately 1635 cm^{-1}, and a strong unassigned absorption at 1330–1340 cm^{-1}.

The isocyanide dichlorides employed in the above reactions were synthesized in the case of the aromatic representatives by chlorination of the corresponding isothiocyanates[1] or by reaction of the formanilides with thionyl chloride and sulfuryl chloride.[2c] Alkylene bis-(isocyanide dichlorides), which to our knowledge have not been previously reported,[3] were obtained by chlorination of the diisocyanates with phosphorus pentachloride in phosphorus oxychloride. This method,[2c] first described for the preparation of alkyl isocyanide dichlorides, gave only unseparable mixtures of chlorina-

(1) G. Ottmann and H. Hooks, *J. Org. Chem.*, **31**, 838 (1966).

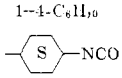
(2) Reactions of isocyanide dichlorides with primary, secondary, and tertiary aliphatic or aromatic amines have been reported to some extent: (a) E. Sell and G. Zinkahl, *Ber.*, **7**, 1228 (1874); (b) G. M. Dyson and T. Harrington, *J. Chem. Soc.*, 191 (1910); (c) E. Käble, *Angew. Chem.*, **74**, 861 (1962).

(3) Only *m*- and *p*-phenylene bis(isocyanide dichloride) are described in the corresponding aromatic series.[2c]

TABLE I

BIS(ISOCYANIDE DICHLORIDES)

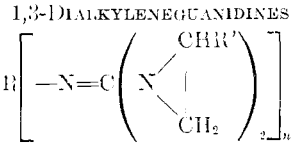
$R(-N{=}CCl_2)_n$

Compd	R	n	Mp, °C	Bp, °C (mm)	n_D (°C)	Yield, %	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N
IIa	1-4-$(CH_2)_4$	2		74–76 (0.03)	1.5094 (24.5)	56	28.81	3.22	55.77	11.23	28.90	3.80	57.20	
IIb	1-6-$(CH_2)_6$	2		118–120 (0.75)	1.5020 (26)	60	34.54	4.35	51.04	10.07	34.73	4.62	51.50	9.95
IIc	1-4-C_6H_4	2	38–39	108 (0.05)		47	34.79	3.65	51.42	10.15	34.50	3.80	52.00	10.15
		1		95 (0.45)	1.5076 (26)	21			32.10	12.67			31.80	12.62
IId		2	50–51[a]			70	33.92	1.58	55.70	8.79	34.08	2.00	55.20	8.47

[a] Recrystallized from pentane.

TABLE II

1,3-DIALKYLENEGUANIDINES



Compd	R	R'	n	Mp, °C	Yield, %	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N	% of nonviable housefly eggs Conen of compd 0.5%	0.1%
Ia	4-ClC_6H_4	H	1	45–46	58	59.59	5.50	16.00	18.90	59.60	5.89	16.60	18.50	51	...
Ib	2-FC_6H_4	H	1	92–93[a]	48	64.37	5.89		20.47	65.10	5.45		20.33	...	...
Ic	3-$NO_2C_6H_4$[b]	H	1	83–84	43	56.89	5.21		24.13	56.85	5.00		23.88	61	...
Id	1-4-C_6H_4[b]	H	2	124–125	62	64.83	6.80		28.36	64.72	7.23		28.50	100	99
Ie	1-4-C_6H_4	CH_3	2	Semisolid	53									4	...
If		H	2	84–85	32	59.21	6.14	10.29	24.37	59.30	6.20	10.60	23.98	98	92
Ig	1,6-[$(CH_2)_6$]$_2$	H	2	220[c]	23	63.12	9.27		27.60	62.91	9.66		26.90	...	... 98[d]

[a] Boiling point (0.05 mm); $n^{25}D$ 1.5662. [b] Compounds Ie and Id have recently been described, see British Patent 978,089 (Dec 16, 1964). The melting point of Ie, which we have observed, is 7° higher than that recorded in the patent. [c] There are some observations suggesting that this melting point is not that of compound Ig but of a polymerization product thereof, since Ig is particularly sensitive to temperature increases. [d] Apholate®.

tion products and no appreciable amount of the desired compounds if applied as such. Pure alkylene bis(isocyanide dichlorides) were eventually obtained by a substantial increase of the suggested ratio of PCl_5 to isocyanate and by chlorination at elevated temperatures. Several new bis(isocyanide dichlorides) are compiled in Table I.

1,3-Diethyleneguanidines and particularly the bis-(1,3-diethyleneguanidines) (I, $n = 2$) having four aziridine moieties per molecule are powerful chemosterilants for the control of a broad spectrum of insect populations[4] (Table II). Compounds Ie and If are comparable in their biological activity with 2,2,4,4,-6,6-hexakis(1-aziridinyl)cyclotriphosphaza-1,3,5-triene (Apholate®).[5]

Experimental Section[6]

The solid **1,3**-diethyleneguanidines were purified by recrystallization from a low-boiling hydrocarbon, preferably pentane or hexane. The use of a higher boiling solvent is not suggested, since some of the compounds listed in Table II are not particularly stable and polymerize or decompose at elevated temperatures. The liquid 2-(*o*-fluorophenyl)-1,3-diethyleneguanidine was purified by distillation; however, caution should be exercised, for violent decompositions have been experienced on occasion. Phenylene-1,4-bis(1,3-dipropyleneguanidine) failed to crystallize; it could not be purified by distillation owing to its instability at higher temperatures.

5-Chlorotolylene-2,4-bis(1,3-diethyleneguanidine) (If) (General Procedure for the Preparation of 1,3-Dialkyleneguanidines).—A solution of 12.5 g of 5-chlorotolylene 2,4-bis(isocyanide dichloride) in 300 ml of dry toluene was added dropwise to a stirred solution of 7.5 g of ethylenimine and 17.3 g of triethylamine in 75 ml of toluene. The exothermic reaction was controlled at 15° by means of a wet ice bath and the rate of addition. After complete addition, the reaction mixture was agitated for 1 to 2 hr at room temperature, and then filtered from triethylamine hydrochloride. The solvent was evaporated, and the remaining heavy syrup was recrystallized from hexane affording pure If.

5-Chlorotolylene 2,4-Bis(isocyanide dichloride) (IId).—Toluene 2,4-diisothiocyanate (86 g) dissolved in 80 ml of chloroform was chlorinated by passing 170 g of chlorine over a period of 23 hr into this solution. During the first 7 hr, the reaction temperature was maintained at 15–20°, and during the next 16 hr at 50–60°. Then, solvent, SCl_2, and HCl were removed *in vacuo*, and the liquid residue (140 g) was dissolved in 100 ml of pentane. After standing overnight at −20°, 92 g (70%) of crude 5-chlorotolylene 2,4-bis(isocyanide dichloride) was removed by suction filtration and recrystallized from 200 ml of pentane affording 70 g of the pure compound. Additional product can be obtained by partial concentration of the mother liquor.

Hexamethylene 1,6-Bis(isocyanide dichloride) (IIb) (General Procedure for the Preparation of Alkylene Bis(isocyanide dichloride).—To a stirred mixture of 225 g of PCl_5 in 165 ml of $POCl_3$ was added dropwise 50 g of hexamethylene 1,6-diisocyanate over a 1-hr period without external cooling. The tem-

(4) The biological tests were done by Dr. S. Ristich, Pesticides Research Group, Olin Mathieson Chemical Corp.

(5) R. Rätz and C. Grundmann, U. S. Patent 2,858,306 (Oct 28, 1958); R. Rätz, E. Kober, C. Grundmann, and G. Ottmann, *Inorg. Chem.*, **3**, 757 (1964).

(6) Melting points and boiling points are not corrected. Melting points were taken on a modified Thiele apparatus.

perature of the reaction mixture increased from 24 to 29°. After standing at room temperature for 2 hr, the mixture was heated to reflux for 1 hr, then cooled and filtered. The filtrate was distilled *in vacuo* over a 15-cm glass-bead-packed column to provide 49 g (60% yield) of pure hexamethylene 1,6-bis(isocyanide dichloride).

X-Ray Media. II. Synthesis of Alkanoylbis(isophthalamic Acids) as X-Ray Contrast Agents[1]

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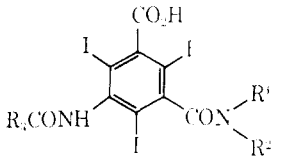
We recently reported[1] that certain triiodoisophthalamic acids (**1**) had been found potentially useful as X-ray diagnostic agents by virtue of the low toxicity and high water solubility of their sodium and N-methylglucamine salts. Subsequent, extensive clinical experience has shown **1** (R_1 = H; R_2 = R_3 = CH_3; iothalamic acid) to be a safe and effective diagnostic agent in the visualization of the kidney, heart, and cerebrovascular system.[2]



1

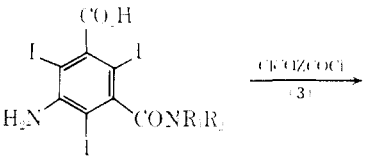
We now wish to describe the synthesis of further compounds of this type wherein our efforts have been directed toward the development of useful intravenous cholangiographic agents for visualization of the gall bladder. 5-Amino-2,4,6-triiodo-N-alkylisophthalamic acids (**2**) have been condensed with acid chlorides (**3**) to give alkanoylbis(isophthalamic acids) (**4**) (Scheme I). Salts of **4** have been found to possess generally low toxicity and high water solubility.

The compounds and their properties are summarized in Table I. The toxicities and solubilities of the lower members of the series compare favorably with those reported earlier for the 5-acylamino analogs.[1]

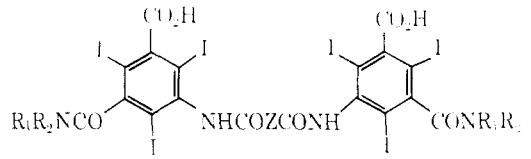
A toxicologic study[3] of the sebacoyl analog **4a** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_8$) as the N-methylglucamine salt (75% solution) gave the results shown in Table II.

When tested in the cat,[4] several of these compounds showed promise as cholangiographic agents. Subsequent clinical investigations on the sebacoyl analog **4a** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_8$) showed it to be substantially free of side effects and to opacify the gall bladder and biliary ducts in a high percentage of cases.[5,6] Unexpectedly, this compound also showed a high degree of kidney excretion.[5] The adipoyl analog **4b** (R_1 = H; R_2 = CH_3; Z = $(CH_2)_4$) has also been found to be nontoxic and excreted *via* the kidneys.[7] The synthesis and biological testing of additional compounds of this general type will be reported at a later date.

SCHEME I



2



4a, R_1 = H; R_2 = CH_3; Z = $(CH_2)_8$
b, R_1 = H; R_2 = CH_3; Z = $(CH_2)_4$

Experimental Section[8]

The following procedure illustrates the general method of synthesis employed. Analyses and yields are given in Table I.

5,5′-Adipoyldiiminobis(2,4,6-triiodo-N-methylisophthalamic acid) (**4**, R_1 = H; R_2 = CH_3; Z = $(CH_2)_4$).—5-Amino-2,4,6-triiodo-N-methylisophthalamic acid (228 g, 0.4 mole) was heated and stirred in dimethylacetamide (400 ml). When the temperature reached 95°, adipoyl chloride (55.0 g, 0.30 mole) was added, half at once, followed by the remainder over a period of 15 min. When addition was complete, the solution was stirred at about 95° for another 15 min, then poured into 2 l. of hot water. As the mixture cooled to room temperature, a gum separated. The mother liquor was discarded and the gum was dissolved in 2 l. of water with sufficient solid NaOH added to complete solution. This solution was acidified with HCl and acetic acid to *ca.* pH 5, treated with decolorizing charcoal, and filtered. The filtrate was then strongly acidified with HCl, and the resulting amorphous granular solid was filtered, digested 0.5 hr with 0.5 l. of hot ethanol, filtered, washed with ethanol, and dried at 110°. The yield of crude 5,5′-adipoyldiiminobis(2,4,6-triiodo-N-methylisophthalmic acid) (**5**) was 183 g.

The acid obtained was reprecipitated twice again from its sodium salt solution. This solid was dissolved in hot dimethylformamide (400 ml), and 1.5 l. of water was added slowly. After digestion, filtration, and cooling, a crystalline product was obtained which, after drying at 110°, weighed 126 g. This solid was dissolved in 1 l. of 10% aqueous NaOH solution, acidified (pH 5), and filtered into a hot stirred solution of 1:3 concentrated HCl–water (100 ml). The mixture was chilled and the solid was

(1) (a) Paper I in this series: G. B. Hoey, R. D. Rands, G. DeLaMater, D. W. Chapman, and P. E. Wiegert, *J. Med. Chem.*, **6**, 24 (1963). (b) See G. B. Hoey, Canadian Patent 720,826 (1965), for a portion of the work described herein.

(2) (a) T. R. Marshall and J. T. Lilg, *Southern Med. J.*, **56**, 1424 (1963); (b) J. W. Linhart, R. E. Whalen, and H. D. McIntosh, *ibid.*, **58**, 793 (1965); (c) A. C. Beall, Jr., G. C. Morris, Jr., H. E. Garrett, W. S. Henly, G. L. Hallman, E. S. Crawford, D. A. Cooley, and M. E. DeBakey, *Arch. Internal Med.*, **60**, 843 (1964), and references therein.

(3) D. H. Baeder, T. W. Tusing, M. Bon, and W. Reiter, *Federation Proc.*, **32**, 182 (1963).

(4) J. O. Hoppe and S. Archer, *Am. J. Roentgenol. Radium Therapy Nucl. Med.*, **69**, 630 (1953).

(5) T. R. Marshall and J. T. Lilg, *ibid.*, **90**, 854 (1963).

(6) Private communications from E. R. Jolly and F. P. Hallett, Research and Development Department, Medicinal Division, Mallinckrodt Chemical Works.

(7) S. Hilal, VIIth Symposium Neuroradiologicum, New York, N. Y., Sept 1964.

(8) All melting points are corrected and were determined in a capillary tube in a Thomas–Hoover or similar melting point apparatus. Neutral equivalents were determined by potentiometric titration; iodine analyses and spectral determinations were carried out by Dr. Perry King and staff of the Analytical Development Group. Solubility measurements were done as described previously.[1] The acute toxicity studies were carried out either at our own laboratories or at Hazleton Laboratories, Falls Church, Va. We thank Dr. David H. Baeder for making biological data available to us. The infrared spectra of all compounds prepared were compatible with postulated structures.