It was identified as homophthalaldehyde by treating 1 g. of the oil with excess *p*-nitrophenylhydrazine and isolating the bis-*p*-nitrophenylhydrazone derivative in quantitative yield. Recrystallization from 80% ethanol gave orange crystals, m.p. 220–221°. The literature[16] listed the m.p. as 185–190°; hence an elemental analysis was obtained.

Anal. Calcd. for $C_{21}H_{18}N_6O_4$: C, 60.28; H, 4.34; N, 20.09. Found: C, 60.29; H, 4.39; N, 19.83.

o-**Hydroxymethylphenylacetaldehyde (V).**—A solution of 14.8 g. (0.1 mole) of homophthaldehyde in 100 ml. of ethanol was stirred vigorously with 200 ml. of 50% acetic acid and an excess of zinc dust for 2 hours at 80°. The zinc dust was added in 1-g. quantities to maintain a constant suspension in the solution. The mixture was filtered and evaporated to dryness under vacuum leaving a yellow gum. This was mixed with 100 ml. of water and ether extracted. The ether solution was washed with dilute sodium carbonate solution and dried over sodium carbonate. Upon evaporation of the ether, *o*-hydroxymethylphenylacetaldehyde was obtained as a yellow oil, b.p. 116–120° (5 mm.), n^{25}_{D} 1.5240.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.03; H, 7.22.

Homophthalyl Alcohol (VI).—To a solution of 20 g. of lithium aluminum hydride in 200 ml. of ether was slowly added 21 g. (0.1 mole) of the peroxide I over a 30-min. period. The solution was vigorously stirred under reflux for an additional 20 minutes and water was added slowly to decompose the excess lithium aluminum hydride. The solution was acidified with 25% sulfuric acid, and the water and ether layers were separated. The water solution was ether extracted with an additional 200 ml. of ether and the ether extracts were combined, washed with dil. sodium carbonate solution, and dried over sodium carbonate. Removal of the ether under vacuum gave 14.5 g. (95%) of colorless oil of homophthalyl alcohol.[17] Identification of the oil was carried out by treating 1 g. of the oil with excess *p*-nitrobenzoyl chloride in pyridine to form the di-*p*-nitrobenzoate derivative, m.p. 134–135°.

Anal. Calcd. for $C_{23}H_{18}O_8N_2$: C, 61.33; H, 4.03; N, 6.22. Found: C, 61.36; H, 4.32; N, 6.24.

Isochroman VII.—The distillation of homophthalyl alcohol at 70° (3 mm.) with a drop of sulfuric acid gave a nearly quantitative yield of isochroman and water. Redistillation yielded a fraction boiling 69–70° at 3 mm. The isochroman[17] was a colorless liquid; m.p. 3–4°, n^{20}_{D} 1.5422, d^{25}_{4} 1.0707.

Anal. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.42; H, 7.26.

o-**Carboxyphenylacetaldehyde (VIII).**—A solution of 21 g. (0.1 mole) of the peroxide (I) in 200 ml. of ethanol was warmed with 200 ml. of 5% sodium hydroxide solution. The mixture turned a dark red as an exothermic reaction occurred and the temperature rose to 50°. The alkaline solution was kept at this temperature for 20 minutes, acidified with acetic acid, and concentrated to a viscous oil under vacuum. The oil was dissolved in ether and extracted with cold 1 *N* sodium hydroxide. Careful neutralization of the alkaline solution with dilute acetic acid precipitated yellow crystals of *o*-carboxyphenylacetaldehyde, 14.7 g. (90%), m.p. 130–140°. This substituted phenylacetaldehyde is unstable and the melting point decreased with standing and the compound finally became an oil. This probably accounts for the range of melting and for the fact that the m.p. observed in this work is higher than that previously reported by Schopf and Kuhne.[19] The semicarbazone derivative melted sharply at 209–210° and analyzed correctly.

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.28; H, 5.06; N, 19.34.

The compound VIII differed from the known isomeric *o*-formylphenylacetic acid[20] whose semicarbazone melts at 220°.

1-Isochromanone (IX).—A solution of 16.4 g. (0.1 mole) of *o*-carboxyphenylacetaldehyde in 200 ml. of isopropyl alcohol was refluxed with 400 ml. of isopropyl alcohol and 82 g. (0.4 mole) of aluminum isopropoxide for 9 hours. The apparatus was arranged with a fractionating column which permitted the slow distillation of acetone and isopropyl alcohol (200 ml.) during the reaction. The solution was evaporated to dryness under vacuum, mixed with 200 ml. of 6 *M* sulfuric acid, and ether extracted. The ether extract was washed with water, dried over sodium sulfate, and evaporated under vacuum. The residue, a yellow oil, was vacuum distilled to yield 12 g. (79%) of 1-isochromanone, b.p. 148–150° (5 mm.), n^{25}_{D} 1.5622, d^{25}_{4} 1.1996; Wegler and Frank[13] report a b.p. of 165° (16 mm.).

Reduction of *o*-carboxyphenylacetaldehyde with excess sodium borohydride in water at 30–40° also gave 1-isochromanone in 40% yield.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.44; H, 5.21.

Acknowledgment.—The authors wish to thank Dr. Philip S. Bailey for valuable suggestions in interpreting these results.

(19) C. Schopf and R. Kuhne, *Ber.*, **83**, 390 (1950).

(20) J. O. Halford and B. Weissmann, *J. Org. Chem.*, **18**, 30 (1953).

IOWA CITY, IOWA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Tetrachloroisoindolines and Related Systems. Alkylation Reactions and Inductive Effects[1]

BY WILLIAM E. ROSEN, VIRGINIA P. TOOHEY AND ANTHONY C. SHABICA

RECEIVED DECEMBER 13, 1956

The basicity of an isoindoline nitrogen atom is profoundly affected by inductive factors. Four chlorine atoms on the four available positions of the benzene ring or a positively charged nitrogen atom β to the isoindoline nitrogen decrease the reactivity of the isoindoline nitrogen toward alkylation. These effects cannot be results of resonance interaction and are, therefore, either steric (unlikely) or inductive (most probable). These conclusions, based on observations of alkylation behavior under certain conditions, are supported by pK_a determinations which are consistent with relative basicities of model amines. Stabilities of quaternized nitrogens, especially those with bromoethyl substituents, are also discussed.

The interesting physiological action of the ganglionic blocking agent 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline dimethochloride (VIIb)[2] has focused attention on the tetrachloroisoindoline system itself. Although isoindolines have been considered[3] typical amines, the alkyla-

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(1) Presented before the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(2) Ecolid (CIBA Trade Mark). See A. J. Plummer, J. H. Trapold, J. A. Schneider, R. A. Maxwell and A. E. Earl, *J. Pharmacol. Exptl. Therap.*, **115**, 172 (1955). An alternative name for VIIb, which can be extended to related isoindolines, is 4,5,6,7-tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium dichloride. The term "ammonio" was originally proposed by J. F. Bunnett and co-workers [*Chem. Revs.*, **49**, 291 (1951); THIS JOURNAL, **75**, 642 (1953)]. It has also been mentioned in A. M. Patterson's column on Nomenclature in *Chem. Eng. News*, **32**, 2320 (1954); **33**, 5262 (1955). It is used in this paper for the tetrasubstituted terminal nitrogen.

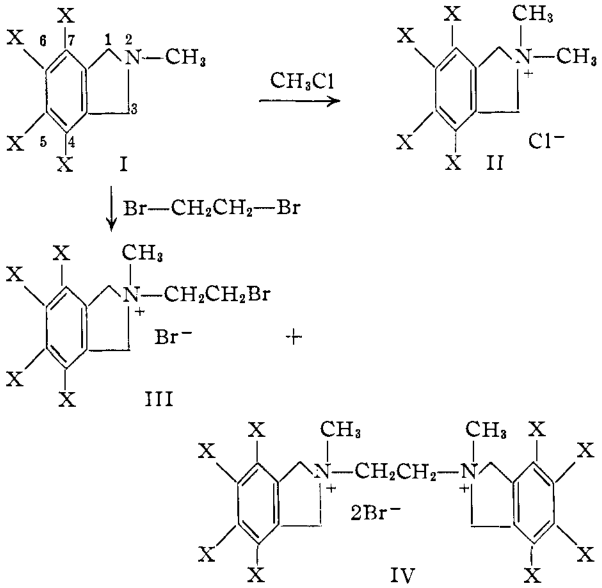
(3) D. R. Boyd and D. E. Ladhams, *J. Chem. Soc.*, 2089 (1928).

tion behavior of the 2-substituted isoindolines proved to be of considerable interest. Rice and coworkers have prepared[4,5] 2-dialkylaminoalkylisoindolines and 2-methylisoindolines, characterizing these compounds as hydrochlorides, picrates and methiodides. The work described in this paper contrasts the alkylation behavior of 2-substituted isoindolines and 2-substituted *tetrachloro*isoindolines.

Methyl iodide is, of course, a better alkylating agent than methyl chloride. 2-Methylisoindoline[5,6] (Ia) and 4,5,6,7-tetrachloro-2-methylisoindoline (Ib) were both alkylated readily by methyl iodide under mild conditions. With methyl chloride, however, a difference in the reactivity of the isoindoline and the tetrachloroisoindoline was evident. Gaseous methyl chloride quaternized 2-methylisoindoline (Ia) completely in chloroform or in hot dimethylformamide solution giving the methochloride salt IIa. Tetrachloro-2-methylisoindoline (Ib), on the other hand, was little affected by methyl chloride in chloroform, although in hot dimethylformamide it was converted to the methochloride IIb in 79% yield.

2-Methylisoindoline (Ia) and ethylene dibromide, in refluxing acetone, gave a bromoethyl salt IIIa in which only one end of the molecule had reacted; it has been reported[5] that no bis-salt IVa forms even when a large excess of base is used. The tetrachloro compound Ib, on the other hand, was completely unaffected under these conditions. It was possible to get 50–60% yields of the tetrachloroisoindolinium bromide IIIb but only at considerably higher temperatures. Under such conditions, a small amount (8%) of the symmetrical dibromide IVb was also isolated.

Although the tetrachloroisoindoline Ib was completely unreactive toward refluxing ethylene dichloride, 2-methylisoindoline (Ia) did form a small amount of 2-(2-chloroethyl)-2-methylisoindolinium chloride; this is consistent with the greater activity of the unchlorinated isoindoline nitrogen toward ethylene dibromide.



a, X = H; b, X = Cl

When the 2-substituent was dimethylaminoethyl, the contrast between isoindoline and tetrachloroisoindoline was even more striking. With the unchlorinated 2-dimethylaminoethylisoindoline (Va) practically no dimethochloride VIIa formed under the mild conditions of chloroform reflux. This was in contrast to the ready quaternization of 2-methylisoindoline (Ia). In hot dimethylformamide, the unchlorinated dimethylaminoethylisoindoline (Va) formed an approximately 1:1 mixture of monomethochloride VIa and dimethochloride VIIa. Under the same conditions, the tetrachloroisoindoline nitrogen was little affected; the monomethochloride VIb[7] was isolated in over 90% yield. In order to get a satisfactory conversion to the dimethochloride VIIb with the tetrachloroisoindoline compound Vb, it was necessary to go to higher pressures.

These alkylation experiments indicate that four chlorine atoms on the benzene ring decrease the basicity of the isoindoline nitrogen. The effect cannot be one of resonance interaction and is not likely to be steric. It therefore appears to be an *inductive* effect. A positively charged nitrogen atom β to the isoindoline nitrogen likewise decreases the reactivity of the isoindoline nitrogen. This decrease is also attributable to inductive factors. These conclusions are supported by pK_a determinations.

As may be seen from Table I, the inductive effect of the aromatic chlorines decreases the basicity of the isoindoline nitrogen almost a thousand-fold (pK_a from 7.7 to 4.8). Replacing the methyl substituent with a group having a β-ammonio cation decreases the basicity about four thousand-fold (pK_a from 7.7 to 4.1). When both influences are present, the basicity is decreased by a factor of about 50,000 to 65,000 (pK_a from 7.7 to 2.9–3.0). A β-ammonio cation decreases basicity one thousand-fold compared with a β-amino group (terminal nitrogen pK_a from 8.2–8.4 to 5.3). Similar inductive effects[8] are known for simple amines. The base strength of the amine nitrogen of ethylenediamine is one thousand times greater than that of ethylenediamine monoacid salt,[11] but it is only about one-fourth as strong as alkylamines[10–12]; benzylamine is a weaker base than either ethylamine (35-fold) or isobutylamine (13-fold).[12] It is interesting that the effect of the β-ammonio cation

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[4] L. M. Rice, E. E. Reid and C. H. Grogan, *J. Org. Chem.*, **19**, 884 (1954).

[5] L. M. Rice, C. H. Grogan and E. E. Reid, THIS JOURNAL, **77**, 616 (1955).

[6] J. v. Braun and Z. Kohler, *Ber.*, **51**, 103 (1918).

[7] First observed by C. F. Huebner and co-workers of these laboratories.

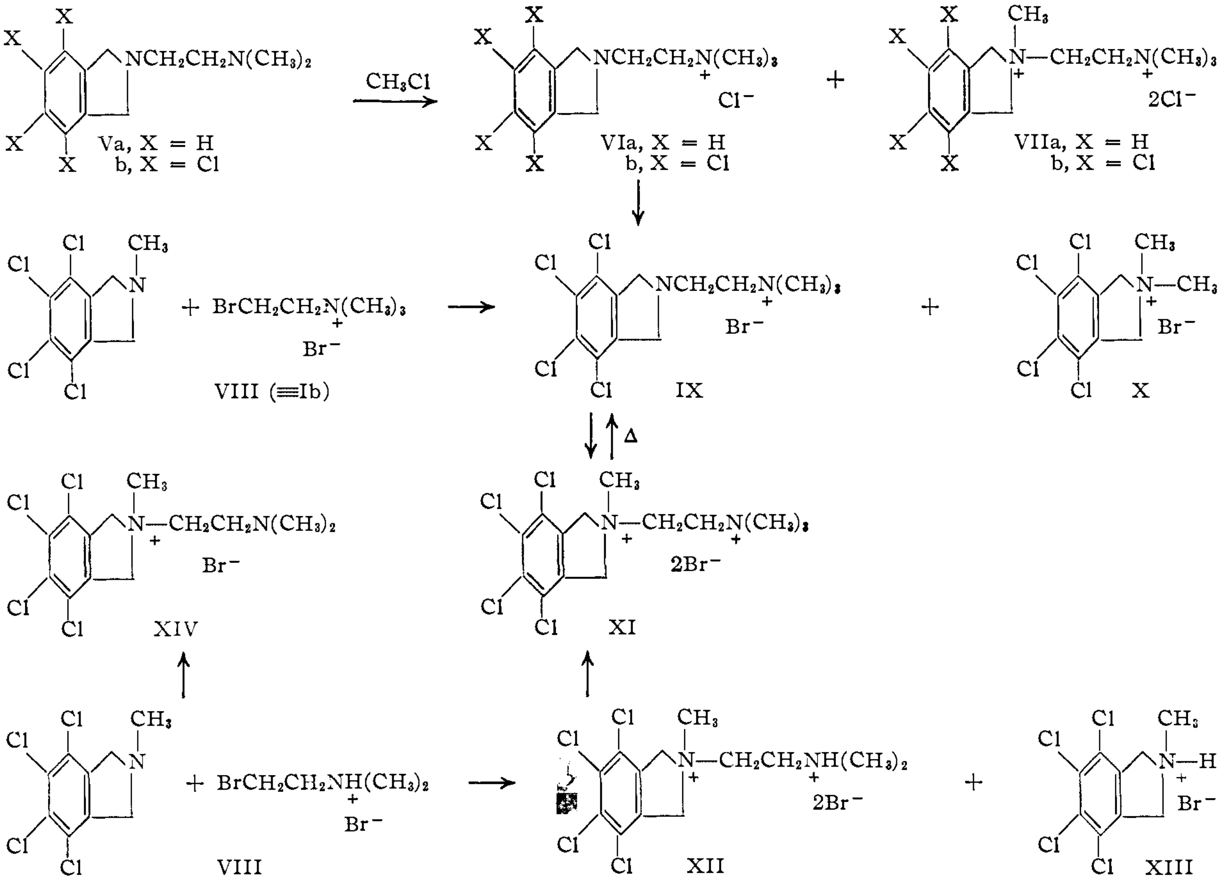
[8] The term "inductive effect" in this paper is meant to include any contribution made by the so-called "direct field effect."[9,10] Although the "direct field effect" has been shown to be considerable with cyclic amines, accounting for one-half[9] or more[10] of the total effect, proportions cannot be assigned in the examples discussed here. The inductive effect of the aromatic system on the isoindoline nitrogen probably has a large "direct field" component, whereas the "direct field effect" of the linear β-ammonio cation is probably small.

[9] J. D. Roberts and W. T. Moreland, Jr., THIS JOURNAL, **75**, 2167 (1953).

[10] H. K. Hall, *ibid.*, **78**, 2570 (1956); C. A. Grob, E. Renk and A. Kaiser, *Chemistry & Industry*, 1222 (1955).

[11] D. H. Everett and B. R. W. Pinsent, *Proc. Roy. Soc.* (*London*), **215A**, 416 (1952).

[12] "Handbook of Chemistry," 8th Ed., Ed. by N. A. Lange, Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 1233.

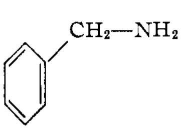
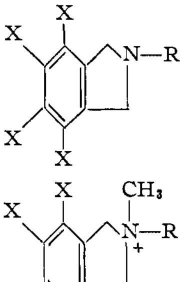
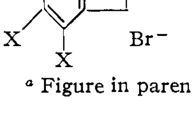


is about the same whether the cation be a quaternary salt or an acid salt.

A series of reactions starting with 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) showed some additional aspects of the chemistry of the isoindoline nitrogen. Bromoethyltrimethylammonium bromide, prepared from ethylene dibromide and trimethylamine, reacted with 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) in refluxing dimethylformamide to give two products. The major product, isolated in 57% yield, was the transquaternized methobromide salt X. The other product, isolated in 7% yield, was 4,5,6,7-tetrachloro-2-(2-trimethylammonioethyl)-isoindoline bromide (IX). This monomethobromide IX was identical with that prepared from monomethochloride VIb by halide exchange. The monomethochloride VIb was formed, as mentioned above, from 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) and methyl chloride gas. The monomethobromide IX was further quaternized by methyl chloride to only a small extent but gave in good yield the diquaternary salt XI with methyl bromide.[13] Evidently the first-formed dimethobromide from VIII and bromoethyltrimethylammonium bromide dequaternized under the reaction conditions. When dimethobromide XI was subjected to these conditions, about 80% monomethobromide IX was isolated.[14] Attempts to isolate the first-formed dimethobromide under these or milder conditions were unsuccessful.

TABLE I

pK_a VALUES OF ISOINDOLINE BASES (IN 80% METHYL CELLOSOLVE)

Isoindoline base	X	R	pKa
 CH₂—NH₂			9.0
 N—R	H	CH_3	7.7
	Cl	CH_3	4.8
	H	$CH_2CH_2\overset{+}{N}H(CH_3)_2Cl^-$	4.1 (8.4)[a]
	Cl	$CH_2CH_2\overset{+}{N}H(CH_3)_2Cl^-$	2.9 (8.2)[a]
	Cl	$CH_2CH_2\overset{+}{N}(CH_3)_3Cl^-$	3.0
 N—R Br⁻	Cl	$CH_2CH_2—N(CH_3)_2$	(5.3)[a]

[a] Figure in parentheses is pK_a of the terminal nitrogen.

An alkylation which went through the other monomethobromide XIV led to the same dibromide. 4,5,6,7 - Tetrachloro - 2 - methylisoindoline (VIII) and bromoethyldimethylammonium bro-

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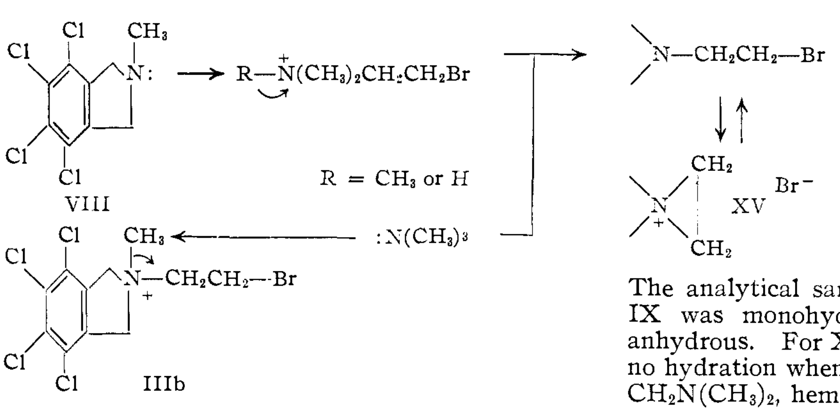
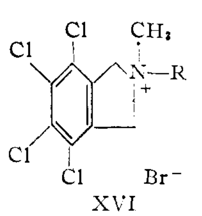
[13] The dimethobromide XI can be prepared directly by the diquaternization of tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) with methyl bromide in hot dimethylformamide (G. A. Nussberger, unpublished work).

[14] The same treatment of dimethochloride VIIb and dimethiodide gave 95% and 75% monomethohalide, respectively.



VIII IIIb XV



XVI

mide[15] in warm dimethylformamide gave 65% of the 2-methyl hydrobromide salt XIII. A 10% yield of the expected monomethobromide monohydrobromide salt XII also was obtained. The monomethobromide-free base XIV corresponding to XII was different from the monomethobromide IX, which was the more stable monomethobromide. Since the monomethobromide XIV is the less stable of the two possible isomers, it must be, in fact, the expected product, *i.e.*, quaternized at the isoindoline nitrogen. As expected for the monomethobromide quaternized at the less reactive nitrogen, methyl chloride, in the presence of sodium acetate, *was* capable of converting XII to a dimethohalide. Methyl bromide, with sodium acetate, gave the dimethobromide XI.

In both of these alkylation reactions of VIII, the major product resulted from abstraction of a group from the bromoethylammonium salt. This was surprising at first, because the isoindoline nitrogen is a much weaker base than a tertiary amine. On the other hand, 4,5,6,7-tetrachloro-2-(2-bromoethyl)-2-methyl isoindolinium bromide (IIIb) was dequaternized in 83% yield by trimethylamine. Evidently the basicity of the nitrogens is not the important factor. In all three cases the nitrogen which was readily dequaternized had a bromoethyl substituent. Bromoethylamine formation may be favored because of its ability to react further as a nitrogen mustard, to give an ethyleneimmonium salt (XV)[17] (or possibly to give a piperazinium salt[15]).

Hydration.—The quaternized terminal nitrogen of XI, rather than the quaternized isoindoline nitrogen, seems to be responsible for hydration. The analytical sample of the monomethobromide IX was monohydrated, but that of XIV was anhydrous. For XVI, the analytical data indicate no hydration when R = CH_3, CH_2CH_2Br, or $CH_2CH_2N(CH_3)_2$, hemihydration when R = H, monohydration when R = $CH_2CH_2\overset{+}{N}(CH_3)_3Br^-$ (and also for IVb) and dihydration when R = $CH_2CH_2\overset{+}{N}H(CH_3)_2Br^-$. The tendency of salts for hydrate formation was found to be chloride salt > bromide salt > iodide salt. Chloride salts were either deliquescent or hygroscopic, bromide salts were sometimes hygroscopic and iodide salts, once dried, remained anhydrous.

Acknowledgment.—The authors are pleased to acknowledge the helpful discussions and coöperation of their many co-workers in the CIBA Research Department. We are also indebted to Mr. Louis Dorfman, head of our Microanalytical Group, and his staff for various determinations and for discussions of technical matters. Microanalyses were carried out by Mr. George Robertson, Mrs. Barbara Pita and Miss June Swantko, infrared absorption spectra by Mrs. Violet Loire and Miss Margaret Jones; and ultraviolet absorption spectra by Miss Natalie Cahoon. We thank Dr. M. J. Allen and Miss Verda Powell for the electrometric titrations.

Experimental[18]

N-(2-Dimethylaminoethyl)-phthalimide.—To a stirred suspension of 35.0 g. (0.236 mole) of phthalic anhydride in 350 ml. of acetic acid was added 27.0 g. (0.242 mole) of 77% dimethylaminoethylamine[19] dropwise over 30 minutes. The colorless solution was refluxed for 4 hr. (yellow color developed), the bulk of the solvent was removed *in vacuo* and the concentrated solution was made basic by slow addition of 15% ammonium hydroxide solution with stirring and cooling. The white solid which separated was collected, washed once with water and dried *in vacuo* at 70°, giving 31.0 g. (60%) of N-(2-dimethylaminoethyl)-phthalimide, m.p. 103–105°. Recrystallization from hexane (charcoal) gave 27.2 g. (53%) of white crystals, m.p. 104–106.5°, R_f 0.52.[20] The imide carbonyl groups absorbed at 1770 cm.$^{-1}$

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[15] An attempt was made to alkylate 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) with the tosylate of dimethylaminoethanol. When tosyl chloride and 2-dimethylaminoethanol were combined in pyridine in an attempt to form the tosylate, and VIII was added, the isoindoline was recovered and some 1,1,4,4-tetramethylpiperazinium dichloride was isolated. When tosyl chloride was added to a dioxane solution of VIII and 2-dimethylaminoethanol, the acid generated resulted in formation of salts (hydrochloric or *p*-toluenesulfonic acid salts) of VIII. In a run using excess VIII in the presence of excess sodium bicarbonate, 1,1,4,4-tetramethylpiperazinium ditosylate was isolated. Evidently dimerization of 2-dimethylaminoethyl tosylate (or chloride) occurred more rapidly than did alkylation of VIII, thereby permitting isolation of starting VIII (or its chloride or tosylate salt) and piperazinium dichloride or ditosylate, depending on the reaction conditions. Dimethylaminoethyl chloride itself is known to dimerize rapidly to 1,1,4,4-tetramethylpiperazinium dichloride.[16]

[16] L. Knorr, *Ber.*, **37**, 3507 (1904); W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 1014 (1927); L. Ruzicka, Pl. A. Plattner and B. A. Engel, *Helv. Chim. Acta*, **27**, 1553 (1944).

[17] G. Girault and P. Rumpf, *Compt. rend.*, **243**, 663 (1956); H. Freundlich and H. Kroepelin, *Z. physik. Chem.*, **122**, 39 (1926).

[18] Melting points were taken on an electrically heated aluminum block in open capillaries and are uncorrected. Infrared absorption spectra were determined on a double-beam Perkin-Elmer model 21 infrared spectrophotometer using a sodium chloride prism. Ultraviolet absorption spectra were determined on a Beckman DK-1 spectrophotometer. Analytical samples were dried at water-pump vacuum over Drierite at 75° for 3–5 hr. and then permitted to equilibrate in air of 40–45% relative humidity at 23°, unless otherwise specified. All *pKa* values were determined in 80% methyl Cellosolve solutions. Melting points of methohalide salts were not reliable indices of purity or identity. Samples varied in decomposition range depending on the method of preparation, the age of the sample, solvation, etc. Mixtures of different salts frequently did not show a depression of melting point

[19] R. A. Turner, THIS JOURNAL, **68**, 1607 (1946).

[20] Paper chromatography of tertiary amines and quaternary ammonium salts was carried out on Whatman No. 1 filter paper, using 1-butanol saturated with 0.1 *N* aqueous ammonia as developing solvent and Dragendorff[21] spray reagent. Details of the paper chromatographic work, together with tabulations and correlations of quaternary

(m) and 1709 cm.$^{-1}$ (s) in the infrared. Moore and Rapala[22] reported m.p. 104–105° for imide prepared in 2.5% yield from equimolar amounts of phthalic anhydride and dimethylaminoethylamine (oil-bath 160–180°, 1 hr.).

N-(2-Dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide.—The tetrachlorophthalimide, m.p. 183–185°, was prepared in 85% yield by the method described above (refluxed 4 hr. in acetic acid). Two crystallizations from chloroform gave yellow prisms, m.p. 183–186°, R_f 0.70; $\lambda_{\max}^{\text{EtOH}}$ 288 mμ (ϵ 570), 298 (shoulder, 540), 322–328 (190), 333–335 (200). The infrared absorption spectrum showed a medium band at 1774 cm.$^{-1}$ and a strong band at 1707 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{10}O_2N_2Cl_4$ (356.06): C, 40.48; H, 2.83; N, 7.87. Found: C, 40.73; H, 3.05; N, 7.55.

The monomethiodide, **N-(2-trimethylammonioethyl)-3,4,5,6-tetrachlorophthalimide iodide**, decomposed at 303–304°, R_f 0.42 (weak), after one crystallization from methanol. The infrared spectrum showed medium absorption at 1776 cm.$^{-1}$ and strong absorption at 1704 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{13}O_2N_2Cl_4I$ (498.00): C, 31.35; H, 2.63; N, 5.63. Found: C, 31.35; H, 2.88; N, 5.63.

N-Methyl-3,4,5,6-tetrachlorophthalimide.—To 500 g. of tetrachlorophthalic anhydride, m.p. 256–259° (Niagara Alkali Co., Niagara Falls, N. Y.), in a 2-liter round-bottomed flask, was added with intermittent shaking and cooling 275 g. (25% excess) of 25% aqueous methylamine over 20 minutes. Water was removed slowly by heating at 100°, after which the yellow material was heated to 250°. The hot liquid was poured into a mortar, allowed to cool and the hard cake was then crushed to a fine, granular, yellow powder. The 516 g. (98%) of crude product, m.p. (s. 159) 203–205° (particles of solid to 230°), could be reduced directly (see below), but one crystallization from 10 to 20 volumes of chloroform (or ethylene dichloride or ethyl acetate, in decreasing order of solubility) gave a 75% yield of N-methyl-3,4,5,6-tetrachlorophthalimide, m.p. 210–212°. The infrared absorption spectrum had bands at 1775 (m) and 1714 (s) cm.$^{-1}$. Allen and Nicholls[23] reported m.p. 210–211° for their pure material, prepared by a sealed tube alkylation of the potassium salt of 3,4,5,6-tetrachlorophthalimide (no yield was given).

3,4,5,6-Tetrachlorophthalimide.—A mixture of 193.0 g. (0.676 mole) of tetrachlorophthalic anhydride and 80.0 g. (1.3 moles) of 29% ammonium hydroxide was heated to 340° and then allowed to cool. An additional 80.0 g. of 29% ammonium hydroxide was added and the mixture was heated again until completely liquid (over 350°). The brown liquid was poured into a mortar and pulverized when cool, m.p. (335) 342–347°. Crystallization from 6–7 volumes of dimethylformamide afforded yellow needles in 85% yield, m.p. (340) 345–347°, soluble in aqueous sodium carbonate; $\lambda_{\max}^{\text{EtOH}}$ 234 mμ (ϵ 8,230), 253 (sh., 8,120), 318 (sh., 2,080), 330 (2,350). The infrared spectrum showed typical imide absorption at 1775 (m) and 1708 (s) cm.$^{-1}$; phthalimide itself absorbs at 1777 (m) and 1752 (s) cm.$^{-1}$.

This procedure is essentially that described in "Organic Syntheses" (Coll. Vol. I, p. 457) for phthalimide. Previous workers have reported: (a) 91% yield, m.p. 336–337°, by fusion of tetrachlorophthalic anhydride and ammonium carbonate[23] and (b) 90% yield, m.p. 338–339°, by heating tetrachlorophthalic anhydride with formamide.[24]

Lithium Aluminum Hydride Reduction of N-(2-Dimethylaminoethyl)-phthalimide to 2-(2-Dimethylaminoethyl)-isoindoline (Va).—After 17.3 g. (0.456 mole) of lithium aluminum hydride had been refluxed in one liter of anhydrous ether for 30 minutes, 24.8 g. (0.114 mole) of N-(2-dimethylaminoethyl)-phthalimide was added portionwise over 10 minutes. The suspension was refluxed for 6 hr. with stirring, and then further stirred at room temperature overnight (16 hr.). The solution was cooled in an ice-bath, decomposed with 70 ml. of 10% aqueous sodium sulfate added dropwise (stirring and cooling) and filtered. The lithium aluminate cake was washed 3 times with 200-ml. portions of ether, and the combined ether solutions were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The 21.1 g. (97.5%) of green oil, R_f 0.89, was suitable for quaternization (see below); it was stored under nitrogen in the refrigerator.

An analytical sample was obtained by fractional distillation. The pure 2-(2-dimethylaminoethyl)-isoindoline (Va) had b.p. 72–75° (0.06 mm.), m.p. (s. 18) 19.5–21.7°, $n^{23}\text{D}$ 1.5276; $\lambda_{\max}^{\text{EtOH}}$ 258 mμ (ϵ 660), 265 (860), 272 (850).

Anal. Calcd. for $C_{12}H_{18}N_2$ (190.29): C, 75.74; H, 9.53; N, 14.72. Found: C, 75.74; H, 9.32; N, 14.58.

2-Methyl-2-(2-trimethylammonioethyl)-isoindolinium Diiodide (Dimethiodide of Va).—A 2.00-g. sample of crude Va was refluxed for 1 hr. with 5 ml. of methyl iodide in 10 ml. of 95% ethanol. The solid was collected, washed with a little ethanol and dried, giving 4.21 g. (84.4% yield from isoindoline oil, 82.3% from phthalimide) of light green solid, m.p. 238–240° dec., R_f 0.13. Three crystallizations from 95% ethanol afforded long white prisms, m.p. 243–245° dec.; $\lambda_{\max}^{\text{EtOH}}$ 216–219 mμ (ϵ 29,440), 266 (490), 272 (490).

Anal. Calcd. for $C_{14}H_{24}N_2I_2$ (474.18): C, 35.46; H, 5.10; N, 5.91. Found: C, 35.41; H, 5.34; N, 5.72.

Lithium Aluminum Hydride Reduction of N-(2-Dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide to 4,5,6,7-Tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb).[7]—A suspension of 3.56 g. (0.01 mole) of N-(2-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide and 1.5 g. (0.04 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether was refluxed for 3 hr. and then stirred at room temperature overnight. The cooled solution was decomposed with 8 ml. of 10% aqueous sodium sulfate and further stirred for 1 hr. The pale yellow ether solution was filtered and the granular white cake was washed 5 times with 25-ml. portions of ether; further extraction with ether or chloroform gave no additional product. The combined ether solution was dried over magnesium sulfate and evaporated to dryness. When the residual oil was triturated with dimethylformamide, white crystals of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) separated, m.p. 67.5–69.5°. Chromatography on alumina and crystallization from acetone gave pure Vb, m.p. 71.5–73°, R_f 0.98; $\lambda_{\max}^{\text{EtOH}}$ 236 mμ (sh., ϵ 18,550), 282 (530), 289–292 (450).

Anal. Calcd. for $C_{12}H_{14}N_2Cl_4$ (328.09): C, 43.93; H, 4.30; N, 8.54. Found: C, 43.98; H, 4.58; N, 8.75.

4,5,6,7-Tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium Diiodide.[7]—The crude Vb oil from lithium aluminum hydride reduction of 3.56 g. (0.01 mole) of imide was stirred and refluxed for 4 hr. with 7 ml. of dimethylformamide and 3 ml. of methyl iodide. After the suspension had been diluted with 20 ml. of acetone and further stirred for 2 hr., the gray crystals were collected, washed with acetone and dried, giving 3.34 g. of crude product, m.p. 232–235° dec. Recrystallization from 500 ml. of methanol plus 25 ml. of water gave 2.34 g. (38% yield from starting phthalimide) of fine off-white needles, m.p. 239–241° dec.; a second crop of 0.45 g. (7.3%) was obtained after concentration of the mother liquors.

An analytical sample was obtained after three recrystallizations, m.p. 241–243° dec., R_f 0.25; $\lambda_{\max}^{\text{EtOH}}$ 237 mμ (sh., ϵ 17,740), 275 (340), 284–286 (350), 295 (260).

Anal. Calcd. for $C_{14}H_{20}N_2Cl_4I_2$ (611.98): C, 27.48; H, 3.29; N, 4.58. Found: C, 27.61; H, 3.41; N, 4.69.

Methyl iodide quaternization of pure Vb under the same conditions gave 93% pure dimethiodide (see below).

4,5,6,7-Tetrachloro-2-methylisoindoline (VII, Ib).—To a cooled and stirred suspension of 20.4 g. (0.54 mole) of lithium aluminum hydride in 400 ml. of ether was added 40.0 g. (0.13 mole) of N-methyl-3,4,5,6-tetrachlorophthalimide portionwise over 20 minutes (exothermic reaction). After the green suspension had been refluxed for 5 hr. and stirred at room temperature overnight, it was decomposed with 80 ml. of 10% aqueous sodium sulfate (stirred 1 hr. at room temperature) and filtered. Five ether and five chloroform washings (each of 100 ml.) of the lithium aluminate cake were combined with the original ether solution, solvent was removed *in vacuo* and the residue was crystallized from 500 ml. of acetone. The 4,5,6,7-tetrachloro-2-methylisoindoline separated as long, white prisms, 15.6 g. (43%), m.p. 156–158°. A reduction using 2 moles of lithium aluminum hydride per

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ammonium salts and tertiary amines, will be published in a separate communication.

[21] H. M. Bregoff, E. Roberts and C. C. Delwiche, *J. Biol. Chem.*, **205**, 565 (1953).

[22] M. B. Moore and R. T. Rapala, This Journal, **68**, 1657 (1946).

[23] C. F. H. Allen and R. V. V. Nicholls, *ibid.*, **56**, 1409 (1934).

[24] D. S. Pratt and G. A. Perkins, *ibid.*, **40**, 198, 214 (1918).

mole of imide yielded only 10% pure plus 24% crude isoindoline.

Using the crude N-methyl-3,4,5,6-tetrachlorophthalimide described above (obtained in 98% yield from anhydride and methylamine) with 3 moles of lithium aluminum hydride afforded 24% pure product, m.p. 159–162° plus 17% crude product. Recrystallization of the pure product from acetone gave white prisms of the same melting point, R_f 0.96.

Anal. Calcd. for $C_9H_7NCl_4$ (270.99): C, 39.89; H, 2.60; N, 5.17. Found: C, 40.24; H, 2.80; N, 5.40.

2,2-Dimethylisoindolinium Halides.—A chloroform solution of 2-methylisoindoline (Ia)[5,6,25] (purified by sublimation and containing 0.5 mole of water, m.p. 45–47°, pK_a 7.7, volatile and unstable. *Anal.* Found: C, 76.02; H, 8.51) was refluxed on the steam-bath for 15 minutes with excess methyl iodide. The methiodide derivative was collected and dried in air, m.p. 253–255° dec., R_f 0.34. Rice and co-workers[5] reported m.p. 253–255°.

The methochloride derivative IIa, m.p. 206–209°, R 0.25, was a deliquescent white solid, prepared by bubbling methyl chloride gas for 0.5 hr. into a chloroform solution of 2-methylisoindoline either at reflux temperature or at 25–30° (or into a hot dimethylformamide solution). Paper chromatographic analysis showed that practically no starting isoindoline remained.

4,5,6,7-Tetrachloro-2,2-dimethylisoindolinium Halides. Chloride Salt IIb.—Gaseous methyl chloride was bubbled for 30 minutes through a heated (steam-bath) solution of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (Ib), m.p. 159–162°, in 10 ml. of dimethylformamide. The 2.80 g. of solid which separated after the solution had cooled to room temperature was collected, washed once with cold acetone and extracted once with boiling acetone. The hot acetone extracted 0.28 g. (11.4%) of starting Ib, m.p. 157–159°, and dilution of the dimethylformamide mother liquor (plus cold acetone wash) with water gave 0.08 g. (3%) more Ib. The 2.52 g. (78.5%) of acetone-insoluble 4,5,6,7-tetrachloro-2,2-dimethylisoindolinium chloride (IIb) melted 304–306°, R_f 0.34. Two crystallizations from methanol–ethyl acetate gave hexagonal white prisms, m.p. (s. 313) 315–317°.

Anal. Calcd. for $C_{10}H_{10}NCl_5$ (321.48): C, 37.36; H, 3.14. Found: C, 37.74; H, 3.27.

A 90.4% yield of IIb, m.p. 307–309°, was obtained when the reaction was run in refluxing dimethylformamide. In refluxing chloroform, on the other hand, 75% of the starting material Ib, m.p. 159–160°, was recovered and paper chromatographic examination of the mother liquors showed only traces of IIb.

Bromide Salt X.—Addition of gaseous methyl bromide to a refluxing chloroform solution of Ib gave the methobromide salt X, m.p. 309–310° sl. dec. (melting point decreased on standing or on grinding to a powder), R_f 0.55, molecular weight determination by isothermal distillation 378 (calcd. 366). The infrared spectrum was very similar to that of the chloride salt IIb.

Anal. Calcd. for $C_{10}H_{10}NCl_4Br$ (365.94): C, 32.82; H, 2.75; N, 3.83. Found: C, 32.91; H, 2.82; N, 3.94.

Iodide Salt.—The corresponding iodide salt, prepared in refluxing chloroform, melted 242–250° dec., R_f 0.61.

2-(2-Bromoethyl)-2-methylisoindolinium Bromide (IIIa)—One gram of 2-methylisoindoline was warmed on the steam-bath with 10 ml. of ethylene dibromide. After 15 minutes, the gray solid was collected and washed with ethylene dibromide and ether, giving 1.54 g. (64%) of light gray solid, m.p. 210.5–211° dec., R_f 0.43. Further heating of the mother liquors for a total of 1 hr. afforded 0.12 g. (5%) of more gray solid, m.p. 219–220° dec. Rice and co-workers[5] reported 223–224°. For yields under other conditions, see following table.

2-(2-Bromoethyl)-4,5,6,7-tetrachloro-2-methylisoindolinium Bromide (IIIb). (1).—Ten grams (0.037 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (Ib) and 30.0 ml. (65.4 g., 0.35 mole) of redistilled ethylene dibromide, b.p. 129–134° (atm.), were refluxed (temperature of the wet cake 135°) for 30 minutes using a heating mantle. After the slurry had cooled, 40 ml. of ether was added with swirling, and the suspension was filtered. The red ether solution on evaporating to dryness left 1.7 g. of red-brown tar. The ether-insoluble tan solid was extracted three times with hot water, (a) 40 ml., (b) 80 ml., (c) 80 ml. First crops from portions a and b and all of portion c darkened over 220° but did not melt to 300°; this combined white solid (6.32 g., 37.3%) was recrystallized from methanol to give 4.34 g. (25.5%) of white platelets of IIIb, shrinking 225°, black > 280°, not melted to 300°; R_f 0.61.

Anal. Calcd. for $C_{11}H_{11}NCl_4Br_2 \cdot CH_3OH$ (490.92): C, 29.35; H, 3.08; N, 2.85. Found: C, 29.27; H, 2.92; N, 3.07.

The aqueous mother liquors from portion a above were stripped to dryness, leaving 1.30 g. (7.7%) of off-white solid, m.p. 278–284° dec. One crystallization from 95% ethanol afforded white crystals of IVb, m.p. 274–289° dec., R_f 0.53.

Anal. Calcd. for $C_{20}H_{18}N_2Cl_8Br_2 \cdot H_2O$ (747.88): C, 32.12; H, 2.70; N, 3.75. Found: C, 32.33; H, 2.86; N, 4.03.

Neither the analysis nor the infrared spectrum nor the R_f value distinguished this compound from the hemihydrate or 4,5,6,7-tetrachloro-2,2-dimethylisoindolinium bromide (X). A molecular weight determination by isothermal distillation, however, gave 837, whereas X gave 378. The data is consistent with assignment of a 1,2-bis-(4,5,6,7-tetrachloro-2-methylisoindolinium)-ethane dibromide structure (IVb) formed by displacement reaction at *both* ends of the ethylene dibromide.

(2).—A suspension of 20.0 g. of 4,5,6,7-tetrachloro-2-methylisoindoline (Ib) in 20 ml. of ethylene dibromide was stirred and heated in an oil-bath to 170° over a period of 1 hr. and was then maintained at 165–175° for 15 minutes (moderate to vigorous boiling). After cooling to room temperature, it was diluted with 40 ml. of ether and filtered. The pink cake was washed twice with 40-ml. portions of ether, and crystallized from methanol. A first crop of 17.4 g. (51.5%) darkened but did not melt to 300°, R_f 0.65, was obtained, followed by 3.5 g. (10%) of a second crop which contained some isoindoline starting material.

(3).—When Ib and excess ethylene dibromide were refluxed in toluene for 6 hr., a 15% yield of white solid separated on cooling; this material darkened but did not melt to 320°, R_f 0.64; λ_{max}^{EtOH} 237 (ϵ 13,055), 284 (402), plateau 294 (347). Increasing the reflux time to 22 hr. raised the yield to 22%.

Anal. Calcd. for $C_{11}H_{11}NCl_4Br_2$ (458.88): C, 28.79; H, 2.42; N, 3.05. Found: C, 28.83; H, 2.51; N, 3.03.

(4).—Survey of reaction conditions for preparation of IIIb and IIIa:

Conditions for reaction of I and ethylene dibromide		Yield, %	
Solvent, reflux	Time, hr.	Of IIIb	Of IIIa
Acetone	0.25^5	0	17
Acetone	5	0	
Methyl ethyl ketone	1	0	
No solvent[a]	1	*ca.* 4	69
Toluene	6	15	
Toluene	22	22	60
Xylene	0.5	3	
Ethylene dibromide	[b]	Up to 60	

[a] Steam-bath. [b] Various times.

(5) **Dequaternization.**—Gaseous trimethylamine was bubbled for 1 hr. into a refluxing solution of 2.00 g. of IIIb in 20 ml. of dimethylformamide. From the cooled solution, 0.56 g. (83%) of tetramethylammonium bromide was collected, not melting to 320°, R_f 0.11.

Anal. Calcd. for $C_4H_{12}NBr \cdot H_2O$ (172.08): N, 8.15. Found: N, 7.99.

2-Methyl-2-(2-trimethylammonioethyl)-isoindolinium Dichloride (VIIa).—Gaseous methyl chloride was bubbled for 45 minutes into a heated (steam-bath) solution of 5.00 g. of 2-(2-dimethylaminoethyl)-isoindoline in 25 ml. of dimethylformamide. The cooled solution was diluted with 25 ml. of acetone, and the dark solid was collected, washed with acetone and dried *in vacuo* at 60° for 16 hr. The 4.04 g. (53% yield) of deliquescent green-brown dimethochloride VIIa melted 209–215° dec., R_f 0.05; it was soluble in water, methanol and isopropyl alcohol and insoluble in acetone, ethyl acetate and chloroform. A paper chromatogram of the mother liquors showed the presence of both mono- (VIa)

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[25] E. W. Cook and W. G. France, *J. Phys. Chem.*, **36**, 2383 (1932).

and dimethochloride (VIIa). Two crystallizations of the solid from 1-butanol–acetone gave deliquescent green prisms of VIIa. A sample was dried *in vacuo* at 75° over Drierite for 24 hr., and precautions were taken to obtain data on the anhydrous material: m.p. 223–225° dec.; $\lambda_{\max}^{\mathrm{EtOH}}$ 254 mμ (ε 300), 256–258 (310), 263 (390), 269 (370).

Anal. Calcd. for $C_{14}H_{24}N_2Cl_2$ (291.28): C, 57.73; H, 8.31; N, 9.62. Found: C, 57.32; H, 8.51; N, 9.38.

4,5,6,7-Tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium Dihalide.—A solution of 1.00 g. of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (Vb) m.p. 71.5–72.5°, in 4.2 ml. of dimethylformamide and 1.3 ml. of methyl iodide was refluxed for 2 hr. with stirring. The dimethiodide product was collected by filtration from the cooled solution and washed twice with acetone. The dried product, m.p. 241–243° dec., R_f 0.25, weighed 1.73 g. (93.5%) and was identical with that described above.

Methyl bromide in dimethylformamide converted Vb into the dimethobromide, m.p. 246–247° dec., R_f 0.23.

A mixture of 32.8 g. (0.10 mole) of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline Vb, 32.8 ml. of formamide and 35.3 g. (0.70 mole, 250% excess) of methyl chloride in a pressure bomb was heated to 90–100° with shaking for 5 hr.; the pressure rose to 172 p.s.i.g. After the bomb had been cooled and vented, the tan-colored formamide cake was diluted with 328 ml. of acetone and chilled. The white crystalline product melted 246–254° dec., and one recrystallization from absolute ethanol afforded 41.2 g. (86.7%) of dichloride VIIb, m.p. 264–266° dec., R_f 0.16. It was identical with material prepared from the dimethiodide by halide exchange.

Anal. Calcd. for $C_{14}H_{20}N_2Cl_6 \cdot {}^1/_2H_2O$ (438.08): C, 38.38; H, 4.83; N, 6.40. Found: C, 38.32; H, 4.96; N, 6.22.

4,5,6,7-Tetrachloro-2-(2-trimethylammonioethyl)-isoindoline Chloride (VIb).—Methyl chloride gas was bubbled into a hot (steam-bath) solution of 5.00 g. of Vb in 50 ml. of dimethylformamide for 0.5 hr. The white crystalline product was collected, washed with acetone and dried *in vacuo*, giving 5.36 g. (93.3%) of monomethochloride VIb, m.p. 256–260° dec. The mother liquors, which contained traces of dimethochloride (R_f 0.16), afforded an additional 0.27 g. (4.7%) of monomethochloride on dilution with acetone. Recrystallization from isopropyl alcohol gave 4.95 g. of product, m.p. 265–267° dec., R_f 0.55, which was dried *in vacuo* over Drierite at 100° for 5 hr.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_5 \cdot {}^1/_2H_2O$ (387.59): C, 40.29; H, 4.68; N, 7.23. Found: C, 40.12; H, 4.70; N, 7.12.

Crystallization from water gave a monohydrate, m.p. 280–281° dec.

Bromoethyltrimethylammonium Bromide.[26]—A clear, colorless solution of 10 ml. (21.8 g., 0.115 mole) of ethylene dibromide and 15 ml. (11.3 g., 0.47 mole) of 25% methanolic trimethylamine was refluxed for 1 hr. When the yellow solution cooled to room temperature, white crystals separated. After being chilled overnight, the solution was filtered and the collected crystals washed once with methanol and dried, giving 3.6 g. (13%) of white prisms, m.p. (s. 238) 251–253° dec. (red, foaming), R_f 0.22. Its water solution gave an immediate precipitate of silver bromide on addition of silver nitrate solution.

Anal. Calcd. for $C_5H_{13}NBr_2$ (247.00): N, 5.67. Found: N, 5.68.

Concentration of the methanol mother liquors gave 1.60 g. (6%) of a second crop, m.p. 239–243° dec. (orange foam); one crystallization raised the melting point to 248–250° dec.

When the reflux period was increased to 2 hr., a 22% yield of salt, m.p. 237–240° dec., was obtained.

A mixture of 25 ml. (0.29 mole) of ethylene dibromide, 10 ml. (0.32 mole) of 25% methanolic trimethylamine and 25 ml. of benzene, after standing at room temperature for three days and then being chilled to 5°, gave 7.7 g. (11%) of product, m.p. 245–247° dec. (orange foam).

4,5,6,7-Tetrachloro-2-(2-trimethylammonioethyl)-isoindoline Bromide (IX) from VIII and Bromoethyltrimethylammonium Bromide.—A mixture of 2.00 g. (7.4 millimoles) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) and 2.00 g. (8.1 millimoles) of bromoethyltrimethylammonium bromide was refluxed (153°) for 3 hr. in 10 ml. of dry dimethylformamide. The liquid darkened on heating, the bromide salt gradually dissolved and the solution became cloudy. After the cloudy solution had been cooled to room temperature and diluted with 10 ml. of acetone, it was filtered, removing 0.20 g. of light yellow solid, which decomposed but did not melt to 320°. The filtrate gave 2.40 g. of pale tan solid, m.p. (s. 226) 238–243° dec., after standing in the refrigerator (*ca.* 5°) for two weeks. Crystallization of this material from methanol afforded a first crop of 0.75 g. of off-white solid, m.p. (s. 255) 262–271° dec., R_f 0.56; the infrared spectrum was identical with authentic 4,5,6,7-tetrachloro-2,2-dimethylisoindolinium bromide (X). A second crop of 0.80 g. from methanol was similar to the first crop, but when slurried with 40 ml. of water at room temperature, it left 0.23 g. of insoluble off-white solid, m.p. (s. 245) 247–250° dec. Recrystallization of this water-insoluble material from methanol afforded 0.05 g. of IX, m.p. (s. 250) 252–255° dec. (reddish melt); R_f 0.55; the melting point was depressed 5° when mixed with X.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4Br \cdot H_2O$ (441.06): C, 35.40; H, 4.34; N, 6.35. Found: C, 35.74; H, 4.46; N, 6.64.

The infrared spectrum was identical with and the melting point was not depressed by authentic 4,5,6,7-tetrachloro-2-(2-trimethylammonioethyl)-isoindoline bromide (IX) (see below).

Treatment of the monomethobromide IX with methyl chloride (DMF, steam-bath, 1 hr.) gave recovered IX containing trace quantities of the dimethohalide (detectable by paper chromatography R_f 0.16). Treatment of IX with excess methyl bromide (DMF, steam-bath, 1 hr.) afforded 4,5,6,7-tetrachloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium bromide (XI), m.p. 246–247.5° dec., R_f 0.23.

Anal. Calcd. for $C_{14}H_{20}N_2Cl_4Br_2 \cdot H_2O$ (536.01): C, 31.37; H, 4.14; N, 5.23. Found: C, 31.31; H, 4.41; N, 5.39.

A mixture melting point with authentic dibromide XI, m.p. 246–247° dec., prepared by methyl bromide quaternization of the diamine Vb, showed no depression. Furthermore, the infrared spectra of the two were identical.

Formation of IX by Demethobromination of XI.—When 2.08 g. of dimethobromide XI, m.p. 246–248° dec., was refluxed in 10 ml. of dimethylformamide for 3 hr., it gradually dissolved. The 1.11 g. (65%) of white needles of monomethobromide IX which separated on cooling melted 252–253° dec., R_f 0.54. An additional 0.40 g. of material was obtained by dilution of the dimethylformamide mother liquors with acetone. This material was separated into 0.23 g. (14%) more IX, plus 0.16 g. (8%) of recovered XI by extraction of IX with 5 ml. of hot dimethylformamide.

Dimethiodide analogous to the dimethobromide XI did not dissolve completely in refluxing dimethylformamide even after 10 hr. The filtered hot solution was evaporated *in vacuo* and the residue was diluted with acetone. The brown solid was washed well with ether, leaving 75% crude monomethiodide. Crystallization from methanol (charcoal) gave yellow crystals, m.p. 230–231° dec., R_f 0.62. The infrared spectrum was very similar to that of the monomethobromide IX.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4I$ (470.03): C, 32.22; H, 3.65; N, 5.96. Found: C, 32.77; H, 3.93; N, 6.20.

Three hours refluxing of VIIb in dimethylformamide gave a 95% yield of VIb.

4,5,6,7-Tetrachloro-2-(2-trimethylammonioethyl)-isoindoline Bromide (IX) from the Chloride VIb.—A 1.00-g. sample of VIb, m.p. 261–263° dec., was dissolved in 25 ml. of water and 25 ml. of 48% hydrobromic acid and boiled gently on a hot-plate for 20 minutes. The cloudy, yellow-brown solution was filtered and allowed to cool. The sticky, off-white semi-solid which separated was taken up in methanol, charcoaled, filtered and diluted with two volumes of ether. An off-white solid (0.39 g.), m.p. 237–264° dec., R_f 0.55, was collected, which was the hydrobromide salt of the desired product. Recrystallization of this material from

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[26] Bromoethyltrimethylammonium bromide was first prepared by A. W. Hofmann, *Jahresb. Chem.*, **11**, 338 (1858). M. Kruger and P. Bergell, *Ber.*, **36**, 2901 (1903), obtained a 71% yield of the salt, m.p. 230–231°, from the reaction of ethylene dibromide and trimethylamine (no solvent), whereas R. R. Renshaw, THIS JOURNAL, **34**, 1615 (1912), got a 90% yield, m.p. 235.5° (corr.), in a bomb tube reaction. A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, *ibid.*, **77**, 3648 (1955), in a study of the reactions of tertiary amines and dibromoalkanes in benzene solution (giving ω-bromoalkyl quaternary ammonium salts), reported m.p. 229° for bromoethyltrimethylammonium bromide but did not give the yield.

methanol containing some sodium acetate (solution color changed from yellow to colorless as the *p*H was raised to about six) gave 0.24 g. (21.4%) of white crystals of 4,5,6,7-tetrachloro-2-(2-trimethylammonioethyl)-isoindoline bromide (IX), m.p. 254–256° dec., R_f 0.55.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4Br \cdot H_2O$ (441.06): C, 35.40; H, 4.34; N, 6.35. Found: C, 35.58; H, 4.42; N, 6.39.

4,5,6,7-Tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium Bromide (XIV).—A suspension of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) and 4.66 g. (0.02 mole) of bromoethyldimethylammonium bromide in 25 ml. of dimethylformamide was heated until completely dissolved, 0.90 g. (0.011 mole) of sodium acetate was added and the solution was swirled and allowed to cool to room temperature. After removal by filtration of 2.60 g. (96%) of starting VIII, m.p. 159–161°, R_f 0.94, the mother liquors were chilled to −15° for several days. The 0.15 g. of off-white solid which precipitated, m.p. (s. 215) 257–275° dec., was recrystallized from methanol. A tiny amount of VIII, m.p. 158–160°, was removed first, and spontaneous evaporation slowly deposited white prisms of 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium bromide (XIV), m.p. (s. 215) 255–265° dec., R_f 0.73.

Anal. Calcd. for $C_{13}H_{17}N_2Cl_4Br$ (423.04): C, 36.91; H, 4.05; N, 6.62. Found: C, 37.05; H, 4.19; N, 6.56.

4,5,6,7-Tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium Bromide Hydrobromide (XII).—A solution of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII) and 4.66 g. (0.02 mole) of bromoethyldimethylammonium bromide[27] in 25 ml. of dimethylformamide was heated on the steam-bath for 3 hr. After the solution had cooled to room temperature, 1.88 g. (53.5%) of 4,5,6,7-tetrachloro-2-methylisoindoline hydrobromide (XIII) was collected and washed with 25 ml. of acetone; m.p. (s. 267) 277–280° dec., R_f 0.94. Chilling the combined mother liquors and acetone washings at −15° for 18 hr. gave 0.40 g. (11.4%) more XIII, m.p. (s. 259) 262–275° dec., R_f 0.94. The first crop of XIII was washed twice with hot acetone and crystallized from methanol, giving white solid decomposing 305–309°.

Anal. Calcd. for $C_9H_8NCl_4Br \cdot {}^1/_2H_2O$ (360.92): C, 29.95; H, 2.51; N, 3.88. Found: C, 30.03; H, 2.46; N, 4.09.

Crystallization from 95% ethanol containing excess sodium acetate gave 4,5,6,7-tetrachloro-2-methylisoindoline (VIII), m.p. 158–160°.

The dimethylformamide–acetone mother liquors deposited 0.50 g. (10%) of white crystals, m.p. 250–265° dec. after standing for several days at room temperature. One crystallization from methanol gave white needles of XII, m.p. (s. 250) 256–264° dec., R_f 0.73, pK_a 5.3.

Anal. Calcd. for $C_{13}H_{18}N_2Cl_4Br_2 \cdot 2H_2O$ (540.00): C, 28.92; H, 4.11; N, 5.19. Found: C, 29.46; H, 4.43; N, 5.32.

Infrared Spectra.—The two products XII and XIII showed absorption in the infrared between 2300–2700 cm.$^{-1}$ typical of hydrohalide salts.[28] 4,5,6,7-Tetrachloro-2-methylisoindoline hydrobromide (XIII) absorbed strongly at 2625, 2548, 2490 and 2384 cm.$^{-1}$, whereas the free base VIII and its methobromide X did not. The hydrobromide XII absorbed at 2636 (ms), 2510 (w) and 2464 (m) cm.$^{-1}$; this region of the infrared spectrum was clear with the corresponding base XIV and the dimethobromide XI.

A solution of 0.10 g. (0.2 millimole) of the hydrobromide XII, 0.05 g. (0.6 millimole) of sodium acetate and excess methyl bromide in 5 ml. of dimethylformamide was warmed on the steam-bath for 1 hr. Solvent was removed *in vacuo* and the residue was taken up in methanol. When the solution was chilled to −15° 0.06 g. (58%) of white crystals separated, m.p. 239–243° dec., R_f 0.23. A mixture melting point with authentic dimethobromide XI, m.p. 246–247° dec., showed no depression. The infrared spectrum was identical with that of the dimethobromide, confirming the paper chromatographic and melting point data.

Treatment of XII with methyl chloride in hot dimethylformamide in the presence of sodium acetate gave the dimethohalide (R_f 0.17).

1,1,4,4-Tetramethylpiperazinium Salts. Dichloride.—A mixture of 1.8 g. (0.02 mole) of 2-dimethylaminoethanol, 1.9 g. (0.01 mole) of *p*-toluenesulfonyl chloride and 10 ml. of dry pyridine (exothermic reaction) was allowed to stand 18 hr. at room temperature. After addition of 2.71 g. (0.01 mole) of 4,5,6,7-tetrachloro-2-methylisoindoline (VIII), the solution was refluxed for 3 hr. The cooled solution deposited 2.9 g. of solid, of which 2.60 g. (96%) was recovered VIII, m.p. 158–160°, isolated by ether extraction. The 0.30 g. of ether-insoluble material was crystallized from methanol, giving material darkening 218–320° without melting, R_f 0.00, positive Beilstein test.

Anal. Calcd. for $C_8H_{20}N_2Cl_2$ (215.18): C, 44.66; H, 9.37. Found: C, 44.26; H, 9.18.

1,1,4,4-Tetramethylpiperazinium dichloride readily is formed from dimethylaminoethyl chloride and is reported to decompose over 300°.[16]

Di-*p*-toluenesulfonate.—To a solution of 2.71 g. (10 millimoles) of VIII in 150 ml. of dioxane was added 1.85 g. (22 millimoles) of sodium bicarbonate, 3.80 g. (20 millimoles) of *p*-toluenesulfonyl chloride and 1.80 g. (20 millimoles) of 2-dimethylaminoethanol. After the suspension had been stirred for 16 hr., the white solid was collected and dried giving 3.18 g. of mixed salts, darkening over 250° but not melting to 310°, positive Beilstein and silver nitrate tests (presence of chloride), no bubbling of an aqueous solution on addition of acid (no bicarbonate). This solid was extracted with hot 95% ethanol, and the filtered ethanol solution deposited 1,1,4,4-tetramethylpiperazinium di-*p*-toluenesulfonate on cooling, not melted to 310°, R_f 0.00, negative silver nitrate test. The infrared spectrum showed strong bands at 1012, 1035, 1124 and 1182 cm.$^{-1}$ typical of *p*-toluenesulfonate anion.

Anal. Calcd. for $C_{22}H_{34}O_6N_2S_2 \cdot {}^1/_2H_2O$ (495.67): C, 53.31; H, 7.12. Found: C, 53.33; H, 7.51.

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[27] F. Cortese, *Org. Syn.*, Coll. Vol. II, Ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 91.

[28] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 13; B. Witkop, THIS JOURNAL, **76**, 5597 (1954).