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An Eight-membered and a Ten-membered Ring System: Benzodiazocine and Dibenzodiazecine

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Hydrogenolysis of an aromatic chlorine by lithium aluminum hydride has been shown to occur during reduction of tetra chlorophthalimides and tetrachlorophthalimidines. The course of the reaction of tetrachloro-*o*-xylylene dibromide with amines was changed by the four chlorine atoms from isoindoline (or diamine) formation tol arger ring formation. The dibenzodiazecine (ten-membered) and the benzodiazocine (eight-membered) ring systems were formed with methylamine and with dimethylaminoethylamine, respectively. The ten-membered diamine ring compound formed only a *mono*-methobromide salt which could be titrated with base, like an acid salt, back to the free diazecine. Base strengths of the nitrogens and stabilities of the salts of the eight- and ten-membered ring compounds are compared.

In our studies of the alkylation reactions of isoindolines and tetrachloroisoindolines,[1] we found that the basicity of the isoindoline nitrogen decreased a thousand-fold when four chlorine atoms were attached to the four available positions of the benzene ring. In the course of that work, our preparative studies on isoindolines indicated that the chlorine atoms affected not only lithium aluminum hydride reduction of phthalimides, phthalimidines and anhydrides, but also the reactions of benzyl nitrogens *not* closed to an isoindoline ring.

Lithium aluminum hydride reductions of phthalimides have been shown[2,3] to give isoindolines, but considerably lower yields were obtained[1] with tetrachlorinated phthalimides. Reduction of the N - (2 - dimethylaminoethyl) - 3,4,5,6 - tetrachlorophthalimide (Ib) in refluxing ether, followed by methyl iodide quaternization gave the dimethiodide IIIb in over-all yields of 35–45%. N-Methyl-3,4,5,6-tetrachlorophthalimide (Ic) also was reduced[1] to 4,5,6,7-tetrachloro-2-methylisoindoline (IIc) in yields below 50%. Even reduction and quaternization of the tetrachlorophthalimidine[4] corresponding to Ib gave only a 47% yield of dimethiodide IIIb. In contrast, reduction and quaternization of the *unchlorinated* phthalimide Ia gave[1] 82% dimethiodide IIIa.[5] Lower yields were also obtained in the lithium aluminum hydride reduction of tetrachlorophthalic anhydride[6] to 3,4,5,6-tetrachloro-*o*-xylylenediol (26–36%) compared with the reduction of phthalic anhydride to *o*-xylylenediol (62%).[7]

The obvious conclusion that the aromatic chlorines were involved in some side reaction was reinforced when paper chromatographic examination[8] of crude dimethiodide IIIb from reduction of tetrachlorophthalimide Ib (or of tetrachlorophthalimidine) showed the presence of some *trichloro*-dimethiodide. When the reduction of Ib was carried out in dioxane at 45–50°, the trichloro analog of IIIb was isolated in 37% yield after methyl iodide quaternization. It is not known with certainty whether the 4-chlorine or the 5-chlorine of IIIb has been replaced.[9] Both chlorine atoms of the original tetrachlorophthalimide (or tetrachlorophthalimidine) are vinylogous[10] carbamic acid chlorides and, therefore, like all acid chlorides, are subject to hydrogenolysis by lithium aluminum hydride.[11,12] Replacement of the aromatic chlorine can still occur after the reduction of the carbonyl groups. Refluxing 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (IIb) in ether with lithium aluminum hydride gave only a 90.5% material recovery, of which 80–85% was starting tetrachloroisoindoline and 15–20% was the corresponding trichloroisoindoline.[11,13,14]

Another method which has been reported for preparing 2-substituted isoindolines[15] or isoindolin-

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[1] W. E. Rosen, V. P. Toohey and A. C. Shabica, THIS JOURNAL, **79**, 3167 (1957).

[2] A. Uffer and E. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

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

[4] A. Pernot and A. Willemart, *Bull. soc. chim. France*, 324 (1953), first reduced phthalimidines to isoindolines with lithium aluminum hydride in yields of 50–83%.

[5] L. M. Rice, C. H. Grogan and E. E. Reid, THIS JOURNAL, **75**, 4911 (1953), described the reduction of N-(2-diethylaminoethyl)-hexahydrophthalimide in 92% yield.

[6] A review of the reactions and properties of tetrachlorophthalic anhydride, which can be used[1] as starting material for the preparation of tetrachloroisoindolines, has been written by F. E. Lawlor, *Ind. Eng. Chem.*, **39**, 1419, 1424 (1947).

[7] R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947), reported a yield of 87% phthalyl alcohol (*o*-xylylenediol) with lithium aluminum hydride, using a Soxhlet extractor for gradual addition of the phthalic anhydride.

[8] For a discussion of the paper chromatographic technique used, see W. E. Rosen, V. P. Toohey and A. C. Shabica, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 625 (1957).

[9] M. J. Allen and J. Ocampo, *J. Electrochem. Soc.*, **103**, 682 (1956), have presented some evidence for the replacement of the carbon-5-chlorine atom by hydrogen during electrochemical reduction of Ib. The trichloro-dimethiodide obtained by lithium aluminum hydride reduction is identical with that obtained by electrochemical reduction (see Experimental section).

[10] N. G. Gaylord, *Experientia*, **10**, 166 (1954), has explained the hydrogenolysis with excess lithium aluminum hydride of aromatic carbonyl or carboxyl groups to methylene or methyl groups in terms of vinylogous amides, esters, etc., when amino, methoxyl or aroxyl groups are substituted in the *o*- or *p*-position.

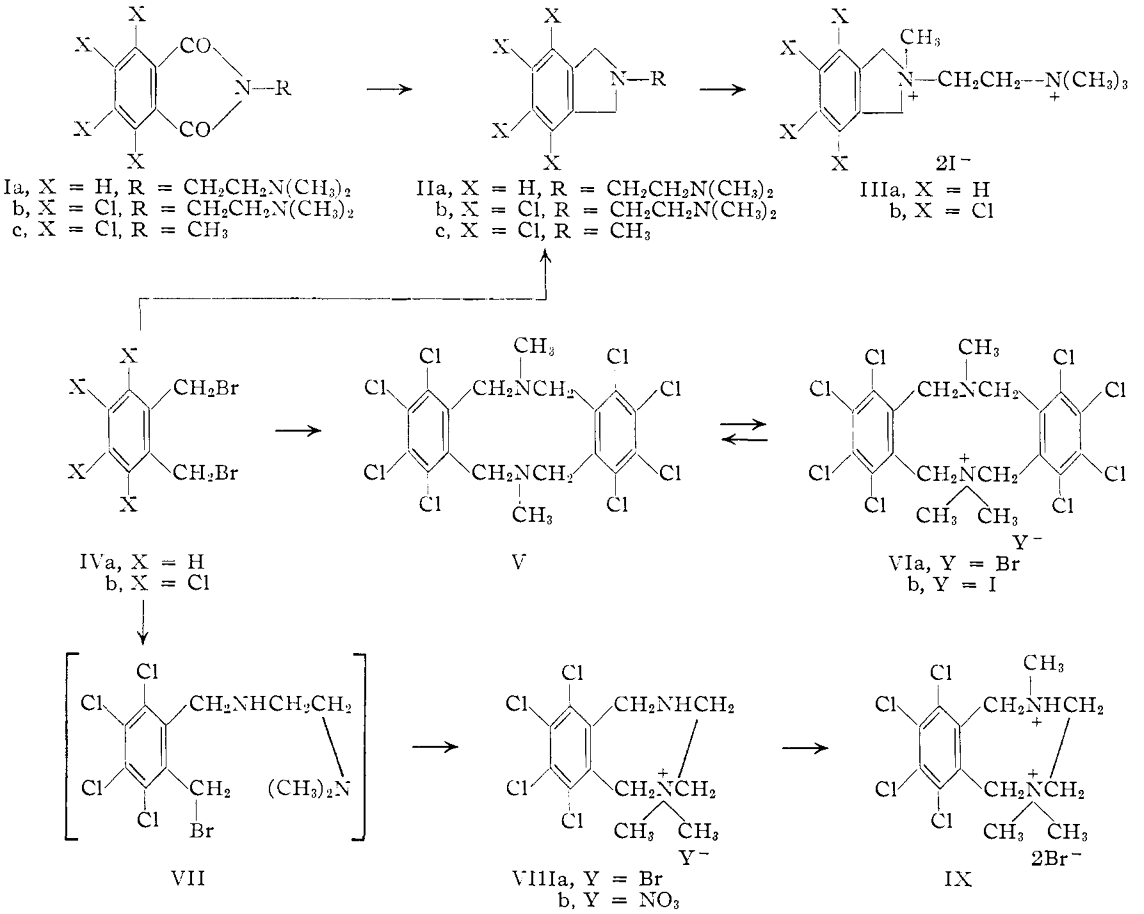
[11] J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951), have reviewed aromatic nucleophilic substitution reactions. Aromatic halogen may be activated for nucleophilic replacement by carbonyl or by halogen groups (page 308). Regarding the nucleophilic reagent itself, the authors point out that in general "the more basic reagents are the more active in effecting aromatic substitution" (page 341); hydride ion is, of course, a powerful base.

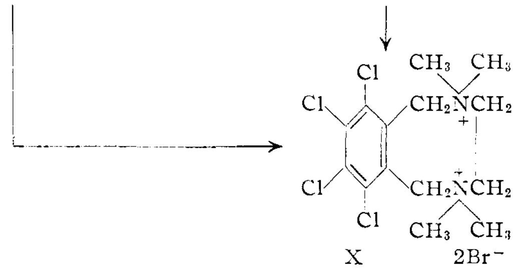
[12] D. S. Pratt and G. A. Perkins, THIS JOURNAL, **40**, 198, 214 (1918), found that one chlorine (probably α) of N-phenyl-3,4,5,6-tetrachlorophthalimide was replaced by an anilino group after several hours in refluxing aniline.

[13] The isoindoline mixture was analyzed by an infrared procedure developed by B. Messikommer and G. A. Nussberger of these laboratories.

[14] The substitution reactions of hexachlorobenzene with nucleophilic reagents has been discussed by A. L. Rocklin, *J. Org. Chem.*, **21**, 1478 (1956).

[15] The isoindoline ring system has been isolated from several different reactions: *o*-xylylenediamine dihydrochloride gave the hydrochloride of isoindoline itself on vigorous heating [S. Gabriel and G. Pinkus, *Ber.*, **26**, 2210 (1893); K. Frankel, *ibid.*, **33**, 2808 (1900)]; chlorophthalazine (or 1-methyl-4-chlorophthalazine) on reduction with zinc or tin and hydrochloric acid gave isoindoline (or 1-methyl-





ium bromide salts is the reaction of *o*-xylylene dibromide (IVa) with a primary or a secondary amine.[16] When this method was tried with methylamine and 3,4,5,6-tetrachloro-*o*-xylylene dibromide[17] (IVb), however, only traces of 4,5,6,7-tetrachloro-2-methylisoindoline (IIc) could be detected. The main product, isolated in over 50% yield, was 1,2,3,4,8,9,10,11 - octachloro - 5,6,7,12,13,14 - hexahydro - 6,13 - dimethyldibenzo[c,h][1,6]diazecine (V).[18] Proof that the product of IVb and methylamine was the ten-membered ring compound V and not a 15- or 20-membered ring was obtained by a Rast molecular weight determination of V itself, and by spectrophotometric determination[19] of molecular weight of the monopicrate salt. The nitrogens of V were very weak bases, and only a monomethobromide (VIa) or a monomethiodide (VIb) could be formed even under fairly vigorous conditions. The methobromide salt could be titrated with base, like an acid salt, back to the free diazecine. The pK_a values of the two nitrogens of V (in 80% methyl Cellosolve) were 4.2 and 3.2. The free nitrogen of the methobromide VIa had pK_a 3.2 and direct base titration of VIa itself indicated pK_a 4.3 for the quaternized nitrogen. When the diazecinium bromide (VIa) was treated with a few drops of ammonium hydroxide in hot methanol, a 94% yield of the free diazecine (V) was isolated. The weak basicity of the nitrogens of V may be explained by the inductive effects of the tetrachlorinated benzene rings.[1] Since amines of similar base strength form stable quaternary

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isoindoline) [S. Gabriel and A. Neumann, *ibid.*, **26**, 521 (1893)]; and catalytic reduction of 2-methylisoindole gave the dihydro derivative 2-methylisoindoline [G. Wittig, H. Tenhaeff, W. Schoch and G. Koenig, *Ann.*, **572**, 1 (1951)]. None of these reactions appeared promising to us as a preparative method.

(16) (a) M. Scholtz, *Ber.*, **31**, 414, 627, 1707 (1898); (b) J. v. Braun, *ibid.*, **43**, 1353 (1910); (c) J. v. Braun and Z. Kohler, *ibid.*, **51**, 100 (1918); (d) M. Tiffeneau and K. Fuhrer, *Bull. soc. chim. France*, **15**, 174 (1914); (e) G. Wittig and H. Ludwig, *Ann.*, **589**, 55 (1954); (f) W. Wenner, U. S. Patent 2,740,795 (1956); (g) G. Wittig, G. Closs and F. Mindermann, *Ann.*, **594**, 89 (1955).

(17) S. D. Ross and M. Markarian, U. S. Patents 2,600,691 (1952) and 2,631,168 (1953).

(18) Displacement of the bromines of *o*-xylylene dibromide and similar dibromides by *two* molecules of amine is known to compete with isoindoline formation.[16] Wittig and co-workers[16g] found that isoindoline formation was favored by the presence of hydrobromic acid. When hydrobromic acid was added to the reaction of IVb and methylamine, the yield of V decreased almost to half, but the yield of isoindoline remained very low. When methylamine hydrochloride was used, 94.5% starting IVb was recovered. M. Scholtz, *Ber.*, **24**, 2402 (1891), described the formation of dibenzo[c,h][1,6]diazecine by a sealed tube reaction of dixylyleneammonium bromide and ammonia.

(19) K. G. Cunningham, W. Dawson and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

salts,[1] however, the instability of VIa toward base must be due to severe steric crowding.[20] A ring containing ten members is usually very difficult to prepare and is one of the most strained when formed. The strain in ten-membered carbocyclic rings is due largely to internal crowding of hydrogen atoms; in the ten-membered ring under consideration (V) such non-bonded interactions are minimal since only four of the ten ring members are tetrasubstituted. Alkylation increases the number of tetrasubstituted ring members, and therefore the internal crowding.[21]

When 3,4,5,6-tetrachloro-*o*-xylylene dibromide (IVb) and dimethylaminoethylamine reacted under conditions similar to those[16e,f] which gave isoindoline derivatives, high yields (up to 78%) of 7,8,9,10-tetrachloro-1,2,3,4,5,6-hexahydro-2,2-dimethyl-2,5-benzodiazocinium bromide (VIIIa) were obtained. The product was *not* the hydrobromide of the expected isoindoline since treatment with base did not generate the known 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline (IIb), and its paper chromatographic behavior was typical[8] of a monomethohalide salt rather than of a hydrobromide salt. The R_f value as well as the solubility properties (soluble in water and methanol, insoluble in most organic solvents) eliminated the isomeric structure VII. Furthermore, treatment of the product with silver nitrate gave an *ionic* nitrate (VIIIb) [λ_{max} 1350(s), cm.$^{-1}$, 846(m) cm.$^{-1}$],[22] whose infrared spectrum was the sum of that of VIIIa and nitrate ion, indicating that there had been no structural change. Molecular weight determinations established that the compound was monomeric. The reaction of IVb with dimethylaminoethylamine probably proceeded normally to VII, but the weak basicity of the tetrachlorobenzyl nitrogen[1] slowed isoindoline formation and permitted intramolecular displacement of the second bromine by the terminal tertiary amine; similar effects probably were involved in the diazecine ring formation from IVb and methylamine. Although the pK_a of VIIIa, which titrated as a monoacidic base, was only 3.5, the salts IX and X were formed easily and were stable—in contrast to the monomethobromide salt VIa of the hindered ten-membered diazecine.

Acknowledgments.—We wish to thank 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, Miss June Swantko and Miss Beverly Kray; infrared spectra by Mrs. Violet Loire and Miss Margaret Jones; and ultraviolet absorption spectra by Miss Natalie Cahoon. We also thank Dr. M. J. Allen and Miss Verda Powell for the electrometric titrations.

Experimental[23]

4,5,?-Trichloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium Diiodide.—A solution of 3.56 g. (0.01 mole) of N-(2-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide (Ib)[1] in 100 ml. of anhydrous dioxane[24] was added dropwise over 20 minutes to a suspension of 1.5 g. (0.04 mole) of lithium aluminum hydride in 100 ml. of dioxane[24] at 10°; the solution developed an orange color. After the suspension had been stirred at 45–50° for four hours and at room temperature overnight, the excess lithium aluminum hydride was decomposed with 2 ml. of 10% aqueous sodium sulfate and further stirred for one hour. The dioxane solution was combined with four ether washings of the lithium aluminate cake, and solvent was removed *in vacuo*. The 3.02 g. of red oil residue was refluxed for two hours with 12 ml. of dimethylformamide and 4 ml. of methyl iodide, 20 ml. of acetone was added, and the grayish-white solid was collected, washed with acetone and dried. The 2.13 g. (37% yield from starting phthalimide) of dimethiodide, m.p. 197–198° dec., was recrystallized from methanol giving off-white crystals, m.p. 202–210° dec.

Anal. Calcd. for $C_{14}H_{21}N_2Cl_3I_2 \cdot H_2O$ (595.55): C, 28.24; H, 3.89; N, 4.70; Cl + I, 60.5. Found: C, 28.49; H, 4.10.

The infrared spectrum and paper chromatographic behavior were identical with those of 4,5,?-trichloro-2-methyl-2-(2-trimethylammonioethyl)-isoindolinium diiodide prepared by electrochemical reduction[9] of N-(2-dimethylaminoethyl)-3,4,5,6-tetrachlorophthalimide (Ib) and isolated by fractional crystallization after methyl iodide quaternization: m.p. (s. 200) 212–217° dec., R_f 0.24; λ_{max}^{EtOH} 237 mμ (sh., ϵ 16,910), 273 (390), 283 (430), 292 (380).

Anal. Found: C, 28.22; H, 3.80; N, 4.78; Cl + I, 59.4.

***o*-Xylylenediol.**—After a suspension of 6.8 g. (0.18 mole) of lithium aluminum hydride in 400 ml. of ether had been refluxed for one hour, it was chilled in an ice-bath and 16.8 g. (0.113 mole) of phthalic anhydride was added portionwise with stirring. The suspension was refluxed for 18 hours, cooled, decomposed with 25 ml. of 10% aqueous sodium sulfate and filtered. Five washings of the lithium aluminate cake with ether and five with chloroform were combined with the ether solution and evaporated to dryness *in vacuo*. The oily residue crystallized on cooling, and one washing with petroleum ether (30–60°) left 9.6 g. (62%) of white crystals, m.p. 65–67.5°. Nystrom and Brown[7] reported m.p. 64°.

3,4,5,6-Tetrachloro-*o*-xylylenediol.—A suspension of lithium aluminum hydride (6.8 g., 0.18 mole) in 400 ml. of ether was refluxed for 1 hour and tetrachlorophthalic anhydride (32.2 g., 0.113 mole) was added to the cooled suspension portionwise over 30 minutes. The green suspension was refluxed with stirring for 4 hours, allowed to stand over-

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[20] An excellent discussion of many-membered ring compounds is given by V. Prelog in "Perspectives in Organic Chemistry," Edited by A. Todd, Interscience Publishers, Inc., New York, N. Y., 1956, pp. 96–133. In the same book, D. H. R. Barton discusses steric strain (p. 77) and points out that sterically hindered amines are hard to quaternize even with methyl iodide. Accordingly, the diazecine V was recovered unchanged after treatment with methyl iodide in refluxing ethanol, and formed only a monomethiodide in hot dimethylformamide.

[21] H. Stetter [*Chem. Ber.*, **86**, 197 (1953)] has described a dihydrochloride salt of 1,2,3,4,5,6,7,8-octahydro-1,8-benzodiazecine, in which eight of the ten members are tetrasubstituted. The instability resulting from alkylation of V, when only five tetrasubstituted ring members are formed, probably is due to the larger size of the methyl groups compared with hydrogen atoms. It is interesting that the alkaloid folicanthine, for which a 1,6-diazecine structure has been proposed [H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1877 (1957)] also forms only a monomethiodide with methyl iodide [K. Eiter and O. Svierak, *Monatsh.*, **83**, 1453 (1952)]. The methiodide of folicanthine is formed under conditions milder than those necessary for alkylation of V, however, even though the diazecine ring of folicanthine—according to Hodson and Smith—contains *eight* tetrasubstituted ring members. If folicanthine is indeed a 1,6-diazecine system, the depressing effect on alkylation of the additional four hydrogen interactions is apparently more than compensated for by the greater basicity of the nitrogens (Hodson and Smith report pK_a values of approximately 6.2 and 7.6, in 60% ethanol).

[22] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 255.

[23] 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, and ultraviolet absorption spectra were determined on a Beckman DK-1 spectrophotometer. All pK_a values were determined in 80% methyl Cellosolve solutions. Analytical samples were dried at water-pump vacuum over Drierite at 75° for 3–5 hours.

[24] Purified by the method described by L. F. Fieser, "Experiments in Organic Chemistry," 3rd Edition, D. C. Heath and Co., Boston, Mass., 1955, p. 285.

night, chilled in an ice-bath, and decomposed with 25 ml. of 10% aqueous sodium sulfate solution. After being stirred for 1 hour, the suspension was filtered, the lithium aluminate cake was washed 5 times with 100-ml. portions of ether, and the combined ether solution was dried and evaporated. Two crystallizations of the residue from chloroform gave 1.94 g. (6.2%) of 3,4,5,6-tetrachloro-*o*-xylylenediol, m.p. 219–221°, which was soluble in methanol and dioxane, moderately soluble in chloroform and ether, and insoluble in water.

Anal. Calcd. for $C_8H_6O_2Cl_4$ (275.96): C, 34.82; H, 2.19. Found: C, 34.94; H, 2.26.

Further extraction of the lithium aluminate cake with five 100-ml. portions of chloroform afforded only 0.19 g. of additional product, m.p. 220–222°. When the reaction was worked up by dioxane extraction of the lithium aluminate cake, rather than by ether or chloroform extraction, crystallization of the crude product from methanol gave 20% pure (m.p. 220–222°) plus 6.2% slightly impure (m.p. 214–218°) product.

When 3 moles of lithium aluminum hydride was used in combination with dioxane extraction of the lithium aluminate cake, a 36% yield was obtained.

3,4,5,6-Tetrachloro-*o*-xylylene Dibromide (IVb).—The conversion of *o*-xylene to 3,4,5,6-tetrachloro-*o*-xylene has been described previously.[17] In our hands, this reaction gave 51% crude product, m.p. 209–224°, after one crystallization from trichloroethylene, and 44% pure product, m.p. 222–226°, after recrystallization from ethylene dichloride or from chloroform.

3,4,5,6-Tetrachloro-*o*-xylene was brominated in a manner similar to that used previously for 2,3-dimethylnaphthylene.[16e,f] A mixture of 50.0 g. (0.21 mole) of tetrachloro-*o*-xylene, 75.0 g. (0.42 mole) of N-bromosuccinimide, 1.00 g. of benzoyl peroxide and 500 ml. of carbon tetrachloride was refluxed with stirring. One-gram portions of benzoyl peroxide were added after 2, 4 and 23 hours (total benzoyl peroxide used, 4.00 g.). After a total reflux time of 24 hours, the yellow suspension was filtered hot and the tan solid (42 g.) was washed well with carbon tetrachloride. The combined carbon tetrachloride solution and washings was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The 85.9 g. of yellow solid residue was dissolved in 210 ml. of hot acetone, cooled and seeded, giving 56.4 g. (68.6%) of yellow crystals, m.p. 111–115°. Two additional crops of product totaling 8.38 g. (10.2%) and melting between 100 and 110° were obtained by concentrating the mother liquors. Recrystallization of the first crop from acetone gave white crystals, m.p. 116–118°. Ross and Markarian, who prepared IVb by bromination with bromine, reported[17] m.p. 115.5–116.5°.

1,2,3,4,8,9,10,11-Octachloro-5,6,7,12,13,14-hexahydro-6,13-dimethyldibenzo[c,h][1,6]diazecine (V).—A mixture of 4.00 g. (10 millimoles) of 3,4,5,6-tetrachloro-*o*-xylylene dibromide (IVb), 4.00 g. (32 millimoles) of 25% aqueous methylamine and 20 ml. of chloroform was refluxed for 20 hours. Chilling to −5° precipitated 1.20 g. (45%) of white crystals of V, m.p. 282–290° dec. One crystallization from acetone gave an analytical sample, m.p. 291–295° dec., pK_a 3.2, 4.2; molecular weight determination (Rast method), calcd. 541.98; found 585.10 (see below).

Anal. Calcd. for $C_{18}H_{14}N_2Cl_8$ (541.98): C, 39.89; H, 2.60; N, 5.17. Found: C, 39.83; H, 2.50; N, 5.01.

The chloroform layer of the mother liquors was washed with water and evaporated to dryness. The 1.70 g. of sticky yellow residue was slurried with pyridine and filtered, giving an additional 0.20 g. (7%) of V, m.p. (s. 278) 293–295° dec., as a pyridine-insoluble white solid. When the residue from the chloroform mother liquors was extracted with hot acetone and the acetone solution was chilled to −5°, 0.17 g. of crude 4,5,6,7-tetrachloro-2-methylisoindoline (IIc), m.p. 104–139°, separated; further purification afforded 0.01 g. of IIc, m.p. 157–159°, whose infrared spectrum was identical with that of authentic[1] material.

When 2.0 ml. (25 millimoles) of 48% hydrobromic acid was added to the initial reaction mixture (the presence of hydrobromic acid reportedly[16g] increases the yield of isoindoline), only 0.64 g. (24%) of V separated on cooling. Work-up of the mother liquors gave 0.45 g. of crude IIc, m.p. 140–160°; 0.46 g. of crude starting IVb, m.p. 115–117°; and 0.43 g. more crude V, m.p. 255–280° dec.

When a mixture of 2.00 g. (5 millimoles) of 3,4,5,6-tetrachloro-*o*-xylylene dibromide (IVb), 1.11 g. (16.5 millimoles) of methylamine hydrochloride, 2.5 ml. of water and 10 ml. of chloroform was refluxed for 20 hours, 1.89 g. (94.5%) of starting IVb, m.p. 115–117°, was recovered.

Molecular Weight Determination; Picrate Salt.[19]—A suspension of 0.40 g. of the diazecine V and 0.80 g. of picric acid in 15 ml. of methanol was boiled for 10 minutes and filtered hot; the 0.45 g. of insoluble yellow crystals melted 247–253° dec. The yellow solution deposited yellow crystals of monopicrate salt slowly on standing, m.p. 242.5–243.5° dec.

Anal. Calcd. for $C_{24}H_{17}O_7N_5Cl_8$ (771.10): C, 37.38; H, 2.22; N, 9.08. Found: C, 37.69; H, 2.20; N, 9.20.

The ultraviolet absorption intensity at 380 mμ permitted calculation[19] of a found molecular weight of 771.67.

1,2,3,4,8,9,10,11-Octachloro-5,6,7,12,13,14-hexahydro-6,6,13-trimethyldibenzo[c,h][1,6]diazecinium Salts. Bromide Salt (VIa).—A suspension of 3.00 g. of V in 23 ml. of 1:1 methyl bromide–dimethylformamide was refluxed for four hours, and then chilled to −5°. The white solid was collected and washed with acetone, giving 2.85 g. of mixed needles and powder; the mother liquors afforded an additional 0.10 g. of white solid on dilution with acetone. The combined solid was extracted repeatedly with hot methanol, leaving behind 1.22 g. (40.7%) of recovered starting V, m.p. 290–295° dec. The combined and concentrated methanol solutions afforded 1.60 g. (45.4%) of monomethobromide, m.p. 272–274°. One recrystallization from methanol raised the melting point to 278–278.5°; pK_a 3.2, 4.3.[25]

Anal. Calcd. for $C_{19}H_{17}N_2Cl_8Br \cdot H_2O$ (654.96): C, 34.84; H, 2.92; N, 4.28. Found: C, 34.77; H, 2.57; N, 4.45.

The unreacted starting material was refluxed again with methyl bromide–dimethylformamide (1.5 hours), the white solid was collected from the chilled mixture and the bromide salt was extracted with hot methanol. The additional 0.96 g. of VIa, m.p. 277–278°, which separated from the methanol solution raised the over-all two-stage yield of methobromide to 2.56 g. (73%).

When gaseous methyl bromide was bubbled through a refluxing suspension of 2.40 g. of V in 15 ml. of formamide for one hour, and the white solid which separated from the cooled suspension was extracted four times with 100-ml. portions of hot methanol, 1.58 g. (56%) of white crystalline VIa separated from the combined, concentrated methanol extracts. The methanol-insoluble solid, 0.71 g. (29.6%), m.p. 287–295° dec., was recovered V.

Iodide Salt (VIb).—To a suspension of 0.10 g. of V in 5 ml. of dimethylformamide was added a mixture of 5 ml. of methyl iodide and 5 ml. of dimethylformamide in small portions over 1.5 hours on the steam-bath. The yellow solution was chilled at −5°, and the pale yellow crystals were collected and washed with dimethylformamide and hot methanol, giving monomethiodide, m.p. 260–262° dec.

Anal. Calcd. for $C_{19}H_{17}N_2Cl_8I$ (683.93): C, 33.37; H, 2.51; N, 4.10. Found: C, 32.62; H, 2.73; N, 4.77.

Dequaternization of VIa to V.—To a clear solution of 0.20 g. of diazecinium bromide (VIa) in 40 ml. of refluxing methanol was added one small drop (0.02 g.) of 29% ammonia in water; a copious white precipitate formed immediately. An additional 5 drops (0.10 g.) caused no further precipitation. After the solution had been cooled to room temperature, the white solid was collected, washed with methanol, and dried, giving 0.16 g. (94.2%) of diazecine V, m.p. 282–285° dec.; the infrared spectrum of this material was identical with that of authentic V.

7,8,9,10-Tetrachloro-1,2,3,4,5,6-hexahydro-2,2-dimethyl-2.5-benzodiazocinium bromide (VIIIa).—A solution of 5.8 g. (0.067 mole) of 2-dimethylaminoethylamine in 3.8 ml. of 48% aqueous hydrobromic acid was prepared by dropwise addition of the amine to the aqueous acid with swirling and cooling. A solution of 7.60 g. (0.019 mole) of 3,4,5,6-tetrachloro-*o*-xylylene dibromide in 38 ml. of chloroform was added and the pink cloudy mixture was refluxed for 20 hours. Solvent was removed from the resultant two-phase system, and the residue was slurried with 25 ml. of 10%

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[25] Electrometric titration of VIa by addition of standard base gave pK_a 4.3; this conversion of the methobromide salt to the diazacine V was as facile as was the conversion of the hydrobromide salt to V (pK_a of V 3.2, 4.2). Electrometric titration of VIa by addition of excess acid followed by back titration with base indicated pK_a 3.2, 4.3.

aqueous sodium hydroxide. The white solid was collected and washed with water, giving 2.91 g. melting 214–215° dec., R_f 0.39; chilling the mother liquors overnight afforded an additional 3.09 g., m.p. 208–211° dec., bringing the total yield of product to 6.00 g. (77.8%). Crystallization from methanol–ethyl acetate did not raise the melting point of the first crop. It was soluble in water (positive silver nitrate test), methanol, and warm ethanol, but insoluble in other organic solvents; R_f 0.39; pK_a 3.5 (80% methyl Cellosolve). Molecular weight determinations by isothermal distillation suggested that the compound was not dimeric, but the results were not completely satisfactory (therefore, see below).

Anal. Calcd. for $C_{12}H_{15}N_2Cl_4Br$ (409.01): C, 35.24; H, 3.70; N, 6.85. Found: C, 35.11; H, 3.71; N, 7.05.

Reaction of 3,4,5,6-tetrachloro-*o*-xylylene dibromide and 2-dimethylaminoethylamine in dioxane according to the method of Wenner[16f] gave the same product.

Nitrate Salt (VIIIb).—A 1.00-g. sample of VIIIa was refluxed for 30 minutes with 0.50 g. of silver nitrate in 15 ml. of methanol. After removal of silver bromide by filtration, solvent was removed *in vacuo*, and the white solid residue, m.p. 223–225° dec. (no mixed melting point depression of starting bromide), was recrystallized from methanol–ethyl acetate. The white crystalline nitrate salt, m.p. 224–227° dec., R_f 0.38, gave a negative silver nitrate test. The infrared spectrum showed all the bands of the starting material plus those characteristic of ionic nitrate (1350 and 846 cm.$^{-1}$).[22]

Anal. Calcd. for $C_{12}H_{15}O_3N_3Cl_4 \cdot CH_3OH$ (423.15): C, 36.90; H, 4.53; N, 9.93. Found: C, 37.53; H, 4.10; N, 10.09.

Molecular Weight Determination; Picrate Salt.—A solution of 0.40 g. of VIIIa in 4 ml. of methanol was added to a solution of 0.80 g. of picric acid in 8 ml. of methanol. The immediate precipitate of 0.40 g. of yellow solid was removed by filtration (m.p. 140–144°). After standing overnight, the filtrate deposited 0.16 g. of yellow crystals, m.p. 235–236° dec., which proved to be 7,8,9,10-tetrachloro-1,2,3,4,5,6-hexahydro-2,2-dimethyl-2,5-benzodiazocinium dipicrate.

Anal. Calcd. for $C_{24}H_{20}O_{14}N_8Cl_4 \cdot {}^1/{}_2CH_3OH$ (802.34): C, 36.68; H, 2.76; N, 13.97. Found: C, 36.91; H, 3.04; N, 14.30. A spectrophotometric determination of the molecular weight[19] gave 812.94.

7,8,9,10-Tetrachloro-1,2,3,4,5,6-hexahydro-2,2,5-trimethyl-2,5-benzodiazocinium Dibromide (IX).—Gaseous methyl bromide was bubbled for 1 hour through a refluxing solution of 3.00 g. of VIIIa in 24 ml. of 95% ethanol. Solvent was removed *in vacuo* and the yellow oily residue was taken up in 24 ml. of methanol. After the solution had been chilled overnight, the white crystals which had separated were collected and washed with methanol, giving 1.05 g. of IX, m.p. 284–286° dec., R_f 0.41. The infrared spectrum showed absorption in the 2500–2700 cm.$^{-1}$ region, typical of acid salts. The mother liquors contained more IX and a small amount of X, according to paper chromatographic examination.

Anal. Calcd. for $C_{13}H_{18}N_2Cl_4Br_2 \cdot H_2O$ (521.98): C, 29.91; H, 3.86; N, 5.37. Found: C, 29.23; H, 3.82; N, 5.73.

7,8,9,10-Tetrachloro-1,2,3,4,5,6-hexahydro-2,2,5,5-tetramethyl-2,5-benzodiazocinium Dibromide (X).—A solution of 3.09 g. of VIIIa in 31 ml. of 50% methyl bromide in dimethylformamide was warmed on the steam-bath with stirring for 1 hour in the presence of 0.77 g. of sodium acetate. The solution was cooled and 3.30 g. of white solid was collected. Crystallization from methanol gave 2.55 g. (65.2%) of dibromide product, m.p. 226–229° dec., R_f 0.12, whose infrared spectrum was completely different from the isomeric dimethobromide of IIb (m.p. 245–247° dec.).

Anal. Calcd. for $C_{14}H_{20}N_2Cl_4Br_2 \cdot 2H_2O$ (554.02); C, 30.35; H, 4.37; N, 5.06. Found: C, 30.51; H, 4.21; N, 5.23.

Conversion of IX to X.—A suspension of 3.7 g. of IX and 0.77 g. of sodium acetate in 37 ml. of 50% methyl bromide in dimethylformamide was refluxed on the steam-bath for 1 hour. The 3.2 g. of white crystals (R_f 0.17) which separated on cooling was crystallized twice from methanol, giving 1.79 g. of X, m.p. 232–234.5° dec. (yellow-orange melt, foamed).

Anal. Calcd. for $C_{14}H_{20}N_2Cl_4Br_2$ (517.99): C, 32.46; H, 3.89. Found: C, 32.39; H, 4.18.

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[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Structure of the Dialdehyde Formed by Periodate Oxidation of Methyl α-L-Rhamnopyranoside[1,2]

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Infrared, optical rotation and methylation data show that the crystalline monohydrate of the dialdehyde, formed by periodate oxidation of methyl α-L-rhamnopyranoside, possesses a cyclic acetal structure Va or Vb.

In a previous communication[3] it was established that hydrogenation at room temperature in the presence of a palladium–charcoal catalyst of the dialdehyde II from the aldohexopyranosides such as methyl α-D-glucopyranoside (I) effected preferential reduction of the aldehyde group at C_4[4] to give III. This behavior of II was attributed to the presence of a ring which engaged the hydroxyl group at C_6 and the aldehydo function at C_2 as in IIa. It was further noted[3] that if the hydroxyl group at C_6 was blocked by a methyl group or was otherwise suitably modified as in the case of a 6-deoxy sugar glycoside, such as methyl α-L-rhamnopyranoside (IV), the corresponding dialdehyde V resisted reduction under those conditions which transformed II into III. In order to explain this result it was suggested that the dialdehyde exists in the cyclic form Va in which the two aldehydic groups at C_2 and C_4 are mutually involved in cyclic hemiacetal formation through the agency of a molecule of water.

This paper is concerned with further evidence in support of the contention that the so-called "dialdehyde"[5,6] obtained upon periodate oxidation of methyl α-L-rhamnopyranoside (IV) exists in the cyclic form.

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[1] Paper No. 3803, Scientific Journal Series, Minnesota Agricultural Experiment Station, University of Minnesota.

[2] Presented in part at the 129th A.C.S. Meeting, Dallas, Texas, April, 1956.

[3] J. E. Cadotte, G. G. S. Dutton, I. J. Goldstein, B. A. Lewis, F. Smith and J. W. Van Cleve, THIS JOURNAL, **79**, 691 (1957).

[4] Unless stated otherwise the numbering of the carbon atoms corresponds to that of the parent glycoside.

[5] E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

[6] W. D. Maclay, R. M. Hann and C. S. Hudson, *ibid.*, **61**, 1660 (1939).