A sample of I, prepared by ammonolysis of dichloroglyoxime diacetate (m.p. 161–162°),[3] was identical in melting behavior and infrared spectra. It had $\lambda_{\max}^{H_2O}$ 233 mμ (log ε 4.03) and R_f 0.69.

Anal. Calcd. for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.44. Found: C, 20.64, 20.29; H, 5.35, 5.24; N, 46.89.

Oxamidoxime gave blue-green solutions with aqueous nickel salts from which the yellow-orange nickel derivative was precipitated by addition of little dilute ammonia or pyridine.[21] Aqueous I was oxidized by aqueous or alcoholic solutions of *p*-benzoquinone with formation of dark-colored products. The reaction with molar equivalents of *p*-benzoquinone leads to destruction of a small portion of I; the remainder was unchanged. Both nickel salts and quinone solutions were used as spray reagents for the paper chromatography of I.

Oxamidoxime Diacetate (II).—An exothermic reaction occurred when I was added to excess boiling acetic anhydride. The mixture was shaken and allowed to cool. Filtering the colorless solid with suction, washing and drying gave 99% of pure diacetate, m.p. 193–194° dec., remelt 165–167°. Its solubility in pyridine at 25° was 2 g. per 100 ml. From dioxan the diacetate crystallized in colorless leaflets, m.p. 193–194°. The corresponding melting points on the Dennis bar were 229° dec., lit. m.p. 184–187°,[2] 206°,[3] 212°.[3]

Anal. Calcd. for $C_6H_{10}N_4O_4$: C, 35.65; H, 4.98; N, 27.72. Found: C, 35.62, 35.40; H, 5.22, 4.96; N, 27.52, 27.55.

Oxamidoxime Disodium Salt.—Oxamidoxime (0.118 g., 0.001 mole) was only partially soluble in 10 ml. of ethanol containing sodium ethoxide (0.002 mole). It was dissolved by adding water (5 ml.). Evaporation of the solution at 0.3 mm. gave 0.22 g. of solvated salt. The anhydrous salt obtained by heating at 100° proved to be very hygroscopic and was not obtained analytically pure.

Anal. Calcd. for $C_2H_4N_4Na_2O_2$: Na, 28.38. Found: Na, 29.69.

Glyoxime diacetate, prepared by acetylation of glyoxime with acetic anhydride, melted at 120–121°, lit. m.p. 120°,[22] 126°.[23]

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.87; H, 4.68; N, 16.28. Found: C, 42.11; H, 4.96; N, 16.25.

Glyoxime, Disodium Salt.—Glyoxime (0.088 g., 0.001 mole) was dissolved in a solution of sodium (0.0460 g., 0.002 mole) in 10 ml. of ethanol. Evaporation at 0.3 mm. gave 0.11 g. of hygroscopic sodium salt which was analyzed as the hydrate.

Anal. Calcd. for $C_2H_2N_2Na_2O_2 \cdot 1.5H_2O$: C, 15.10; H, 3.16; N, 17.62. Found: C, 14.83; H, 2.61; N, 18.07.

N.m.r. Spectra. All proton n.m.r. spectra were obtained at 56.4 Mc./sec. and 28°. Because of the low solubilities, the most prominent resonances in all cases are those of DMF.

Other solvents, including acetone, water, carbon tetrachloride, dioxane, and pyridine, were tried. In all cases, however, the solubilities were insufficient or the solvent spectrum interfered with that of the oximes. Chemical shifts are given in parts per million. The internal reference substance in this study was tetramethylsilane, the chemical shift of which was taken as 0.00 p.p.m. Relative concentrations of protons were determined by electronic integration techniques. All concentration ratios quoted in the discussion have been rounded to the nearest simple ratio of integral numbers. In all cases the measured values were within ±5% of the reported values.

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[21] L. Tschugaef and J. Surenjanz, *Ber.*, **40**, 181 (1907); M. Kuras, *Mikrochim. Acta*, **32**, 192 (1944); R. Pallaud, *Chim. anal.*, **33**, 239 (1951); further references are found in A. E. C. Research and Development Report ISC-794.

[22] B. Lach, *Ber.*, **17**, 1573 (1884).

[23] A. Hantzsch, *ibid.*, **25**, 708 (1892).

Halogenation of Estrone and Derivatives[1]

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The halogenation of estrone and certain of its analogs has been investigated. Bromination, even with excess bromine, resulted only in substitution of the aromatic ring. Chlorination using sulfuryl chloride, chlorine, or N-chlorosuccinimide gave 10-chlorodien-3-one derivatives with chlorine substitution in rings A and D. Mixtures of different products, separable by chromatography, were obtained in all experiments. While substitution of the 2-position in estrone by halogen or nitro groups precluded chlorination in the 4-position, a similar substitution at carbon 4 did not interfere with the entrance of chlorine into the 2-position.

An observation made in this laboratory[2] that tumor growth in animals was inhibited by certain pentacyclic terpenoid methylene quinones such as pristimerin[3] led us to attempt the preparation of such structures from steroidal estrogens. Oxidation of estrone and similar estrogens with lead tetraacetate resulted in dienone–quinols with a hydroxyl group in the 10-position.[4] However, attempts to convert these substances into $\Delta^{9,10}$-methylene quinones by eliminating the 10-hydroxyl group as water were unsuccessful. Consequently, we decided to study the elimination of hydrogen halide from 10-halogenated estrogens. It was thought that the latter compounds would be formed by a reaction comparable to the action of bromine on *para*-substituted phenols.[5] While such work was in progress in this laboratory, Mukawa[6] reported that isocyanuric chloride converted estradiol 17-acetate (A-III) into 2,4,10β-trichloro-17-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-I) and Mills, *et al.*,[7] obtained a number of 10β-chloro-$\Delta^{1,4}$-estradien-3-one derivatives by the action of N-chlorosuccinimide on aromatic steroids. These authors assigned the beta configuration to the halogen in the 10-position.

We began the present investigation by repeating Woodward's work[8] on the bromination of estradiol (A-II) with N-bromoacetamide. Even with a large excess of the same or other brominating agents only 2,4-dibromoestradiol (A-VI) was isolated by direct crystallization, though a small amount of 2,4-dibromoestrone (A-V) which was not found by Woodward, was separated from the crude reaction product using Girard's reagent. In agreement with Woodward, no dienone formation was observed. Similarly, estrone gave only 4-bromoestrone (A-IV) and 2,4-dibromoestrone (A-V), depending upon the amount of bro-

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[1] Supported by Grant No. 4550 from the U. S. Public Health Service, National Cancer Institute, Institutional Grant No. EIN-56 from the American Cancer Society and a grant from the Massachusetts Division of the American Cancer Society.

[2] E. Schwenk, to be published in *Arzneimittel-Forsch*, **12**, 1143 (1962).

[3] R. Harada, H. Kakisawa, S. Kobayashi, M. Musya, K. Nakanishi, and Y. Takahashi, *Tetrahedron Letters*, **17**, 603 (1962).

[4] A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958).

[5] D. Auwers and R. Rapp, *Ann.*, **302**, 153 (1898); *Zincke Th. Ber.*, **28**, 3125 (1895).

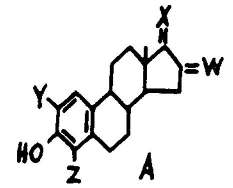
[6] F. Mukawa, *Tetrahedron Letters*, **14**, 17 (1959).

[7] J. S. Mills, T. Barrera, E. Olivares, and H. Garcia, *J. Am. Chem. Soc.*, **82**, 5882 (1960).

[8] R. B. Woodward, *ibid.*, **62**, 1625 (1940).

minating agent used, while estradiol 17-acetate (A-III) gave 2,4-dibromoestradiol 17-acetate (A-VII). We did not find any of the 16-bromo compound reported by Inhoffen[9] to be formed by the bromination of estrone acetate.

Our search for a useful halogenating agent was successful with the finding that either sulfuryl chloride in large excess or a solution of chlorine in chloroform converted both estrone and estradiol 17-acetate into dienone derivatives in good yield. The reaction took a similar course with estrone or estradiol using N-chlorsuccinimide but not with N-chloroacetamide as the chlorinating agent.



I. X = O; Y = Z = H; W = H_2

II. X = $\left\langle\begin{matrix}\mathrm{OH}\\ \mathrm{H}\end{matrix}\right.$; Y = Z = H; W = H_2

III. X = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{OCOCH_3}\end{matrix}\right.$; Y = Z = H; W = H_2

IV. X = O; Y = H; Z = Br; W = H_2

V. X = O; Y = Z = Br; W = H_2

VI. X = $\left\langle\begin{matrix}\mathrm{OH}\\ \mathrm{H}\end{matrix}\right.$; Y = Z = Br; W = H_2

VII. X = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{OCOCH_3}\end{matrix}\right.$; Y = Z = Br; W = H_2

VIII. X = O; Y = Cl; Z = H; W = H_2

IX. X = O; Y = H; Z = Cl; W = H_2

X. X = O; Y = Z = Cl; W = H_2

XI. X = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{OCOCH_3}\end{matrix}\right.$; Y = H; Z = Cl; W = H_2

XII. X = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{OCOCH_3}\end{matrix}\right.$; Y = Z = Cl; W = H_2

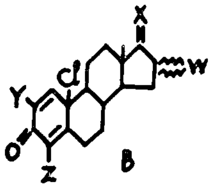
XIII. X = O; Y = NO_2; Z = H; W = H_2

XIV. X = O; Y = H; Z = NO_2; W = H_2

XV. X = O; Y = NH_2; Z = H; W = H_2

XVI. X = O; Y = Cl; Z = NH_2; W = H_2

XVII. X = O; Y = Z = Cl; W = Cl_2



I. X = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{OCOCH_3}\end{matrix}\right.$; Y = Z = Cl; W = H_2

II. X = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{OCOCH_3}\end{matrix}\right.$; Y = Z = Br; W = H_2

III. X = O; Y = Z = Cl; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

IV. X = O; Y = Z = Cl; W = Cl_2

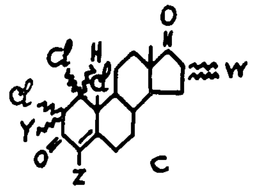
V. X = O; Y = Cl; Z = H; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

VI. X = O; Y = Z = Br; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

VII. X = O; Y = Cl; Z = NO_2; W = Cl_2

VIII. X = O; Y = Cl; Z = NO_2; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

IX. X = O; Y = H; Z = NO_2; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$



I. Y = H; Z = H; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

II. Y = H; Z = Cl; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

III. Y = NO_2; Z = H; W = Cl_2

IV. Y = NO_2; Z = H; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

V. Y = Cl; Z = NO_2; W = $\left\langle\begin{matrix}\mathrm{H}\\ \mathrm{Cl}\end{matrix}\right.$

An amount of chlorinating agent slightly in excess of one mole gave resins whose infrared spectra suggested the presence of a dienone structure. In the case of estrone, chromatography of the crude reaction mixture gave only 4-chloroestrone (A-IX). Repeated recrystallization of a similar chlorination product from estradiol 17-acetate gave 4-chloro-estradiol 17-acetate (A-XI) as the sole crystalline product. This substance was identified by alkaline hydrolysis and subsequent oxidation to 4-chloroestrone, an authentic sample of which was obtained by demethylation of 4-chloroestrone methyl ether.[10] For comparison, 2-chloroestrone was also prepared similarly.

Mukawa[6] also isolated A-XI but did not establish the position of the chlorine atom. The 17-acetoxy-10β-chloro-$\Delta^{1,4}$-estradien-3-one from which he obtained this substance could not be found in our reaction products.

When estradiol 17-acetate was treated with 3.6 moles of chlorine in chloroform solution or with a large excess of sulfuryl chloride which also served as the solvent, the principal reaction product was found to be 2,4,10β-trichloro-17-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-I). Contrary to Mukawa's[6] observation, reduction of this compound with zinc dust and acetic acid gave 2,4-dichloroestradiol 17-acetate (A-XII), in good yield. Similar chlorination experiments with estradiol gave intractable resins.

A more complicated course of reaction was observed in the chlorination of estrone, which when allowed to react with a large excess of sulfuryl chloride for four hours gave a product readily isolated in solid form. Its infrared spectrum showed a split band in the carbonyl region suggesting the presence of a mixture of compounds of dienone character. Several components could be isolated by chromatography on silica gel. One of these was shown by analysis to be a tetrachloroenone with an absorption at 247 mμ in the ultraviolet and was reduced by zinc and acetic aicd to give estrone. Another chlorination product isolated was a pentachloroenone which absorbed in the ultraviolet at 266 mμ and upon reduction gave 4-chloroestrone, identified

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[9] H. H. Inhoffen (to Schering A.G.), German Patent 720015; *Chem. Abstr.*, **37**, 2520 (1943).

[10] H. J. Thomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959).

by comparison with an authentic sample. These findings suggest that in both substances four chlorine atoms are in positions which allow reductive elimination with nascent hydrogen. Of these, two are accounted for by chlorine atoms in 10β- and 16ξ-positions. In the infrared spectrum the band of the 17-keto group was indeed displaced to 1753 and 1754 cm.$^{-1}$, respectively, under the influence of the 16-chloro atom. The n.m.r. spectrum of the tetrachloro compound displayed a peak at τ 4.008 (C=CH in 4), and peaks at τ 5.150 and 5.500 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 1 and in 16). In the n.m.r. spectrum of the pentachloro compound there was no indication of a proton on the 4-position but only peaks at τ 5.178 and 5.520 representing $\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in the 1- and 16-positions were found. The two chlorine atoms which were readily eliminated by reduction must necessarily be *ortho* to each other. As indicated by the n.m.r. spectra they can be only in positions 1 and 2 but not in 4 and 5 of ring . This assumption is supported by the fact that after reduction of the pentachloro product, the remaining fifth chlorine atom was found to be in the 4-position where a double bond protects it from reductive elimination. Accordingly, the substances are considered to be 1ξ,2ξ,10β,16ξ-tetrachloro-Δ^4-estrene-3,17-dione (C-I), giving estrone with zinc and acetic acid, and 1ξ,2ξ,4,10β,16ξ-pentachloro-Δ^4-estrene-3,17-dione (C-II), which was reduced to 4-chloroestrone. When chlorination of estrone was extended to twenty hours, chromatography of the crude reaction product on silica gel gave three well defined substances. The first two eluted from the column were a tetrachloro- and a pentachlorodienone. Their properties and their analytical composition characterized them as different from C-I and C-II. Their infrared spectra particularly were significantly different, showing 17-keto bands at 1760 and 1771 cm.$^{-1}$, respectively. This suggests that in the pentachloro compound the 17-keto group is vicinal to two chlorine atoms at carbon 16. In C-I and C-II the 17-keto band usually found around 1740 cm.$^{-1}$ was shifted by 14 units to 1753 and 1754 cm.$^{-1}$ by the presence of one *ortho* chlorine atom. In the new pentachloro compound another shift of 17 units is superimposed on this by the second chlorine atom at C-16.[11] Unfortunately the amount of substance was too small to permit reduction of the new pentachloro derivative with zinc and acetic acid. The substance is tentatively formulated as 2,4,10β,16,16′-pentachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IV). The principal reaction product, a tetrachloro compound, and the third substance which analysis showed to be a trichlorodienedione, were identical with the products obtained from the chlorination of 2,4-dichloroestrone and 2-chloroestrone, respectively, using excess sulfuryl chloride as described below. From these latter two reactions we were able to isolate as the main products, 2,4,10β,16ξ-tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) and 2,10β,16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V) so cleanly that recrystallization without chromatography sufficed to obtain them in pure form.

These formulations are supported by the n.m.r. spectra. The tetrachloro compound showed peaks at τ 2.667 (C=CH in 1), 5.550 and 5.617 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), 8.958 ($\mathrm{CH_3}$ in 18), while the trichloro compound had τ 3.825 (C=CH in 4), 5.542 and 5.625 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), and 8.958 ($\mathrm{CH_3}$ in 18).

For further confirmation, the crude reaction product resulting from treatment of estrone with excess sulfuryl chloride was reduced directly with zinc and acetic acid and the product chromatographed. 2,4-Dichloroestrone, 4-chloroestrone, and estrone were isolated. These must be derived from B-III and B-IV, and from C-I and C-II, respectively. Surprisingly, both 2,4-dichloro- and 4-chloroestrone were converted to the same tetrachloro compound (B-III), by excess sulfuryl chloride, while 2-chloroestrone gave exclusively 2,10β,-16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V).

Although no 2-chloroestrone was found by chromatography, the isolation of 2,10β,16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V), in the foregoing experiment suggested that it might also have been formed as an intermediate, and it was thought that dilution of the reactants would favor such a reaction. When estrone at a dilution of 0.2% in chloroform was treated with excess sulfuryl chloride, a resin was formed whose infrared spectrum showed dienone character. Chromatography on silica gel gave only one crystalline substance which was a chlorinated phenol and was not identical with any of the chlorinated estrones described above. It was also different from 16α-chloroestrone.[12,13] Analysis showed the new compound to be a tetrachloroestrone. The infrared spectrum had a 17-keto band at 1760 cm.$^{-1}$, which together with a band at 800 cm.$^{-1}$, characteristic for $>\mathrm{C}{<}^{\mathrm{Cl}}_{\mathrm{Cl'}}$, suggests that the compound is 2,4,16,16′-tetrachloroestrone. The resinous fractions, when reduced with zinc and acetic acid, gave only 4-chloroestrone and estrone by chromatography. No 2-chloroestrone was found.

Chlorination of estrone with 4.8 moles of chlorine in chloroform or with 4 moles of N-chlorosuccinimide gave results similar to those obtained from the sulfuryl chloride reaction.

The chlorination reactions take a simpler course when the 2,4-dibromo derivatives of estrone (A-V), or of estradiol acetate (A-VII), are submitted to the action of excess sulfuryl chloride.

We obtained 90% yields of 2,4-dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI), and 2,4-dibromo - 10β - chloro - 17 - acetoxy - $\Delta^{1,4}$ - estradien-3-one (B-II), respectively. Upon reduction with zinc and acetic acid both reverted to the starting materials.

A very complex course of the reaction was observed in the treatment of 2-nitro- or 4-nitroestrone with excess sulfuryl chloride, while 2,4-dinitroestrone did not react even when boiled with this agent. From 2-nitroestrone, two substances were obtained by chromatography of the crude reaction product on silica. The principal product was tetrachlorinated together with

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(11) Compare: N Tosho and J. Fishman, *J. Org. Chem.*, **26**, 4569 (1961).

(12) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958).

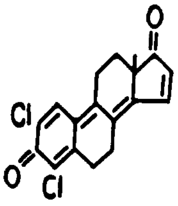
(13) The authors are grateful to Dr. G. P. Mueller of G. D. Searle & Co. for a sample of this compound.

a lesser amount of a pentachloro compound. When either the crude reaction mixture or the tetrachloroderivative was reduced with zinc and acetic acid, only the chlorine-free 2-aminoestrone was isolated. All chlorine atoms in the two compounds must therefore be in positions from which they are easily eliminated by nascent hydrogen. The infrared spectrum of the pentachloro substance showed the 17-keto band at 1773 cm.$^{-1}$ suggesting substitution with two chlorine atoms at the 16-position. In the tetrachloro compound this band was found at 1759 cm.$^{-1}$ corresponding to one chlorine atom at carbon 16. The placement of the 3-keto bands at 1706 and 1692 cm.$^{-1}$, respectively, attests to *ortho* substitution of this group by a chlorine atom and the nitro group. The elimination of the remaining two chlorine atoms by reduction requires them to be at carbons 1 and 2 or at 4 and 5. The n.m.r. spectra were found to answer this question, showing peaks at τ 4.016 and 4.008 for a proton in the 4-position and τ 4.858 and 4.870 for a $\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ grouping at carbon 1. Accordingly, the two substances are formulated as 2-nitro,1ξ,2ξ,10β,16ξ-tetrachloro-Δ^4-estrene-3,17-dione (C-IV) and 2-nitro,1ξ,2ξ,10β,16,16′-pentachloro-Δ^4-estrene-3,17-dione (C-III).

Chromatography of the crude product formed from 4-nitroestrone with excess sulfuryl chloride gave four compounds not all of which could be identified completely because of the small yields of purified material. The first substance off the column showed an analysis nearly that of a pentachloro nitroderivative. Its infrared spectrum had the 17-keto band at 1754 cm.$^{-1}$ with the 3-keto band at the unusually high value of 1711 cm.$^{-1}$. The n.m.r. spectrum located one chlorine atom as $\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ at carbon 16 (τ 5.550) and another at carbon 1 (τ 5.250). The high absorption for the 3-keto group in the infrared suggests a substitution of two chlorine atoms at carbon 2. In all probability the substance is 1ξ,2,2′,10β,16ξ-pentachloro-4-nitro-Δ^4-estrene-3,17-dione (C-V). The second substance gave the analysis of a tetrachloro compound. It showed the 17-keto band of the infrared at 1770 cm.$^{-1}$, corresponding to a 16,16′-dichloro compound, while the 3-keto band at 1692 cm.$^{-1}$ indicated the substitution of a chlorine atom at carbon 2. The substance is formulated as 2,10β,16,16′-tetrachloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VII). The third compound was a trichloro derivative with the infrared spectrum showing keto bands at 1759 cm.$^{-1}$ (17-keto, 16-chloro) and 1692 cm.$^{-1}$ (3-keto, $\Delta^{1,4}$-2-chloro-4-nitro). The n.m.r. spectrum with τ 2.667 (C=CH in 1) and τ 5.567 and 5.633 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16) indicates an agreement between the two spectra with the formulation as 2,10β,16ξ-trichloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VIII). The last substance to be eluted from the column was a dichloro derivative whose n.m.r. spectrum showed only one chlorine atom as $\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16. It is formulated as 10β,16ξ-dichloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IX).

Upon reduction with zinc and acetic acid of the crude chlorination product of 4-nitroestrone or of the crude trichloro fraction separated from the column, a chloroamino estrone was isolated which gave an orange diazo oxide upon diazotization. Reduction with hypophosphorous acid produced 2-chloroestrone, which was identified by comparison with the same substance prepared from 2-aminoestrone methyl ether. The chlorine atom must, therefore, be in the 2-position. Accordingly, the compound is formulated as 2-chloro-4-aminoestrone, in agreement with its analysis, thus supporting the formulation of the products derived from the chlorination of 4-nitroestrone.

Some preliminary attempts[14] were made to eliminate hydrogen chloride from some of the compounds described, but only treatment with dimethylformamide and lithium chloride[7] gave a new compound. Thus from 2,4-dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI) a deep blue substance was produced which gave red solutions in organic solvents. Analysis suggested the presence of five or six double bonds and showed that the bromine atoms had been exchanged for chlorine atoms. A similar reaction was observed only recently by Diassi, *et al.*[15] The analysis allows a preliminary formulation of the substance as 2,4-dichloro - $\Delta^{1,4,8(14),9(10),15}$ - estrapentaene - 3,17 - dione (D) or 2,4 - dichloro - $\Delta^{1,4,6,8(14),9(10),15}$-estrahexaene-3,17-dione (E). Dehydrohalogenation of B-I in the same manner afforded an orange substance which was not obtained in pure form.



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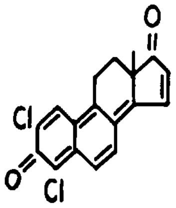

E

It is interesting to consider the difference between our experiment and the course of the dehydrohalogenation carried out by Mills, *et al.*[7] Their starting material had no substitution in the 2- and 4-positions and the newly formed 9(10) double bond shifted to 9(11) while the molecule reverted to its initial aromatic structure. In our case, 2,4-substitution seems to stabilize the 9(10) double bond, which then together with that at 15(16) may cause dehydrogenation at 8(14) and possibly also at 6(7). The deep color of the compound, unprecedented for a steroid derivative, is in agreement with such a conjugated double bond system. A similar accumulation of double bonds was suggested by Roberts[16] for purpurogenone, a deep red methylenequinone.

Our experiments show that bromination of the phenolic steroids is a straightforward process. In agreement with Zincke's assumption[5] that in *p*-cresol bromine first substitutes the positions *ortho* to the hydroxyl before *para* substitution takes place, we find that bromine substitutes in estrone only one or both *ortho* positions, while even excess bromine does not attack the position *para* to the hydroxy group, possibly because

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[14] The senior author has retired from active laboratory work and the dehydrohalogenation experiments which must be considered as preliminary will not be continued by him.

[15] P. Diassi, J. Fried, M. Palmere, and E. F. Sabo, *J. Am. Chem. Soc.*, **83**, 4249 (1961).

[16] J. C. Roberts, Antibiotics and Mold Metabolites, Symposium, Special Publications No. 5 of the Chemical Society, London, 1956, p. 36 ff.

of steric hindrance. The action of chlorinating reagents on extrone (A-I) and estradiol acetate (A-III) is much more complex. With only about one mole of chlorine substitution apparently occurs mainly in the 10β-position with concomitant conversion of the aromatic ring to a quinolic system, possibly through a carbanion as suggested by Mills, *et al.*[7] Such 10β-monochlorodien-3-ones could not be isolated in our work, but were obtained by Mukawa[6] and by Mills, *et al.*[7] They may rearrange to the 4-chloro derivative thus reverting to the aromatic structure. Aromatic substitution on carbon 2 also occurs, although only to a small degree. Excess chlorinating reagents, however, give largely 2,4-dichloro substitution with A-I and exclusively so with A-III. The formation of tetra- and pentachloro compounds C-I and C-II from A-I is difficult to understand. It is possible that in this case 4-monochloro- and 2,4-dichlorodienone derivatives are the first reaction products and that subsequently the Δ^1-double bond (but surprisingly not Δ^4) is saturated by the addition of chlorine in a manner similar to that observed by Kirk, *et al.*,[17] in the case of Δ^4-cholesten-3-one.

It is interesting to consider that in the aromatic steroids studied, halogenation prefers the 4- over the 2-position, while in the case of estrone, nitration affords nearly equal yields of 2- and 4-nitro estrone. The Mannich reaction, however, as Patton[18] has shown, substitutes in the 2-position exclusively, with no further reaction in position-4 even with a large excess of reagents. Similarly, in the present work, 2-chloro- or 2-nitroestrone react with an excess of sulfuryl chloride to give only 10β,16ξ-dichloro derivatives without substitution in the 4-position, while 4-chloro- and 4-nitroestrone are both substituted by chlorine at the 2-carbon atom.

Experimental[19]

4-Bromoestrone (A-IV).—Estrone (540 mg.) was dissolved in 50 ml. of absolute ethanol and 300 mg. of N-bromoacetamide added. After standing overnight the reaction mixture was diluted with water and the product was filtered and washed with water. Recrystallization from chloroform–methanol gave 400 mg. of material, m.p. 281–283°. Repeated recrystallization from the same solvents gave an analytical sample with melting point unchanged, $[\alpha]^{23}\mathrm{D}$ +147° (*c* 0.7), $\lambda_{\max}$ 231 (319), 282 (2234), 299 (2340); $\nu_{\max}$ 3452 (arom, OH), 2980, 2916 (C—H), 1739 (17-keto), 1598, 1480, (arom. C=C), 812 (1,2,3,4 arom. subst.), 792 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{21}O_2Br$: C, 61.90; H, 6.06; Br, 22.88. Found: C, 61.90; H, 6.06; Br, 23.07.

Methylation of this compound with methyl iodide gave 4-bromoestrone-3-methyl ether, m.p. 289°, with infrared identical to that of authentic material.[20]

2,4-Dibromoestrone (A-V) and 2,4-Dibromoestradiol (A-VI) from the Bromination of Estradiol (A-II).—The crude product (2.65 g. m.p. 212–215°) obtained according to Woodward[8] and 2 g. of Girard's reagent T were dissolved in 50 ml. of absolute ethanol containing 10% acetic acid and refluxed for 45 min. The reaction mixture was diluted with water and thoroughly extracted with ether. The extracts were then repeatedly washed with water and the combined water layers acidified with hydrochloric acid and again extracted with ether. After drying with magnesium sulfate and evaporation of the ether, the semicrystalline residue was recrystallized from methanol and gave 125 mg. (3%) of white crystals, m.p. 235–237°. Repeated crystallization from the same solvent gave an analytical sample of 2,4-dibromoestrone, A-V, m.p. 235–237°, $[\alpha]^{23}\mathrm{D}$ +63° (*c* 0.5); $\lambda_{\max}$ 230 (4070), 285 (2900), 293 (3206); $\nu_{\max}$ 3332 (arom. OH), 2987, 2911 (C—H), 1731 (17-keto), 1551, 1486 (arom. C=C), 873 (1,2,3,4,5 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2Br_2$: C, 50.49; H, 4.71; Br, 37.33. Found: C, 50.63; H, 4.64; Br, 37.33.

The original ether extract from the Girard reagent separation was dried over sodium carbonate, evaporated, and recrystallized from methanol to give 2.34 g. of the known 2,4-dibromoestradiol, A-VII, m.p. 214–215°. 2,4-Dibromoestrone was also obtained from estrone using N-bromoacetamide in ethanol or with bromine in acetic acid or in chloroform. Reduction of 2,4-dibromoestrone with sodium borohydride in methanol gave 2,4-dibromoestradiol (A-VI).

2,4-Dibromoestradiol 17β-Acetate (A-VII) by Acetylation of A-VI.—2,4-Dibromoestradiol (500 mg.) was dissolved in 25 ml. of glacial acetic acid and refluxed for 4 hr. after which the acetic acid was distilled under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with water, potassium bicarbonate, and water. After drying the ethyl acetate solution over magnesium sulfate and distillation of the solvent, the product was recrystallized from methanol and weighed 320 mg. (62%), m.p. 185–187°. The analytical sample was obtained from methanol–chloroform, $[\alpha]^{23}\mathrm{D}$ +30.5° (*c* 1.7); $\lambda_{\max}$ 292 (3250), 285 (2500); $\nu_{\max}$ 3437 (arom. OH), 2932, 2867 (C—H), 1733 (acetate C=O), 1467 (CH_2), 1247 (acetate CO stretch), 880 (1,2,3,4,5 arom. subst.), cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_3Br_2$: C, 50.87; H, 5.12; Br, 33.84. Found: C, 51.14; H, 5.07; Br, 35.02.

The same 2,4-dibromoestradiol 17-acetate was obtained from the bromination of estradiol 17-acetate with bromine in chloroform solution.

Anal. Calcd. for $C_{20}H_{24}O_3Br_2$: C, 50.87; H, 5.12; Br, 33.84. Found: C, 50.84; H, 5.39; Br, 33.78.

4-Chloroestradiol 17β-Acetate (A-XI).—A solution of 942 mg. of estradiol 17β-acetate (A-III) in 15 ml. of chloroform was agitated magnetically while 445 mg. (1.1 moles) of sulfuryl chloride in chloroform was added dropwise. After 2 hr. the reaction mixture was washed with 10% potassium bicarbonate solution and with water, dried over magnesium sulfate, and evaporated under reduced pressure. The infrared spectrum of the partly crystalline residue showed the disappearance of the hydroxyl band and the development of a band at 1666 cm.$^{-1}$ characteristic of a 1,4-dien-3-one system of about the same intensity as the acetate carbonyl. However, repeated crystallization from chloroform–methanol afforded 250 mg. (24%) of white crystals, m.p. 254–254.5°, $[\alpha]^{24}\mathrm{D}$ +31.3° (*c* 2.4), $\nu_{\max}$ 3525 (arom. OH), 3025 (C—C), 2950 (C—H), 1720 (acetate C=O), 1617, 1579, 1502 (arom. C=C), 1445 (CH_2) 1278 (acetate CO stretch) 801 (1,2,3,4 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{25}O_3Cl$: C, 68.86; H, 7.22; Cl, 10.16. Found: C, 68.27; H, 7.11; Cl, 10.29.

That this material was 4-chloroestradiol 17β-acetate (A-XI) was shown by correlating it with 4-chloroestrone, as described in the following section. Chromatography of another batch on a silica column again gave the aromatic 4-chloro derivative, A–XI, as the only crystallized product.

4-Chloroestrone (A-IX) from A-XI.—The chlorination was repeated and the isolated material was dried by azeotropic distillation with benzene. The product (yield 93%) had an infrared spectrum identical with that of the substance obtained in the first experiment. A 348-mg. portion was refluxed overnight in 50 ml. of a 4% solution of ethanolic sodium hydroxide containing 5 ml. of water. The solvent was distilled under reduced pressure until precipitation started, and the slurry was then poured into water, filtered, and washed on the filter with water. The infrared spectrum showed the disappearance of the characteristic acetate bands and the appearance of a second hydroxyl band. The crude product was oxidized directly by dissolving it in 100 ml. of reagent grade acetone and adding 2 ml. of an aqueous 8 *N* chromium trioxide solution. After stirring for 30 min. the solvent was partially removed under reduced pressure at 25° and the product precipitated with water. Recrystallization from chloroform gave

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(17) D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 627, 1184 (1956).

(18) T. L. Patton, *J. Org. Chem.*, **25**, 2148 (1960); *ibid.*, **26**, 1677 (1961).

(19) All melting points were observed on a Fischer hot stage and are uncorrected. Rotations were determined in chloroform solution. All ultraviolet spectra were made in methanol solution using a Cary Model 11 spectrophotometer. The infrared spectra for the chromatograms were taken with potassium bromide planchets on a Perkin–Elmer Infracord spectrophotometer, while the final infrared spectra were obtained with potassium bromide planchets on a Beckman infrared instrument. N.m.r. spectra were obtained with a Varian Associates HR60 spectrophotometer.

(20) Kindly supplied by Dr. J. P. Horwitz, Detroit Institute of Cancer Research, Detroit, Mich.

195 mg. (54%), m.p. 272–274°. Mixed melting point and infrared spectrum showed the substance to be identical to authentic 4-chloroestrone.

4-Chloroestrone (A-IX) from 4-Chloroestrone-3-methyl Ether.—A 900-mg. sample of the latter compound, prepared according to Thomson, *et al.*,[10] was dissolved in 2.5 ml. of glacial acetic acid, and 2.5 ml. of 48% aqueous hydrobromic acid was added. After refluxing for 2 hr. the reaction mixture was poured into water, extracted with chloroform, washed with potassium bicarbonate and water, and dried over sodium sulfate. The solvent was removed under reduced pressure. Chromatography of the tarry residue gave only oils which could not be induced to crystallize. The combined fractions were sublimed at 240° and 150–200-μ pressure. The white sublimate was recrystallized from chloroform and afforded 340 mg. (40%) of material, m.p. 273–275°, $[\alpha]^{23}\mathrm{D}$ +112° (*c* 1.0) $\lambda_{\max}$ 285 (2470), $\nu_{\max}$ 3444 (arom. OH), 2961, 2896 (C—H), 1737 (17-keto), 1598, 1484 (C═C), 1373 (—CH_3), 821 (1,2,3,4 arom. subst.).

Anal. Calcd. for $C_{18}H_{21}O_2Cl$: C, 70.93; H, 6.94; Cl, 11.63. Found: C, 70.31; H, 6.85; Cl, 11.80.

2-Chloroestrone (A-VIII) from 2-Chloroestrone Methyl Ether.[10]—The conditions of this experiment were the same as those described for the preparation of the 4-chloro isomer. After crystallization from chloroform–methanol there was obtained a small yield of a white substance, m.p. 223–224.5°, $[\alpha]^{23}\mathrm{D}$ +162° (*c* 0.12) $\lambda_{\max}$ 227 (6100), 285 (1967), 294 (1706); $\nu_{\max}$ 3369 (arom. OH), 2957, 2888 (C—H), 1738 (17-keto), 1611, 1496 (C═C), 1378 (—CH_3), 1208 (C—O stretch phenol), 886 (1,2,4,5 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{21}O_2Cl$: C, 70.93; H, 6.94; Cl, 11.63. Found: C, 70.67; H, 6.92; Cl, 11.63.

2-Chloroestrone (A-VIII) from 4-Nitroestrone (A-XIV).—A somewhat better yield was obtained when 3 g. of 4-nitroestrone was chlorinated with 30 ml. of sulfuryl chloride and worked up as described in a later section of this paper. The crude material was dissolved in 30 ml. of warm acetic acid and 1.5 g. of zinc dust was added over a 1.5-hr. period. The reaction mixture was filtered and the zinc residue washed with acetic acid. The washes were combined with the filtrate, chloroform was added, and the mixture was neutralized with bicarbonate solution and finally washed with water. The solvent layer was dried with sodium sulfate and distilled to a crude residue which was dissolved in 480 ml. of water containing 6 ml. of sulfuric acid and filtered. The cooled filtrate was diazotized with 650 mg. of sodium nitrite. An orange diazo oxide precipitated which was filtered and washed with water. It was then suspended in 60 ml. of 50% hypophosphorous acid, stirred for 2 days at room temperature, and finally heated for 0.5 hr. The insoluble material was filtered, dried, and sublimed *in vacuo*. Finally, it was recrystallized several times from chloroform–methanol to give 320 mg. of 2-chloroestrone identical in melting point and infrared spectrum with that described above.

2,4-10β-Trichloro-17β-acetoxy-Δ^{1,4}-estradien-3-one (B-I).—Estradiol 17β-acetate (A-II) (3 g.) was suspended in 15 ml. of sulfuryl chloride. After 2 min. solution was complete and the reaction mixture was poured into water and stirred to decompose the sulfuryl chloride. The resultant slurry was extracted with chloroform and washed with 10% potassium bicarbonate solution and with water. After drying over sodium carbonate the chloroform was evaporated under reduced pressure to a small volume. Further evaporation at atmospheric pressure with concomitant addition of methanol afforded 2.63 g. (64%) of product. An analytical sample was prepared by repeated crystallization from chloroform–methanol, m.p. 201–202°, $[\alpha]^{23}\mathrm{D}$ +10.8° (*c* 4.2), $\lambda_{\max}$ 260 mμ (16,000) $\nu_{\max}$ 2982, 2885 (C—H), 1731 (acetate C═O), 1690 (3-keto), 1605 (C═C), 1248 (acetate), 895 cm.$^{-1}$. N.m.r.: τ 2.658 (C═CH in 1), 5.358, 5.475 (17α-H), 7.917 (CH_3 in acetyl), 9.050 (CH_3 in 18).

Anal. Calcd. for $C_{20}H_{23}O_3Cl_3$: C, 57.50; H, 5.55; Cl, 25.46. Found: C, 57.87; H, 5.77; Cl, 25.23.

Reaction of estradiol 17β-acetate in chloroform with 3.3 moles of chlorine in a 2% chloroform solution gave again B-I in excellent yield.

Anal. Calcd. for $C_{20}H_{23}O_3Cl_3$: C, 57.50; H, 5.85; Cl, 25.46. Found: C, 57.00; H, 5.46; Cl, 26.08.

2,4-Dichloroestradiol 17β-Acetate (A-XII) by Reduction of B-I.—A solution of 100 mg. of B-I in 10 ml. of acetic acid was refluxed for 10 min. with 250 mg. of zinc dust, after which an additional 250 mg. of zinc dust was added and reflux continued for 15 min. The clear solution was decanted into ice–water and the zinc residue washed with acetic acid by decantation and finally with acetone. The washes were combined and added to the ice–water. The precipitate was collected by filtration and washed with water. Two recrystallizations from acetone–water gave 63 mg. of 2,4-dichloroestradiol-17β-acetate, m.p. 199–200°, $[\alpha]^{25}\mathrm{D}$ +40° (*c* 0.75), $\lambda_{\max}$ 230 (10280), 284 (2730), 290 (2636), $\nu_{\max}$ 3434 (arom. OH), 1730 (acetate C═O), 1566 (C═C arom.), 1379 (C—CH_3), 1269 (acetate CO stretch), 1190 (phenol CO stretch), 869 (1,2,3,4,5 arom. subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_3Cl_2$: C, 62.67; H, 6.31; Cl, 18.50. Found: C, 62.56; H, 6.30; Cl, 18.18.

1ξ,2ξ,10β,16ξ-Tetrachloro-Δ^4-estrene-3,17-dione (C-I) and 1ξ,2ξ,4,10β,16ξ-Pentachloro-Δ^4-estrene-3,17-dione (C-II) by Reaction of A-I with Excess Sulfuryl Chloride, First Experiment.—Estrone (2 g.) was magnetically agitated with 10 ml. of sulfuryl chloride. Aliquots were removed periodically and after 4 hr. the infrared spectra showed no further change. The reaction mixture was then poured into water, agitated until the sulfuryl chloride had decomposed, and the solid material was washed on the filter with 10% potassium bicarbonate solution and with water. The infrared spectrum showed a split band in the carbonyl region. Since crystallization failed to separate the components the material was chromatographed on a silica gel column. Elution with benzene in small portions gave 30 semicrystalline fractions ranging in ultraviolet absorption from 266 to 259 mμ. The column was then stripped with ethyl acetate and the material thus obtained crystallized to give 370 mg. of C–I. Several recrystallizations from chloroform–methanol afforded an analytical sample, m.p. 243–245° dec., $[\alpha]^{25}\mathrm{D}$ +141° (*c* 0.92), $\lambda_{\max}$ 247 mμ (13500), $\nu_{\max}$ 2961, 2875 (C—H), 1754 (17-keto, 16-chloro), 1695 (3-keto, 2-chloro-Δ^4), 894 cm.$^{-1}$. N.m.r.: τ 4.008 (C═CH in 4), 5.150 and 5.500 ($\mathrm{C}\langle^{\mathrm{H}}_{\mathrm{Cl}}$ in 1 and 16), 8.967 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{20}O_2Cl_4$: C, 52.71; H, 4.92; Cl, 34.57. Found: C, 52.23; H, 4.70; Cl, 34.72.

The fractions with ultraviolet absorption above 258 mμ were combined (930 mg.) and rechromatographed on silica gel. Elution with 3:1 benzene–hexane gave 200 mg. of material which absorbed in the ultraviolet between 266 and 264 mμ. Subsequent eluates ranged down to 248 mμ. The first fractions were combined and recrystallized several times to give 84 mg. of C-II, m.p. 217–219° dec., $\lambda_{\max}$ 266 mμ (10,700), $\nu_{\max}$ 2955, 2870 (C—H), 1753 (17-keto, 16-chloro), 1706 (3-keto, 2-chloro, Δ^4), 1582 (C═C), 928 cm.$^{-1}$. N.m.r.: τ 5.178 ($\mathrm{C}\langle^{\mathrm{H}}_{\mathrm{Cl}}$ in 1), 5.520 ($\mathrm{C}\langle^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), 8.986 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}O_2Cl_5$: C, 48.63; H, 4.31; Cl, 39.87. Found: C, 49.30; H, 4.59; Cl, 39.41.

Zinc–Acetic Acid Reduction of C-I.—Following the procedure described for reduction of B-I, 100 mg. of C-I gave 68 mg. of estrone which after two recrystallizations had a m.p. of 257–259°. Mixed melting point and infrared spectra were identical with that of authentic estrone.

Zinc–Acetic Acid Reduction of C-II.—Following the above procedure, 30 mg. of C-II gave 11 mg. of 4-chloroestrone as shown by mixed melting point and infrared spectra.

2,4,10β,16,16′-Pentachloro-Δ^{1,4}-estradiene-3,17-dione (B-IV) from A-I with Excess Sulfuryl Chloride, Second Experiment.—Estrone (2 g.) was dissolved in 15 ml. of sulfuryl chloride and left overnight for 20 hr. at room temperature in darkness in a flask protected from moisture by a calcium chloride tube. The solution was poured into ice and water and stirred until all sulfuryl chloride had decomposed. The reaction product, a white powder, was filtered, washed with water, and ground with 10% potassium bicarbonate solution in a mortar, again filtered, washed neutral with water, and then dried over phosphorus pentoxide *in vacuo;* yield, 3.3 g. This material was dissolved in benzene and chromatographed on 150 g. of silica. Four fractions were taken: one each of 1.8 g. and 0.32 g. with benzene, one of 0.64 g. with benzene–ether (9:1), and 0.14 g. with ether. Each fraction was dissolved in benzene–hexane (50:50) and again put on a silica column but elution was started with benzene–hexane (50:50) and continued with mixtures containing 70, 72.5, 75, and 100% benzene. Finally, benzene–ether mixtures containing 2.5, 5, and 10% ether were used. Using infrared spectra as a guide, corresponding fractions were combined and recrystallized from benzene–hexane mixtures. Three main fractions were obtained in this way which gave good analyses though the yields were very small for in some cases ten recrystallizations were necessary. The compound from fraction I is formulated as 2,4,10β,16,16′-pentachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IV), m.p. 197–198°, $[\alpha]^{24}\text{D}$ +47° (*c* 1.48), λ_{max} 258 (16720), ν_{max} 2961, 2887 (C—H), 1771, (17-keto,16,16′-dichloro), 1687 (3-keto, $\Delta^{1,4}$-2,4-dichloro), 1592 (C═C), 1452 (CH_2) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{17}O_2Cl_5$: C, 48.85; H, 3.87; Cl, 40.05. Found: C, 48.88; H, 3.96; Cl, 39.68.

The product from fraction II had an infrared spectrum and properties identical with that of the later described 2,4,10β,16ξ-tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) as confirmed by analysis. The n.m.r. spectrum supports this formulation, with peaks at τ 2.700 (C═CH in 1), 5.520 ($C\begin{smallmatrix}H\\Cl\end{smallmatrix}$ in 16).

Anal. Calcd. for $C_{18}H_{18}O_2Cl_4$: C, 52.97; H, 4.45; Cl, 34.74. Found: C, 52.70; 53.11; H, 4.92; 4.51; Cl, 34.58, 34.37.

Fraction III material showed an infrared spectrum and properties identical with that of the later described 2,10β,16ξ-trichloro-$\Delta^{1,4}$-estradiene-3,17-dione, as confirmed by analysis.

Anal. Calcd. for $C_{18}H_{19}O_2Cl_3$: C, 57.85; H, 5.12; Cl, 28.46. Found: C, 57.97, 57.72; H, 4.86, 5.13; Cl, 29.09.

In the above experiment in which the reaction was extended for 20 hr., the tetra- and pentachloro compounds, C-I and C-II, isolated in the first experiment (4 hr.), could not be found. However when the experiment was repeated and again worked up after only 4.5 hr., C-I and C-II were identified as well as B-III and B-IV.

4-Chloroestrone (A-IX) and 2,4-Dichloroestrone (A-X) from Estrone.—Estrone (1.5 g.) was dissolved in 7.5 ml. of sulfuryl chloride left for 20 hr. in the dark and the reaction mixture was treated as described above. After drying of the product over phosphorus pentoxide *in vacuo*, the yield was 1.45 g. The substance was dissolved in 50 ml. of acetic acid and reduced by refluxing with 20 g. of zinc dust, added in portions during 1 hr. After another hour of refluxing, the solution was decanted into ice and water and the residue was extracted with small amounts of acetic acid and of acetone which were added to the ice–water mixture. The precipitate was filtered and washed with water. After drying over phosphorus pentoxide, there was obtained 1.3 g. of a buff-colored powder. This was dissolved in benzene and adsorbed on a column of 150 g. of silica gel prepared with benzene. Elution with 10% chloroform in benzene gave a crystalline material A (425 mg.) which was followed by another crystalline substance B (490 mg.) when the chloroform in the eluent was raised to 20%. Finally, a third crystalline compound C (160 mg.) was obtained using the same concentration of chloroform. Each of the three substances was three times recrystallized from benzene–hexane and then from acetone–water. Compound A was 2,4-dichloroestrone, m.p. 212–213°, $[\alpha]^{25}\text{D}$ +129° (*c* 0.73) λ_{max} 284 (2933), 292 (3000), ν_{max} 3335 (arom. OH), 2961, 2906 (C—H), 1730 (17-keto), 1557, 1473 (arom. C═C), 872 (arom. 1,2,3,4,5 subst.) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2Cl_2$: C, 63.73; H, 5.94; Cl, 20.90. Found: C, 63.98; H, 6.07; Cl, 20.70.

Compound B was identical in all its properties with 4-monochloroestrone, A-IX.

Anal. Calcd. for $C_{18}H_{21}O_2Cl$: C, 70.93; H, 6.94; Cl, 11.63. Found: C, 70.81; H, 7.03; Cl, 11.71.

The third substance, C, was unchanged estrone.

2,10β,16ξ-Trichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-V) from 2-Chloroestrone (A-VIII).—2-Chloroestrone (200 mg.) was dissolved in 5 ml. of sulfuryl chloride and after standing 6 hr. at room temperature, poured with stirring into ice and water. The solid material was filtered, washed with water, ground with sodium bicarbonate solution and again filtered and washed thoroughly with water. Drying over phosphorus pentoxide *in vacuo* gave 180 mg. (73%). After three crystallizations from benzene–pentane the substance melted at 203°, $[\alpha]^{25}\text{D}$ +22.7 (*c* 0.74), λ_{max} 252 mμ (13,250) ν_{max} 2966, 2896 (C—H), 1762 (17-keto-16-chloro), 1675 (3-keto-$\Delta^{1,4}$-2-chloro) cm.$^{-1}$. N.m.r.: τ 3.825 (C═CH in 4), 5.542 and 5.625 ($C\begin{smallmatrix}H\\Cl\end{smallmatrix}$ in 16), 8.958 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}O_2Cl_3$: C, 57.85; H, 5.12; Cl, 28.46. Found: C, 57.88; H, 5.38; Cl, 28.71.

2,4,10β,16ξ-Tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) from 2,4-Dichloroestrone (A-X).—A 100-mg. sample of 2,4-dichloroestrone was dissolved in 5 ml. of sulfuryl chloride and left in the dark for 6 hr. The reaction mixture was decomposed with ice and water under stirring and the white powder which resulted was filtered, washed with water, and then treated as before with 10% potassium bicarbonate solution, and water. It was dried over phosphorus pentoxide *in vacuo* and recrystallized from benzene–hexane. Three crystallizations gave needles, m.p. 189–191°, $[\alpha]^{25}\text{D}$ +50 (*c* 0.62), λ_{max} 258 mμ (13,400), ν_{max} 2961, 2886 (C—H), 1760 (17-keto, 16-chloro), 1688 (3-keto-$\Delta^{1,4}$-2,4-dichloro) cm.$^{-1}$ N.m.r.: τ 2.667 (C═CH in 1), 5.550 and 5.617 ($C\begin{smallmatrix}H\\Cl\end{smallmatrix}$ in 16), 8.985 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}O_2Cl_4$: C, 52.97; H, 4.45; Cl, 34.74. Found: C, 52.77, 52.92; H, 4.64, 4.67; Cl, 34.64, 34.40.

2,4,10β,16ξ-Tetrachloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-III) from 4-Chloroestrone (A-IX).—4-Chloroestrone (200 mg.) was dissolved in 2 ml. of sulfuryl chloride and after 6 hr. in the dark, the reaction mixture was worked up as in the preceding experiment. Several recrystallizations from benzene–hexane gave analytical material with analysis, properties, and infrared spectrum identical with those of B-III in the foregoing experiment.

Anal. Calcd. for $C_{18}H_{18}O_2Cl_4$: C, 52.97; H, 4.45; Cl, 34.74. Found: C, 52.92; H, 4.65; Cl, 34.70.

2,4,16,16′-Tetrachloroestrone (A-XVII).—One gram of estrone was dissolved in 400 ml. of chloroform and a solution of 5 g. of sulfuryl chloride in 100 ml. of chloroform was added with stirring. The solution, which evolved gas, was held at room temperature for 20 hr. and then washed with water, 10% potassium bicarbonate solution, and again with water, and dried with anhydrous sodium sulfate. After evaporation of the solvent a resin was obtained whose infrared spectrum showed dienone character. Elution with benzene from a column of silica gel gave a crystalline substance which after four recrystallizations from benzene–hexane was obtained in glass-like colorless plates. They became opaque at 100°, softened at 178°, and melted at 180–182°, $[\alpha]^{25}\text{D}$ +142° (*c* 1.0), λ_{max} 230 inflection (8562), 283 (2362), 292 (2509), ν_{max} 3494 (phenol-OH), 3095, 3046, (arom. CH), 1766 (17-keto, 16,16′-dichloro), 1590 1574, (arom. C═C) and 1170 (phenol C—O) cm.$^{-1}$. The compound is formulated as 2,4,16,16′-tetrachloroestrone.

Anal. Calcd. for $C_{18}H_{19}O_2Cl_4$: C, 52.84; H, 4.68; Cl, 34.66. Found: C, 52.97; H, 4.52; Cl, 34.85.

All eluates from the column were combined and reduced with zinc and acetic acid. The material which was isolated was chromatographed on a silica gel column and eluted with benzene and increasing amounts of chloroform. Only 4-chloroestrone could be obtained in crystalline form.

2,4-Dibromo-10β-chloro-17β-acetoxy-$\Delta^{1,4}$-estradien-3-one (B-II).—2,4-Dibromoestradiol 17β-acetate (1 g.) was suspended in 2 ml. of sulfuryl chloride and dissolved completely after 30 min. The reaction mixture was poured into water and agitated magnetically to decompose the excess sulfuryl chloride. The slurry was then extracted with methylene chloride and the extract was washed successively with water, 10% potassium bicarbonate solution, and water. After drying over magnesium sulfate the solvent was removed under reduced pressure and the product was crystallized twice from methylene chloride–methanol, to give 930 mg. (87%) of white crystals, m.p. 195–197°. Repeated crystallization gave an analytical sample, m.p. 197–198°, $[\alpha]^{23}\text{D}$ +9.1° (*c* 4.4) λ_{max} 271 (16,900), ν_{max} 2942, 2877 (C—H), 1730 (acetate C═O), 1678 (3-keto, $\Delta^{1,4}$, 2,4-dibromo), 1596 (C═C), 1373 (C—CH_3), 1243 (acetate CO stretch) cm.$^{-1}$. N.m.r.: τ 2.425 (C═CH in 1), 5.400, 5.517 (17α-H), 7.950 (CH_3 in acetyl) 9.092 (CH_3 in 18).

Anal. Calcd. for $C_{20}H_{23}O_3ClBr_2$: C, 47.41; H, 4.58; Cl, 7.00; Br, 31.54. Found: C, 47.56; H, 4.56; Cl, 7.08; Br, 31.93.

Reduction of B-II.—To a solution of 100 mg. of B-II in 5 ml. of warm glacial acetic acid was added 400 mg. of zinc dust. The reaction was terminated after 20 min., and the reaction mixture was worked up as before. The residual pale yellow oil solidified and after two recrystallizations from chloroform–methanol gave 51 mg. (57%) of material with mixed melting point and infrared spectrum identical with authentic 2,4-dibromoestradiol 17β-acetate.

2,4-Dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI) from 2,4-Dibromoestrone (A-V) with Sulfuryl Chloride.—A slurry of 1.3 g. of 2,4-dibromoestrone in 10 ml. of sulfuryl chloride was allowed to stand at room temperature. After 4.5 hr. solution was complete and the reaction mixture was poured into water and stirred until the sulfuryl chloride had decomposed. The solid was filtered and ground in a mortar with bicarbonate solution. After filtration, the product was thoroughly washed with water and dried *in vacuo* over phosphorus pentoxide. The yield was 1.6 g. (92%). The analytical sample prepared by recrystallization from benzene–hexane melted at 197–198° dec. $[\alpha]^{23}\mathrm{D}$ +19° (*c* 0.05), λ_{max} 271 (17,000) ν_{max} 1760 (17-keto, 16 chloro), 1678 (3-keto, $\Delta^{1,4}$,2,4-dibromo) 1590, 1451, 1386, 1205, 1030, 990, 931, 885, 853, 726, 691 cm.$^{-1}$. N.m.r.: τ 2.408 (C=CH in 1), 5.533 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), 8.958 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}O_2Cl_2Br_2$: C, 43.49; H, 3.65; Cl, 14.26; Br, 32.15. Found: C, 44.22; H, 3.88; Cl, 14.55; Br, 32.79.

2,4-Dibromo-10β,16ξ-dichloro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VI) from 2,4-Dibromoestrone with Chlorine.—A slurry of 800 mg. of dibromoestrone in 10 ml. of chloroform was treated with 13.5 ml. of 2.1% chlorine solution in chloroform and left in the dark for 4 hr. The final solution was diluted with ether and washed successively with water, potassium bicarbonate, and water. After drying with sodium sulfate, the solvent was removed under reduced pressure. The yellow residue was triturated with ether and after recrystallization from benzene–hexane gave white crystals identical with B-VI, prepared in the previous experiment.

Anal. Calcd. for $C_{18}H_{18}O_2Cl_2Br_2$: C, 43.49; H, 3.65; Cl, 14.26; Br, 32.15. Found: C, 43.40; H, 3.64; Cl, 14.30; Br, 32.24.

Reduction of B-VI with zinc dust and acetic acid gave 2,4-dibromoestrone identical with authentic material.

1ξ,2ξ,10β,16,16′-Pentachloro-2-nitro-Δ^4-estrene-3,17-dione (C-III) and 1ξ,2ξ,10β,16ξ-Tetrachloro-2-nitro-Δ^4-estrene-3,17-dione (C-IV) by Chlorination of 2-Nitroestrone A-XIII.—To a 2-g. portion of 2-nitroestrone was added 15 ml. of sulfuryl chloride and the yellow solution which soon formed was left at room temperature in the dark for 20 hr. It was decomposed with ice and water under vigorous stirring until the reaction product became solid. This was filtered, ground in a mortar with 10% potassium bicarbonate solution and then with water. After drying over phosphorus pentoxide *in vacuo* 2.5 g. of a yellowish powder resulted which was put on a silica column prepared with benzene–hexane (1:1). Using infrared spectra as a guide the column was eluted with increasing benzene concentrations in the benzene–hexane mixture and then with benzene–ether mixtures. The latter gave oily material but two crystalline fractions resulted with benzene–hexane (1:1 and 5:1) and with benzene alone. They were both repeatedly recrystallized from benzene–hexane. The less polar substance gave slightly yellowish white needles, m.p. 182–184° dec., $[\alpha]^{28}\mathrm{D}$ +120° (*c* 0.78), λ_{max} 241 (8766), 243 (9640), 252 (11,101); ν_{max} 3123, 3073 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$), 3031 (=CH), 1773 (17-keto, 16,16′-dichloro), 1706 (3-keto-2-nitro-2-chloro-Δ^4), 1630, (C=C), 1574 (C—NO_2), 800 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$), 681 (C—$Cl_2$) cm.$^{-1}$. N.m.r.: τ 4.008, (C=CH in 4), 4.70 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 1), 8.825 (C—CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}NO_4Cl_5$: C, 44.16; H, 3.71; N, 2.86; Cl, 36.20. Found: C, 44.56; H, 3.99; N, 2.70; Cl, 36.43.

This substance may be formulated as 1ξ,2ξ,10β,16,16′-pentachloro-2-nitro-Δ^4-estrene-3,17-dione (C-III).

The more polar substance also formed slightly yellowish needles, m.p. 186–187°, $[\alpha]^{25}\mathrm{D}$ +127° (*c* 0.97), λ_{max} 242 (24,444), 253 (27,777); ν_{max} 3082 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$), 1759 (17-keto,16-chloro), 1692 (3-keto, 2-nitro, 2-chloro, Δ^4), 1612 (C=C), 1548 (C—NO_2) cm.$^{-1}$. N.m.r.: τ 4.016 (C=CH in 4), 4.858 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 1), 5.586 and 5.653 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), 9.000 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}NO_4Cl_4$: C, 47.50; H, 4.21; N, 3.08; Cl, 31.16. Found: C, 47.10, 47.68; H, 4.02, 4.10; N, 3.02, 3.24; Cl, 31.53, 30.98.

The structure of this substance is 1ξ,2ξ,10β,16ξ-tetrachloro-2-nitro-Δ^4-estrene-3,17-dione (C-IV).

2-Aminoestrone (A-XV) by Reduction of the Chlorination Product of 2-Nitroestrone (A-XIII).—Reduction of the crude chlorination product or of the isolated tetrachloro compound with zinc and acetic acid was carried out on the water bath and the acetic acid solution was decanted after 0.5 hr. from any unused zinc. It was diluted with water, neutralized with bicarbonate, and extracted with chloroform. The residue left after evaporation of the solvent was taken up in a solution of oxalic acid, which after filtration from resinous material was neutralized with potassium bicarbonate solution. Thereupon the amino compound precipitated as a white crystalline powder which was filtered, washed, and then dried over phosphorus pentoxide *in vacuo*. The substance gave a negative Beilstein reaction and its infrared spectrum was identical with that of a sample prepared by reduction of 2-nitroestrone.[10] Both samples showed no melting point, but decomposed over 280°. The analytical sample was recrystallized from acetone–water.

Anal. Calcd. for $C_{18}H_{23}NO_2{}^1/_2H_2O$: C, 73.44; H, 8.22; N, 4.76. Found: C, 74.07, 73.95; H, 7.99, 8.23; N, 4.35, 4.55.

Chlorination of 4-Nitroestrone (A-XIV) with Sulfuryl Chloride.—Two experiments with 1 g. and 1.6 g. of 4-nitroestrone were carried out. The nitro steroid was suspended in 10 and 16 ml. sulfuryl chloride, respectively, and left in the dark for 20 hr., during which time both experiments formed a yellow solution. This was decomposed with ice and water and worked up as before. There was obtained 1.2 and 2.1 g. of a buff powder. It was chromatographed on silica columns with benzene in the first and benzene–hexane (1:1) in the second experiment. Elution was made in the second case with increasing benzene concentrations while only benzene was used in the first experiment. Separation of the fractions was controlled by changes in the infrared spectra.

Corresponding fractions were combined. They contained oily material which was eliminated by trituration with ether before recrystallization. The first experiment gave three fractions weighing 430, 210, and 340 mg. and the second gave four fractions weighing 330, 430, 620, and 450 mg. All fractions were recrystallized repeatedly from benzene–hexane and benzene–pentane mixtures. Dark brown material remained on the column and the crude fractions when not immediately recrystallized slowly became yellow and oily.

1ξ,2,2′,10β,16ξ-Pentachloro-4-nitro-Δ^4-estrene-3,17-dione (C-V).—White needles, m.p. 217–218°, $[\alpha]^{25}\mathrm{D}$ +139° (*c* 0.59), λ_{max} 264 (13,000) ν_{max} 2956, 2886 (C—H), 1754 (17-keto, 16-chloro), 1711 (3-keto, 2,2′-dichloro, Δ^4-4-nitro), 1632, 1581 (C=C), 1550 (C—NO_2), 1449 (CH_2), 1379 (C—CH_3) cm.$^{-1}$. N.m.r.: τ 5.250 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 1), 5.550 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), 8.986 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}NO_4Cl_5+{}^1/_2C_6H_6$: C, 47.70; H, 4.00; N, 2.65; Cl, 33.54. Found: C, 48.72; H, 4.07; N, 2.47, 2.95; Cl, 33.95, 32.23.

2,10β,16,16′-Tetrachloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VIII).—White needles, m.p. 206–208°, ν_{max} 3082 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$), 2966, 2885 (C—H), 1770 (17-keto, 16,16′-dichloro), 1692 (3-keto, $\Delta^{1,4}$-2-chloro-4-nitro), 1611 (C=C), 1547 (C—NO_2), 801 (C=Cl_2) cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{19}NO_4Cl_3$ + $1/2C_6H_6$: C, 51.14; H, 4.29; N, 2.83; Cl, 28.75. Found: C, 51.84; H, 4.33; N, 2.68; Cl, 28.33.

2,10β,16ξ-Trichloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-VIII).—White needles, m.p. 208° dec., $[\alpha]^{25}\mathrm{D}$ +14° (*c* 0.87), λ_{max} 242 (9035), 254 (10,619), ν_{max} 3082 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$), 2956, 2911 (C—H), 1759 (17-keto, 16-chloro), 1692 (3-keto, $\Delta^{1,4}$-2-chloro-4-nitro), 1612 (C=C), 1548 (C—NO_2) cm.$^{-1}$. N.m.r.: τ 2.667 (C=CH in 1), 5.56, 5.633 ($\mathrm{C}{<}^{\mathrm{H}}_{\mathrm{Cl}}$ in 16), 8.958 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{18}NO_4Cl_3$: C, 51.65; H, 4.33; N, 3.35; Cl, 25.40. Found: C, 51.51; H, 3.88; N, 3.30; Cl, 26.80.

10β,16ξ-Dichloro-4-nitro-$\Delta^{1,4}$-estradiene-3,17-dione (B-IX).—Square plates, m.p. 192–195°, $[\alpha]^{21}\mathrm{D}$ +47° (*c* 0.46), λ_{max} 242 (14,600), ν_{max} 2996, 2911 (C—H), 1765 (17-keto, 16-chloro), 1690 (3-keto, $\Delta^{1,4}$-4-nitro), 1621 (C=C), 1547 (C—NO_2) cm.$^{-1}$.

N.m.r.: τ 2.750, 2.938 (C═CH in 1), 3.645, 3.825 (C═CH in 2), 5.608 ($C\langle^{H}_{Cl}$ in 16), 8.996 (CH_3 in 18).

Anal. Calcd. for $C_{18}H_{19}O_4NCl_2$: C, 56.28; H, 4.98; N, 3.64; Cl, 18.46. Found: C, 56.12; H, 4.90; H, 3.59; Cl, 18.54.

2-Chloro-4-aminoestrone (A-XVI).—The residue from the second benzene eluate (150 mg.) in the foregoing experiment was dissolved on the water bath in 7 ml. of acetic acid and 1 g. of zinc dust was added in small portions over a 0.5-hr. period. After further heating for 0.5 hr. under stirring, the solution was decanted and the zinc residue was washed with a small amount of acetic acid and with acetone. The combined solution and washes were neutralized with potassium bicarbonate solution and extracted with chloroform. After washing with water the solvent was distilled *in vacuo* and the brown oily residue was dissolved in water containing 200 mg. of oxalic acid. The hot solution was filtered and neutralized with 10% potassium bicarbonate solution. A white crystalline precipitate was obtained, which was filtered, washed well with water, and then dried *in vacuo* over phosphorus pentoxide. Several recrystallizations were necessary from benzene–hexane to obtain pure material, m.p. 218–222°. In a similar experiment, elimination of the amino group by diazotization gave 2-chloroestrone as reported above. This substance, therefore, must be 2-chloro-4-aminoestrone as confirmed by analysis.

Anal. Calcd. for $C_{18}H_{22}NO_2Cl + {}^1/_2C_6H_6$: C, 70.26; H, 7.02; N, 3.92; Cl, 9.87. Found: C, 70.48; H, 7.41; N, 4.42; Cl, 9.23.

Dehydrogenation of 2,4-Dibromo-10β,16ξ-dichloro-$\Delta^{1,5}$-estradiene-3,17-dione (B-VI).—To 1 g. of B-VI in 20 ml. dimethylformamide was added 2 g. of lithium chloride and the solution was refluxed for 5.5 hr. It soon became red and finally, dark purple. It was poured into ice and water, to which 2 g. of potassium acetate had been added. The blue precipitate was filtered and washed well with water, then dissolved in methanol, and again precipitated as before. This procedure was repeated twice with methanol and three times with acetone as solvent. The last mother liquor was almost colorless. After washing well with water the deep blue powder was dried over phosphorus pentoxide *in vacuo*. It was easily soluble with a deep red color in the usual organic solvents from which it was precipitated by the addition of either pentane or hexane. No way of crystallizing the substance could be found; yield 100 mg., m.p. 116–118°, λ_{max} 224 (27,276), 236 (12,727), 258 (14,090), ν_{max} 3445 (H_2O), 2961 (C—H), 1751 (17-keto, Δ^{15}), 1702 (3-keto-$\Delta^{1,4}$-2,4-dichloro), 1620 (C═C) cm.$^{-1}$. N.m.r.: τ 3.875, 4.675 (C═CH in 1 and 6?), 6.108, 7.116, 7.645, 8.811, 8.953 (CH_3 in 18), 9.253.

Anal. Calcd. for $C_{18}H_{12}O_2Cl_2 + {}^1/_2C_3H_6O + H_2O$: C, 61.91; H, 4.53; Cl, 18.75; for $C_{18}H_{14}O_2Cl_2 + {}^1/_2C_3H_6O + H_2O$: C, 61.53; H, 5.03; Cl, 18.63. Found: C, 61.17; H, 4.88; Cl, 18.59.

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The Autoxidation of Nonvicinal Glycols Ester Formation *via* Cyclic Ethers and Their Peroxides

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Nonvicinal glycols can be readily autoxidized to the keto alcohols; they give high peroxide yields comparable to those obtainable from simpler secondary alcohols when the carbinol groups are separated by more than four carbon atoms. In the case of the 2,5-hexane- and 2,6-heptanediols, the formation of keto alcohols is accompanied by a significant production of 2-acetoxybutanes and -pentanes. The origins of these esters have been traced to a peroxide-consuming reaction sequence proceeding from cyclic hemiketal through tetrahydrofuran or pyran peroxides to the final ester cleavage products. This sequence is supported by syntheses and degradation studies of some cyclic ether peroxides. By analogy with 2,5-dimethylhexane, 2,5-hexanediol might have been expected to be autoxidized by intramolecular peroxy radical attack to the diketone, this reaction occurs to only a minor extent, if at all.

The autoxidation of simple secondary alcohols produces ketones and peroxide as major products and hydrocarbons with two equivalent tertiary hydrogens such as 2,4-dimethylpentane undergo intramolecular oxidation of the order of 90+% to yield principally the 2,4-dihydroperoxide. In contrast, 2,4-pentanediol[1] shows neither high peroxide yields nor evidence of intramolecular oxidation. It was concluded in the latter case that the reactivity of the intermediate peroxy radical was attenuated by internal hydrogen bonding and that the oxidation involved a considerably modified reaction chain.

The effect of interposing additional methylenes between the carbinol groups has now been studied by autoxidizing 2,5-, 2,6-, 2,7-, and 2,8-dihydroxyalkanes. Although Milas, Peeler, and Mageli[2] did not report ring opening by carbon–carbon bond cleavage in their studies of the vapor phase pyrolyses of tetrahydropyran hydroperoxide and *t*-butyl tetrahydropyran peroxide in glass wool packed tubes, such cleavages are postulated here to explain aliphatic ester formation from diols. Accordingly, certain tetrahydrofuran and -pyran peroxides have been synthesized and thermally degraded.

Experimental

Materials.—Unless otherwise noted heart cuts from fractionation through a Piros-Glover spinning band column were used.

2,5-Hexanediol was prepared by hydrogenation of 2,5-hexanedione in isopropyl alcohol over nickel. The yield of product with b.p. 88°/1 mm. and $n^{20}D$ 1.4470–1.4473 was about 90%.

2-Methyl-2,5-hexanediol was prepared from γ-valerolactone and methyl magnesium bromide; b.p. 107°/4 mm., $n^{19.7}D$ 1.4500. On standing, this material solidified, m.p. 36–37°.

Anal. Calcd. for $C_6H_{14}O_2$: C, 63.6; H, 12.2. Found: C, 63.5; H, 12.2.

5-Methyl-5-hydroxyhexan-2-one was prepared by oxidation of the glycol with chromic anhydride; b.p. 72–73°/13 mm., $n^{20}D$ 1.4361; 2,4-dinitrophenylhydrazone, m.p. 106–107°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.5; H, 10.8. Found: C, 64.3; H, 10.8.

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