Toxic Chlorinated Methanoisobenzofuran Derivatives

E. D. Weil, J. G. Colson (1), P. E. Hoch, and R. H. Gruber

Central Research Department, Hooker Chemical Corporation

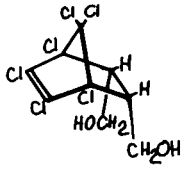
Upon treatment with alcoholic base, 1,4,5,6,7,7-hexachloro-5-norbornene-*endo-cis*-2,3-dimethanol (I) yields a tricyclic ether (III) which is converted by sulfuric acid to two epimeric 4,6,7,8,8-pentachloro-octahydro-4,7-methanoisobenzofuran-5-ones (III A & B). These relatively non-toxic isomers, upon introduction of two chlorine atoms α and α' to the ether oxygen, yield two epimeric products of high toxicity to insects and mammals. These 1,3,4,6,7,8,8-heptachloro-octahydro-4,7-methanoisobenzofuran-5-ones (IV A & B) upon transannular dehydrochlorination yield a toxic tetracyclic ketone (VI A). Reduction of this ketone by lithium aluminum hydride affords an alcohol (VII) of similarly high insecticidal toxicity. Nuclear magnetic resonance and infrared spectra are presented as evidence for the indicated structures. Results of this study are interpreted as indicative of the regions of the molecule which are critical in regard to toxicity.

In the course of a study of transannular nucleophilic reactions in substituted hexachloronorbornenes, 1,4,5,6,7,7-hexachloro-5-norbornene-*endo-cis*-2,3,-dimethanol (I) was found to undergo ring closure upon treatment with an alkoxide in alcoholic medium to form a cyclic ketal (II) (2).

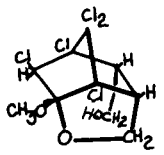
Cleavage of II with sulfuric acid opens the originally formed tetrahydrofuran ring with reclosure to a new tetrahydrofuran ring forming two isomeric ketones (IIIA and IIIB) of the empirical formula, $C_9H_7Cl_5O_2$.

Both IIIA and IIIB, which were found to be substantially non-toxic, could be chlorinated by substitution, yielding two isomeric heptachloro ketones (IVA and IVB) having a high degree of insecticidal and mammalian toxicity (Table I). These isomers were interconvertible.

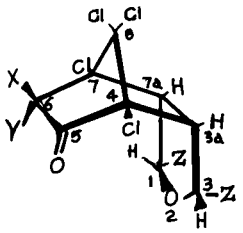
Chlorination of IVA in acetonitrile yielded a single highly insecticidal octachloroketone (V) which was dichlorinated on Carbon-6 as shown by nuclear magnetic resonance (nmr) evidence. The isomer IVB was resistant to chlorination in acetonitrile and evidently did not equilibrate fast enough under the experimental conditions to permit the chlorination to proceed *via* IVA. This observed difference in chlorination rate is understandable on the basis of the assigned configurations of C-6 in IVA and IVB (see below).



I



II



IIIA: X = H, Y = Cl, Z = H
IIIB: X = Cl, Y = H, Z = H
IVA: X = H, Y = Cl, Z = Cl
IVB: X = Cl, Y = H, Z = Cl
V: X = Y = Cl Z = Cl

The structures of IIIA, IIIB, IVA, IVB and V were established on the basis of elemental analyses, infrared and nmr evidence (Table II). None of these compounds showed infrared bands characteristic of hydroxyl groups or carbon-carbon double bonds, but each showed strong C-O stretching bands. Each of these compounds exhibited a carbonyl stretching band at 1797 cm^{-1} which is close to the position (1786 cm^{-1}) reported for the carbonyl stretching band of 1,2,3,4,7,7-hexachlorobicyclo[2,2,1]-hept-2-en-5-one (3).

The likelihood that IIIA and IIIB differ only in their configuration at C-6 was shown by the epimerization of IIIB to IIIA by brief exposure to sodium methoxide followed by acidification. Analogous epimerizations are known in the 3-halonorbornanone series, but since equilibria involving approximately equal amount of *exo* and *endo*-halo epimers have been reported (4), we could not assign the configuration of IIIA and IIIB by analogy based on the observed direction of epimerization. However the configuration at C-6 was established by comparison of the

TABLE I

Insecticidal and Mammalian Toxicity Data (a)

90% Lethal Concentration (ppm)

Compound	Houseflies (24 hour test)	Acute oral LD (Rat) (mg./kg)^{50}
IIIA, IIIB	10,000 (as mixture)	3160
IVA	0.5	7(b)
IVB	0.5	7(b)
V	2	3(c)
VIA	0.25	1
VII	7-8	not measured
VIII	10,000	not measured
IX	10,000	not measured
X	0.5	4.8-5.5 (d)

(a) Insecticidal activity determined by Mr. Alvaro Goenaga, Boyce Thompson Institute for Plant Research, Yonkers, N.Y. (b) Determined at Wisconsin Alumni Research Foundation, Madison, Wisconsin, on male adult albino rats of the Sprague-Dawley Strain (range finding procedure employing 2 animals at each of five dosage levels; single dose administered by stomach). (c) As (b) but determined at Hazleton Laboratories, Inc., Falls Church, Va. (d) From technical data bulletin on Telodrin published by Shell International Chemical Company.

nmr spectra of these four compounds.

The nmr spectrum of IIIA shows its furthest downfield proton at δ 5.25 and this shows a small splitting (J = 1.3 Hz), whereas IIIB has its furthest downfield peak at δ 4.88 and is unsplit. All other protons in the two spectra show more complex splitting patterns. Because of their extreme downfield position and the absence of complex splitting, the peaks at δ 5.25 in IIIA and δ 4.88 in IIIB are readily assigned to the proton at C-6. It then becomes evident that in IIIA the C-6 proton is *exo*. The relative low field position is explained by the proton's position in the deshielding zone of the carbon-chlorine bond (5) at C-8 and the observed splitting is consistent with the presence of a W-arrangement with respect to the 7a proton (6).

The C-6 proton in IIIB is not split since it lacks this spatial relationship to the proton at 7a. Further evidence for the proposed configuration of IIIA is the multiplet at δ 4.9 assignable to the proton at C-1, which is shifted about 0.6 ppm downfield from its corresponding position in IIIB, this shift being explainable by the close proximity of the *endo* chlorine atom to the C-1 proton in IIIA.

The nmr spectra of IVA and IVB gave further support to the proposed structural assignments. The peaks for the C-6 protons, as would be expected, were not greatly changed by the introduction of the two chlorines *exo* in the tetrahydrofuran ring. In IVA the C-6 proton appeared as a close doublet (J = 1.6 Hz) at δ 5.27 and IVB as a singlet at δ 4.45 consistent with what was observed in IIIA and IIIB and explainable on the same basis. As a result of the *α,α'*-dichlorination of the tetrahydrofuran ring the 1 and 3 protons now appeared much further downfield. In IVA a one-proton singlet was observed at δ 7.16 and a one-proton doublet (J = 1.2 Hz) at δ 6.02, whereas in IVB the one proton singlet appeared at δ 6.5 and the one proton doublet (J = 1.4 Hz) at δ 6.0. The doublet at δ 6.02 in IVA or δ 6.00 in IVB was assigned to the C-3 proton which has substantially the same environment in either epimer. The other extreme downfield peak must be assigned to the proton at C-1. In IVA, this proton would be expected to be deshielded by proximity to the chlorine atom at C-6, and thus the extreme downfield shift of the C-1 proton in IVA is consistent with the assignment of IVA as the 6-*endo*-Cl-*exo*-H epimer.

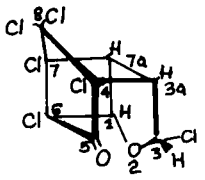
Further confirmation of the validity of these assignments was given by the nmr spectrum of the 6,6-dichlorinated derivative (V) in which the most deshielded protons were at δ 7.05 (singlet) and δ 6.00 (doublet, J = 2.5 Hz). Thus, in respect to the protons "inside" the box, V resembled IVA rather than IVB, as required by the assigned structures.

The fact that the C-1 proton in IVA, IVB and V is a singlet indicates that the C-1 chlorine is *exo*, since such a configuration puts the protons at 1 and 7a at about 90° dihedral angle, thus effectively uncoupling them. The small splitting (J = 1.2-1.4 Hz) shown by proton 3 in IVA, IVB and V suggests that here also the 3 proton is at nearly 90° dihedral angle to the 3a proton; *i.e.*, that the C-3 chlorine atom is also *exo*. The fact that the 1-7a and 3-3a couplings differ suggests that the tetrahydrofuran ring is somewhat twisted so that carbons 1,3,3a and 7 are not exactly coplanar.

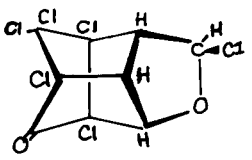
Upon stirring a solution of IVA or IVB in a water immiscible organic solvent with water or with aqueous buffer solutions of *p*H 4-10, dehydrochlorination occurred to give a product $C_9H_4Cl_6O_2$, the same product being produced from either isomer of the starting material. Its insecticidal and mammalian toxicity was of a high order, resembling that of IVA or IVB. The infrared spectrum of this product shows a carbonyl band at 1802 cm^{-1}, compared to 1797 cm^{-1} in IVA and IVB respectively, suggesting that the cyclic ketone structure in the dehydrochlorination product was at least as strained as in IVA or IVB.

Since no carbon-carbon double bonds were observed in the infrared spectrum of the dehydrochlorinated product, the dehydrochlorination must have occurred transannu-

larly with formation of either structure VIA or VIB.



VIA: (numbering as in IIIA)



VIB

The most plausible mechanism for the formation of either VIA or VIB involves loss of a proton to produce a carbanion at carbon 6, which then effects an intramolecular attack on carbon 1 or 3 with displacement of chloride. Examination of flexible molecular models indicated that in IVA or IVB, carbon 6 is closer to C-1 than to C-3 but that in some attainable conformations the approach of C-3 to C-6 is close enough that structure VIB cannot be excluded *a priori*. The assignment of structure VIA to the dehydrochlorination product was made by nmr on the basis of the observed J value (6.8 Hz) for the splitting of the two ring juncture protons (3a and 7a using the numbering system of the isobenzofuran ring system for consistency). Examination of models of VIA and VIB and the Karplus equation calculation from the observed dehydral angles indicated that VIA would have J3a,7a = 6-7, and VIB would have J3a,7a = 2-3. The difference is believed large enough so that the Karplus equation can be applied with reasonable confidence (7,8).

Reduction of VIA with one equivalent of lithium aluminum hydride yielded a monohydric alcohol, $C_9H_6Cl_6O_2$, which, surprisingly, retained insecticidal activity, and was formulated as VII on the basis of nmr. Treatment of VIA with excess lithium aluminum hydride yielded the structurally related but non-insecticidal alcohol (VIII) having the α-chlorine removed.

The structures of VII and VIII were confirmed by nmr. The spectrum of VII showed a one proton doublet (J = 10 Hz) at δ 4.12. Addition of deuterated water caused the doublet at δ 2.95 to disappear, indicating it to be the signal of the -OH proton, and the doublet at δ 4.12 simultaneously collapsed to a singlet, indicating it to be the signal of the proton α to the -OH. Since this proton did not show long range splitting by interaction with the 3a proton (using the numbering system of the isobenzofurans), the proton was considered most likely to be *endo*, and the hydroxy group *exo*. This *exo*-hydroxy configuration is consistent with that reported in the lithium aluminum hydride reduction of 3-*exo*-bromobicyclo[2.2.1]heptan-1-one wherein the reagent attack occurred from the *endo* side (4).

The nmr spectrum of VIII differed from that of VII most notably in that the singlet at δ 6.3 which was identified with the 3 proton of VII was replaced in VIII by a two-proton multiplet at δ 4.3, establishing that the chlorine adjacent to the ether linkage had been replaced by the hydrogen.

In contrast to their behavior in a heterogeneous aqueous mixture, IVA and IVB in a homogeneous aqueous solution underwent hydrolysis to a single non-toxic product formulated as a diol diether (IX).

The structure of IX was assigned on the basis of the infrared and nmr spectra. The infrared spectrum showed -OH and C-O but no C=C stretching bands. The nmr spectrum of IX (run in deuterioacetone because of poor solubility in chloroform) shows two hydroxyl protons. When deuterium oxide is added, these signals disappear and a broad one-proton singlet at δ 6.17 becomes a narrow singlet, indicating that this proton is located α to a hydroxyl group. The decision as to whether this proton is located 6-*endo* or 1-*endo* (either of the two locations would explain the absence of coupling to any other protons) is made on the basis of its extreme downfield chemical shift. The alcohols (VII and VIII) have their α'-protons no further downfield than δ 4.12 and δ 4.70 respectively, so it seems improbable that the δ 6.17 signal of IX could be that of an α-proton at position 6-*endo*, even allowing for solvent shifts. The δ 6.17 signal of the α-proton is more easily explained by assigning it to a *endo* proton shifted downfield because of its spatial proximity to a 6-*endo* chlorine. This interpretation then requires a 6-*exo* proton. The doublet at δ 4.90 (J = 2.3) can reasonably be assigned to the 6-*exo* proton, which would be W-coupled to the 7a proton. W-coupling constants as high as 3 c.p.s have been reported (9). The doublet of doublets at δ 3.37 (J = 10,J = 2.3) is then assignable to the 7a proton, the 10 c.p.s. coupling being that between the 7a proton and the 3a proton at δ 3.79, which in turn is also coupled (J = 5.0) to the 3 proton whose signal appears as a doublet at δ 5.89. Further confirmation of the correctness of these assignments is given by the observation that addition of deuterium oxide causes the doublet at δ 4.90 to become sharper and higher, which is explainable on the basis that a vicinal -OH had caused line broadening.

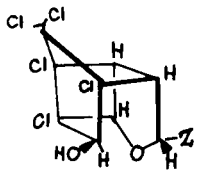
The formation of IX from either IVA or IVB is explainable by considering that an equilibrium occurs in aqueous solution between IVA, IVB, and the hydrate of IVA (steric hindrance probably would prevent hydration of IVB). Highly chlorinated polycyclic ketones are known to form hydrates which are acidic in character (10). The *endo*-anion from hydrated IVA then has a suitable configuration to permit attack on carbon 3 with displacement of chloride.

TABLE II

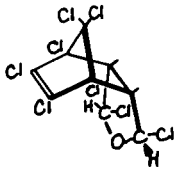
Nuclear Magnetic Resonance Spectra (a)

Compound	1-endo	1-exo	3-endo	3-exo	3a	5-endo	6-endo	6-exo	7a
IIIA	4.9dd		complex multiplets					5.25d(1.3)	multiplet
IIIB			complex multiplets				4.88S		multiplet
IVA	7.16S		6.02d(1.2)		4.03dd(11.4, 1.2)			5.37d(1.6)	4.30dd(11.4, 1.6)
IVB	6.50S		6.00d(1.4)		4.01dd(10.5, 1.4)		4.45S		4.37d(10.5)
V	7.05S		6.00d(1.5)		4.15dd(10.5, 2.5)		4.45S		4.66d(10.5)
VIA		5.01dd(6.8, 1.0)	6.20S		3.90dd(7.5, 1.0)				4.30dd(7.5, 6.8)
VII (b)		4.95dd(5.0, 2.5)	6.25S		3.78M	4.12dd(a0.0)			3.78dM.
VIII (c)		4.7dd							
IX (d)	6.17S			5.89d(5.0)	3.79dd(10.0, 5.0)			4.90d(2.3)	3.37(10.0, 2;3)
X (e)	6.12S		6.12S		4.10S				4.10S

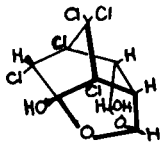
(a) Run in 10% deuteriochloroform solution unless otherwise noted. Chemical shift (δ) values in p.p.m. relative to tetramethylsilane; J values (Hz) given in parentheses. All spectra were determined on a Varian HA-100 nmr spectrometer. (b) Hydroxyl proton at 2.95d, signal removed by addition of deuterium oxide, with collapse of 4.12d to singlet. (c) Hydroxyl proton at 3.0d, signal removed by addition of deuterium oxide. (d) Hydroxyl protons at 6.2 and 7.0, signals removed by addition of deuterium oxide. Run in deuteriodimethylsulfoxide. (e) Data from Reference 11 presented for comparison. Bands are nearly singlets but can be recognized as narrow multiplet under highest resolution.



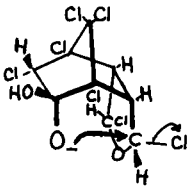
VII: Z = Cl
VIII: Z = H



X



IX



The resultant intermediate, then quickly undergoes hydrolysis of its remaining α-chlorine (at 1) probably by an SN_1 displacement with retention of configuration (because of steric restrictions) as is known for nucleophilic displacements on related α-chloroethers having this same skeleton (11).

Structure-Toxicity Relationship

The level of insecticidal activity on *Diptera* and the level of mammalian toxicity of IVA, IVB, V and VIA (Table I), are comparable to those of the known insecticide Telodrin ® (X) (12), which has a similar molecular skeleton and pattern of chlorine substitution. The compounds found in the present study may be viewed as relatives of X wherein substantial molecular changes have been made at carbons 5 and 6, or 3,5 and 6 without loss of the characteristic toxicity provided that the region of the molecule encompassing carbons 1,3a,4,7,7a and 8 has been left substantially unchanged. It may be hypothesized therefore that at the site of toxic action (as yet unknown) the side of the molecule containing carbons 5 and 6 faces away from the biological receptor site on which action is extended. If this hypothesis is correct, there may be much further latitude for molecular modifications at the 5 and 6 positions without loss of the characteristic toxicity.

This hypothesis is consistent with the postulate of Perkow (13) who considered that the methine groups at 3a and 7a attached to electron withdrawing substituents play the crucial role in the mechanism of action of the polychlorobicyclo[2.2.1]heptene class of insecticides.

EXPERIMENTAL (14)

3a,4,4,5,6-Pentachlorohexahydro-7-hydroxymethyl-6a-methoxy-3,5-methano-2*H*-cyclopenta[*b*]furan (II).

The preparation of this compound is described in Reference 2; however the following procedure was found more suited to large scale preparations.

A solution of sodium hydroxide (400 g.) in methanol (2500 g.) was heated to reflux with stirring, and 1,4,5,6,7,7-hexachloro-5-norbornene-*endo-cis*-2,3-dimethanol (I) (800 g.) was added over 2 hours. The syspension was refluxed and stirred for an additional 2 hours. Two-thirds of the methanol was permitted to distill off. The remaining slurry was poured into three volumes of water causing the organic product to precipitate. The product was collected on a filter, washed with water, and dried in an oven to obtain a substantially quantitative yield of crude product. Crystallization from carbon tetrachloride yielded a nearly colorless solid, m.p. 157-158°.

Anal. Calcd. for $C_{10}H_{11}Cl_5O_3$: C, 33.78; H, 3.27; Cl, 49.7. Found: C, 33.70; H, 3.14; Cl, 49.5.

4,6,7,8,8-Pentachloro-octahydro-4,7-methanoisobenzofuran-5-one Isomers: (IIIA and IIIB).

Compound II (750 g.) was added with stirring to concentrated (97%) sulfuric acid (6800 g.) at 93 to 95°. The mixture was heated at 95° for 5 hours and then cooled to room temperature. The solution was poured slowly into cold water with stirring, and the precipitated solid was removed by filtration, washed with water, and dried to give a gray solid in 89% yield. The material, a mixture of IIIA and IIIB, had a m.p. of 198-204°.

The crude ketone was separated into two isomers by recrystallization (611 g.) from ethanol (2 l.). The solids were recrystallized from carbon tetrachloride to give IIIB, a nearly colorless solid, m.p. 195-196°.

Anal. Calcd. for $C_9H_7Cl_5O_2$: C, 33.32; H, 2.17; Cl, 54.64. Found: C, 33.09; H, 2.07; Cl, 54.7.

The second stereoisomer (IIIA) was obtained by collecting a second crop of crystals by cooling and partial evaporation of the ethanol from the above-described crystallization, and then recrystallizing this substance several times from heptane. This isomer has a melting point of 217-220° affected by rate of heating

Anal. Calcd. for $C_9H_7Cl_5O_2$: C, 33.32; H, 2.17; Cl, 54.64. Found: C, 33.15; H, 2.04; Cl, 54.7.

Epimerization of IIIB to IIIA.

To a solution of IIIB (0.3 g.) in methanol (50 ml.) at 0-5° was added 1 *N* methanolic sodium methoxide (1.00 ml.). After 10 seconds the solution was added to an excess of dilute aqueous nitric acid. The product was isolated by extraction with methylene chloride, which on evaporation yielded IIIA (0.15 g.) identified by its infrared and n.m.r. spectra.

A similar experiment at room temperature and 2-minute-reaction time afforded IIIA contaminated with a greater amount of a probable ester (infrared bands at 1760, 1248, and 1100 cm^{-1}) believed to be formed by ring cleavage. Volhard titration revealed that 0.6 equivalents of chloride had been released per mole of IIIB.

It was not found possible to epimerize IIIB by dissolution in concentrated sulfuric acid (20 minutes) or in acetic acid saturated with hydrogen chloride (16 hours), IIIB being recovered unchanged.

1,3,4,6,7,8,8-Heptachloro-octahydro-4,7-methanoisobenzofuran-5-one Isomers (IVA and IVB).

(a) Preparation of IVA.

A solution of IIIA (482 g., 1.5 mole) in carbon tetrachloride (5 l.) was heated at reflux and illuminated by a 400-watt high

pressure mercury vapor arc lamp while a stream of chlorine was introduced. The evolved hydrogen chloride was trapped in water and the chlorination was terminated (about 10 hours) when slightly over the theoretical two molar equivalents of hydrogen chloride had been collected. The reaction mixture was evaporated under aspirator vacuum and the residual syrup was crystallized from cyclohexane and again from cyclohexane containing 10% benzene to give the product (100 g.) as nearly colorless crystals, m.p. 130-130.5°. The infrared spectrum indicated the crude product to be mostly IVA and the low recovery of pure isomer is attributed to recrystallization losses.

Anal. Calcd. for $C_9H_7Cl_5O_2$: C, 27.43; H, 1.28; Cl, 63.10. Found: C, 27.42; H, 1.14; Cl, 63.3.

(b) Preparation of IVB.

Compound IIIB was chlorinated in the same manner as described above. Tenacious by-products prevented the formation of a crystalline product, but by repeated recrystallization from hexane and cyclohexane, a constant melting, nearly colorless, solid, m.p. 91-92°, was obtained. The identical product was formed using as starting material either the lower or higher melting isomer of $C_9H_5Cl_7O_2$, or a mixture thereof.

Anal. Calcd. for $C_9H_5Cl_7O_2$: C, 27.48; H, 1.28; Cl, 63.10. Found: C, 27.38; H, 1.18; Cl, 63.3.

Equilibration of IVA and IVB.

A solution of IVB (20 mg.) in acetonitrile (10 ml.) was allowed to stand for 12 days, then evaporated under aspirator vacuum. The residue was analyzed by infrared and found to contain about 56% IVB and 31% of IVA. Similar treatment of IVA yielded a mixture found by infrared analysis to contain 46% IVB and 54% IVA.

1,3,4,6,6,7,8,8-Octachloro-octahydro-4,7-methanoisobenzofuran (V).

A 0.9 *M* solution of chlorine in acetonitrile (300 ml.) in which was dissolved 11.8 g. (0.03 mole) of IVA was allowed to stand in the dark for one week, then evaporated at 30° under aspirator vacuum. The residue was recrystallized twice from a hexane-benzene mixture, removing a small amount of a less soluble by-product by filtration, to give V (7.5 g., 58% yield) as a nearly colorless solid, m.p. 108-109°.

Anal. Calcd. for $C_9H_4Cl_8O_2$: C, 25.27; H, 0.94; Cl, 66.31. Found: C, 25.29; H, 1.01; Cl, 66.5.

1,3,6,9,10,10-Hexachloro-5-oxatetracyclo[5.3.0.$0^{3,9}$.$0^{4,8}$]decan-2-one (VIA).

A solution of $C_9H_5Cl_7O_2$ (3.9 g., either IVA or IVB or a mixture thereof) in ether (50 ml.) was stirred vigorously with a buffer solution (*p*H 8) consisting of 0.1 *M* boric acid (900 ml.) and 0.1 *N* sodium hydroxide (100 ml.) until Volhard titration of a small aliquot showed that substantially 1 molar equivalent of chloride ion had been evolved per mole of $C_9H_5Cl_7O_2$. This required about 41 hours at room temperature. The ether was allowed to evaporate as the reaction mixture continued to be stirred and the resultant solid precipitate was then removed by filtration to obtain colorless crystals (3.1 g.), m.p. 134-134.5°. Recrystallization of this product from hexane raised the m.p. to 137-138°.

Anal. Calcd. for $C_9H_4O_2Cl_6$: C, 30.29; H, 1.13; Cl, 59.61; MW, 356.86. Found: C, 30.29; H, 1.21; Cl, 59.6; MW, 344.

The same product was also obtained by conducting the hydrolysis in the above-described manner using, in place of the aqueous borate buffer, a series of phosphate and citrate buffers covering the range from *p*H 4 to *p*H 10, indicating that the *p*H of the aqueous medium is not critical.

A solution of $C_9H_5Cl_7O_2$ (2 g., either IVA or IVB) in xylene (10 ml.) was emulsified in water (2000 ml.) by means of an alkyl acid phosphate emulsifier (2 ml.). The emulsion was stirred and aliquots were periodically titrated for hydrochloric acid. When one molar equivalent of hydrochloric acid per mole of $C_9H_5Cl_7O_2$ had been released (requiring about one day at room temperature), the mixture was extracted with methylene chloride and the solvent was then evaporated leaving a residue of solid product found by infrared examination to be VIA.

In the absence of the emulsifier, the reaction proceeded much more slowly, giving only 15% conversion in 2 days.

In an alternative procedure, a solution of IVA or IVB (5 g.) was added to silica gel (280 g., activated by heating at 130°) and allowed to stand overnight at room temperature. The organic product was extracted with carbon disulfide and found by infrared examination to consist of a mixture of VIA and $C_9H_5Cl_7O_2$ (mixture of IVA and IVB). A similar result was obtained using activated alumina or activated fuller's earth in place of silica gel.

1,3,6,9,10,10-Hexachloro-5-oxatetracyclo[5.3.0.$0^{3,9}$.$0^{4,8}$]decan-2-ol (VII).

A solution of VIA (5 g.) lithium aluminum hydride (1 g.) and ethyl ether (275 ml.) was refluxed overnight, then filtered and the filtrate was evaporated. The residue was recrystallized three times from cyclohexane to give a colorless crystalline solid (2.3 g.), m.p. 153-154°.

Anal. Calcd. for $C_9H_6Cl_6O_2$: C, 30.12; H, 1.69; Cl, 59.28. Found: C, 30.15; H, 1.71; Cl, 59.1.

1,3,9,10,10-Pentachloro-5-oxatetracyclo[5.3.0.$0^{3,9}$.$0^{4,8}$]decan-2-ol (VIII).

A mixture of VIA (6 g.) and lithium aluminum hydride (2 g.) in ethyl ether (500 ml.) was refluxed under nitrogen for 5 days. Then water (3 ml.) was slowly added and when the excess hydride had decomposed, magnesium sulfate was added and the mixture was filtered. The filtrate was concentrated and the residue was crystallized from cyclohexane and benzene and finally from aqueous 2-propanol to give a colorless crystalline solid, m.p. 226-227°.

Anal. Calcd. for $C_9H_7Cl_5O_2$: C, 33.32; H, 2.17; Cl 54.64. Found: C, 33.58; H, 2.22; Cl, 54.5.

1,2,10,11,11-Pentachloro-3,7-dihydroxy-4,6-dioxatetracyclo[6.3.0.-$0^{3,10}$.$0^{5,9}$]undecane (IX).

A solution of IVA (5.35 g.) in tetrahydrofuran (180 ml.) was diluted with water (325 ml.) and allowed to stand at room temperature for 2 days. The resultant solution was evaporated to dryness and the residue recrystallized from benzene-hexane mixture to give a colorless solid (3 g.), m.p. 246-248° (dec.)

Anal. Calcd. for $C_9H_7Cl_5O_4$: C, 30.33; H, 1.98; Cl, 49.74. Found: C, 30.30; H, 1.97; Cl, 49.4.

The same product was obtained by hydrolysis of IVB under identical conditions. Under these reaction conditions, compounds IIIA and IIIB underwent no hydrolysis as determined by Volhard titration of their solutions after four days.

By conducting the hydrolysis of either IVA or IVB for only 6 hours at which time only one molar equivalent of chloride was evolved (as determined by Volhard titration of an aliquot), the crude product was found by infrared analysis to consist of IX and a mixture of IVA and IVB

Treatment of IX (1.78 g.) with acetone (10 ml.) and 2,2-

dimethoxypropane (5 ml.) in the presence of *p*-toluenesulfonic acid (0.2 g.) for 60 hours yielded only unchanged IX on evaporation, suggesting the absence of a *cis*-1,1-diol structure.

REFERENCES

(1) To whom correspondence should be addressed.

(2) P. E. Hoch, G. B. Stratton, and J. G. Colson, *J. Org. Chem.*, **34**, 1912 (1969).

(3) W. K. Johnson and V. Mark, *ibid.* **26**, 4105 (1961).

(4) H. Krieger, *Suomen Kemistilehti* **31** B, 320 (1958).

(5) R. F. Zürcher, "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol 2, Pergamon Press, P. 227 (1967).

(6) E. Tobler, D. E. Battin and D. J. Foster, *J. Org. Chem.* **29**, 2834 (1964).

(7) M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963).

(8) K. Williamson, *ibid.*, **85**, 516 (1963).

(9) E. W. Garbisch, *Jr. Chem. & Ind.* **41**, 1715 (1964).

(10) H. E. Ungnade and E. T. McBee, *Chem. Rev.* **58**, 282 (1958) and references cited therein.

(11) H. Singer and K. Ballschmiter, *Chem. Ber.* **101**, 17-23 (1968).

(12) H. Feichtinger and H. W. Linden, *Chem. and Ind.* **42**, 1938 (1968).

(13) W. Perkow, *Z. Naturforsch*, **12b**, 92 (1957).

(14) Infrared spectra reported herein were determined by using a Beckman IR-9 or IR-12 spectrophotometer. Nmr Spectra were determined using a Varian HA100 spectrometer. Chemical shifts and coupling constants were taken directly from the spectra. No calculations were attempted. Melting points are uncorrected.

Received May 12, 1969 Niagara Falls, New York 14302