Agr. Biol. Chem., **40** (2), 405～410, 1976

Further Syntheses of Lindane Analogs†

Makoto KISO, Masahide NOHTA, Hiroyuki OHASHI, Norio KURIHARA* and Minoru NAKAJIMA

*Department of Agricultural Chemistry, and *Radioisotope Research Center, Kyoto University, Kyoto*

Received October 22, 1975

dl-(1245/36)-4,5,6-Trichloro-1,2,3-trimethoxycyclohexane and *dl*-(1245/36)-2,3,4,5,6-pentachloro-1-methylthiocyclohexane were synthesized from (1245/36)-3,4,5,6-tetrachlorocyclohexane-1,2-diol. *dl*-(1245/36)-1,4,5,6-Tetrachloro-2-methoxy-3-methylthiocyclohexane and *dl*-(1245/36)-1,4,5,6-tetrachloro-2,3-dimethoxycyclohexane were synthesized from (12345/6)-1,4,5,6-tetrachloro-2,3-epoxycyclohexane. *meso*-(1245)-1,2,4,5-Tetrachlorocyclohexane was synthesized from benzene *via* cyclohexadiene-1,4.

We have synthesized various analogs of lindane (γ-isomer of BHC),[1~7] which are classified according to the position of substituents other than chlorine, as *meso*- and *dl*-type analogs.[5] A preliminary study suggested somewhat different roles for the *meso* and *dl* substituents in insecticidal activity.[8] To examine as closely as possible the structure-activity relationship of lindane analogs, we have further synthesized the *dl*-type methylthio analog, and some mixed-type analogs in which the chlorine atoms at both the *meso* and *dl* positions are replaced by other substituents. *Meso*-(1245)-1,2,4,5-tetrachlorocyclohexane was synthesized to elucidate the effect of the two chlorine atoms at the *meso* position on insecticidal activity. As possible metabolites of the *dl*-type methylthio analog, the corresponding sulfoxide and sulfone derivatives were synthesized. Studies of the insecticidal activity and metabolism of these compounds will be reported elsewhere. We here report the syntheses of these lindane analogs.

SYNTHETIC METHODS

1) dl-(1245/36)-4,5,6-Trichloro-1,2,3-trimethoxycyclohexane (IV)

(12345/6)-4,5,6-Trichloro-2,3-epoxy-1-methoxycyclohexane (II) was synthesized by the methylation of (12345/6)-4,5,6-trichloro-2,3-epoxycyclohexanol (I)[9] (Fig. 1,A). The cleavage of the epoxide using BF_3 in abs. methanol gave two products, III and III′, whose configurations were confirmed by PMR analyses. The major product was (1245/36)-4,5,6-trichloro-1,3-dimethoxycyclohexan-2-ol (III) with the γ-configuration (*aaaeee*). The minor product was (1235/46)-2,3,4-trichloro-5,6-dimethoxycyclohexanol (III′) with the δ-configuration (*aeeeee*). Further methylation of III gave the corresponding trimethoxy analog (IV) (Fig. 1, A).

2) dl-(1245/36)-1,4,5,6-Tetrachloro-2,3-dimethoxycyclohexane (VIII) and dl-(1245/36)-1,4,5,6-tetrachloro-2-methoxy-3-methylthiocyclohexane (IX)

(12345/6)-1,4,5,6-Tetrachloro-2,3-epoxycyclohexane (V) was synthesized from α-BTC *cis*-epoxide according to the method previously reported.[5] The epoxide was cleaved using BF_3-methanol and BF_3 etherate-dimethyl sulfide to give the corresponding cyclohexanol derivatives, (1245/36)-1,4,5,6-tetrachloro-3-methoxycyclohexan-2-ol (VI) and (1245/36)-1,4,5,6-tetrachloro-3-methylthiocyclohexane (VII), respectively. The experimental conditions and mechanism of epoxide cleavage with the methylthio group were described in a previous paper.[7] The mixed-type analogs, VIII and IX, were obtained by

† Studies on BHC Isomers and Related Compounds. Part XVI.

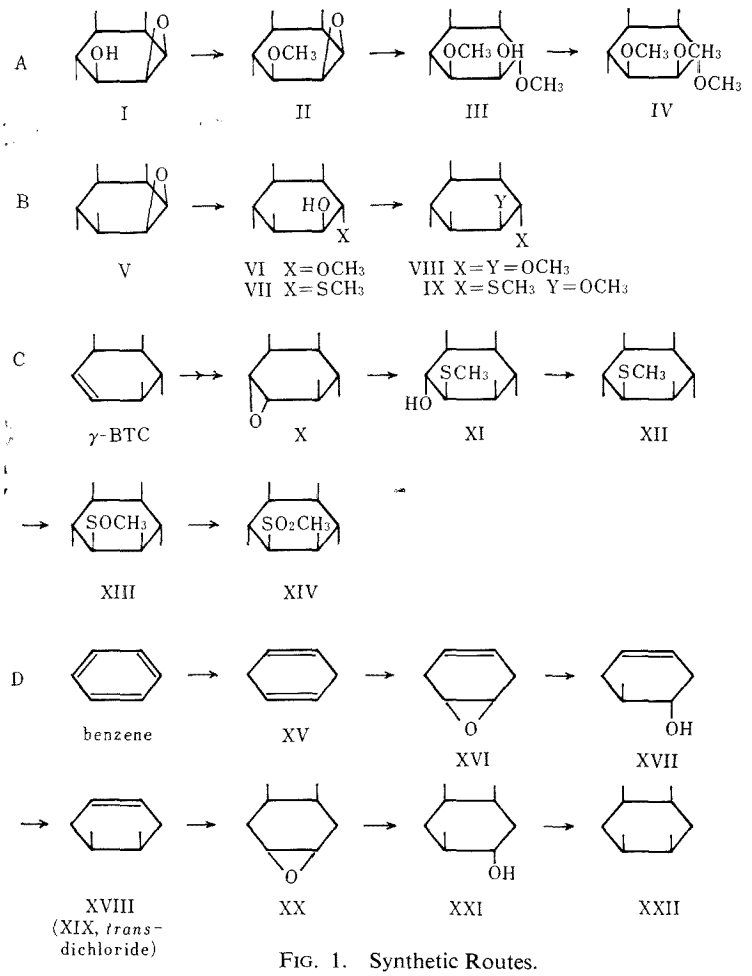

FIG. 1. Synthetic Routes.

Short vertical lines represent Cl substituent.

the methylation of compounds VI and VII, respectively (Fig. 1, B).

3) dl-(1245/36)-2,3,4,5,6-Pentachloro-1-methylthiocyclohexane (XII)

(124/356)-3,4,5,6-Tetrachloro-1,2-epoxycyclohexane (X) was synthesized from γ-BTC.[9] Cleavage of the epoxide with the methylthio group was carried out using BF_3 etherate and dimethyl sulfide by a method similar to that used in the synthesis of VII to give tetrachloromethylthiocyclohexanol (XI) with the γ-configuration. The structure of XI was analyzed by 90 MHz PMR spectroscopy. Chlorination of XI with $POCl_3$ and PCl_5 proceeded quantitatively with the retention of configuration affording the *dl*-type methylthio analog XII (Fig. 1, C).

4) dl-(1245/36)-2,3,4,5,6-Pentachlorocyclohexyl methyl sulfoxide (XIII) and dl-(1245/36)-2,3,4,5,6-pentachlorocyclohexyl methyl sulfone (XIV)

The methylthio analog (XII) was treated with sodium periodate to afford the sulfoxide (XIII). Elemental analysis and mass spectrometry confirmed the structure. When compound XII was oxidized with *m*-chloroperbenzoic acid, the sulfone (XIV) was obtained (Fig. 1, C).

5) meso-(1245)-1,2,4,5-Tetrachlorocyclohexane (XXII)

Cyclohexadiene-1,4 (XV) was synthesized

by the Birch reduction of benzene with sodium metal and ethanol in liquid ammonia.[10] The amount of XV was estimated by its titration with bromine. Its mono epoxidation was carried out using perbenzoic acid at −10°C over a period of 1 week to give 4,5-epoxycyclohexene (XVI).[11] This epoxide was easily cleaved with HCl at room temperature to quantitatively afford 2-chlorocyclohex-4-en-1-ol (XVII). *cis*-4,5-Dichlorocyclohexene (XVIII) was prepared by chlorination of the hydroxyl group of XVII using a modified Arbusov reaction where pure crystallized triphenyl phosphite dichloride[12] was used as the chlorinating agent to prevent any chlorine addition to the double bond. This reaction proceeded with the Walden inversion almost exclusively to give the *cis*-dichloro derivative (XVIII). In this reaction, formation of the *trans*-dichloro isomer (XIX) due to retention of cofiguration increased with a decrease in the relative amount of DMF in the reaction mixture.

The configurations of XVIII and XIX were confirmed by comparing their PMR spectra with that of *trans*-4,5-dichlorocyclohexene[13,14] independently synthesized from cyclohexadiene-1,4.

Epoxidation of XVIII was carried out with peroxytrifluoroacetic acid to give the *trans*-epoxide (XX) (*trans* to the chlorine atoms) as the single product. This configuration was determined by PMR analyses of the acetyl derivative of XXI using spin decoupling techniques (see EXPERIMENTAL, Fig. 4). The epoxide ring of XX was cleaved with HCl, then chlorinated to afford *meso*-(1245)-1,2,4,5-tetrachlorocyclohexane (XXII) in a good yield (Fig. 1, D).

The structure of XXII was also established by PMR analyses. In its PMR spectrum (Fig. 2, A), two pairs of two equivalent methylene protons; (H-3a, H-6a) and (H-3b, H-6b), appeared at 2.8 ppm as a quintet ($J_{gem}=14$, $J_{2,3a}=J_{4,3a}=J_{1,6a}=J_{5,6a}=7.0$ Hz) and at 2.3 ppm as a double-multiplet ($J_{gem}=14$, $J_{2,3b}=J_{4,3b}=J_{1,6b}=J_{5,6b}=3$ Hz) (*a* and *b* indicate the *cis* and *trans* configurations to the four chlorine atoms, respectively). Of the isomers expected as chlorination products from XXI, only one having an entire *cis* configuration of chlorine atoms occurred.

To obtain further evidence for the assumed configuration, (124/5)-1,2,4,5-tetrachlorocyclohexane (XXV, Fig. 3) was synthesized independently by an ionic chlorine addition to XVIII. This compound corresponds to the chlorination product from XXI with retention of its configuration, and its PMR spectrum was quite different from that of XXII (Fig. 2, B). In the synthesis of XXV, (34/6)-3,4,6-

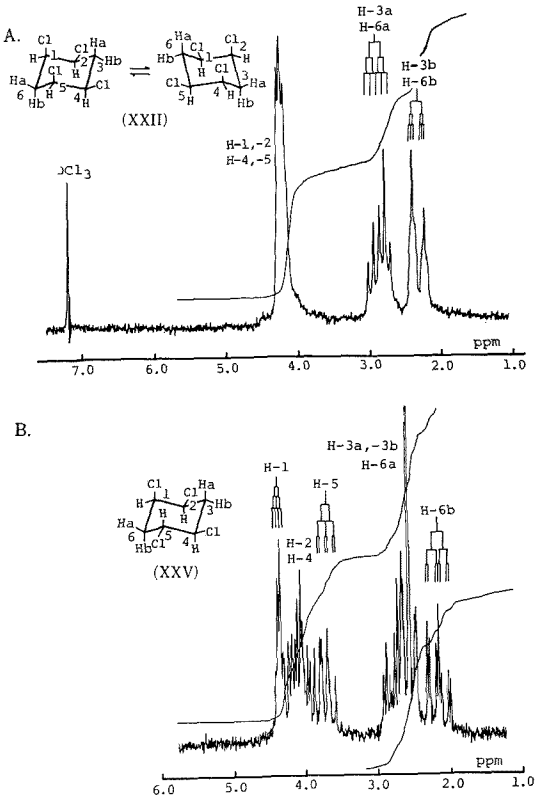

FIG. 2. PMR Spectra of XXII (A) and XXV (B).

trichlorocyclohexene (XXVI) was obtained as the major product which suggests the chloronium intermediate reaction mechanism shown in Fig. 3. A comparison of this data with that for the chlorination of cyclohexene[15] under similar conditions shows that diaxial cleavage of XXIII by the chloride anion would be very difficult due to hindrance of the axial chlorine atom at the homoallylic position.

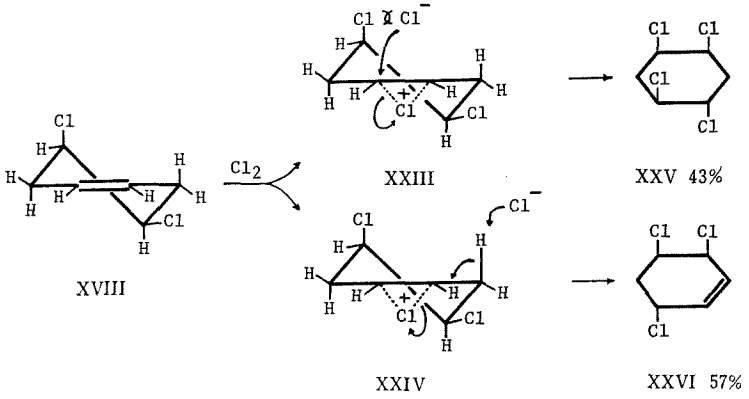

FIG. 3. Chloronium Ion Intermediate Mechanism.

EXPERIMENTAL

PMR data were recorded by the method given in a previous paper.[5]

dl-(1245/36)-4,5,6-Trichloro-1,2,3-trimethoxycyclohexane (IV)

The methylation of I was carried out according to the method reported by Kuhn and Trishman[16] to give II in a 50~60% yield. Compound II (0.5 g) was dissolved in a solution of the BF_3 methanol complex (4 ml) and abs. methanol (2 ml), then the mixture was heated at 60~80°C for 5 hr. After being treated with alkali, the reaction mixture underwent extraction with ether. Evaporation and column chromatography (silicic acid, elution with $CHCl_3$) gave III as the major product (60~70%, mp 84~85°C) and III′ as the minor product (5~10%, mp 140~141°C).

The PMR data for III (90 MHz, in $CDCl_3$) δ: 2.3 (1H, d., OH), 2.9 and 3.06 (6H, s., $2OCH_3$), 3.22 (1H, d.d., H-1), 3.55 (1H, t., H-3), 3.82 (1H, m., H-2) and 4.0~4.3 (3H, m., H-C-Cl); for III′ (90 MHz, in $CDCl_3$) δ: 2.02 (1H, s., OH), 2.7 (1H, t., H-1 or H-2), 3.05 (1H, d.d., H-3 or H-5), 3.35 and 3.46 (6H, s., $2OCH_3$), 3.98 (1H, t., H-4), 4.2 (1H, d.d., H-6) and 3.22~3.5 (other protons).

Compound III was further methylated by the method of Kuhn *et al.*[16] to afford IV (62% yield), which was recrystallized from *n*-hexane/chloroform, mp 99~100°C.

Anal. Found: C, 38.65; H, 5.33. Calcd. for $C_9H_{15}O_3Cl_3$: C, 38.94; H, 5.45%.

dl-(1245/36)-1,4,5,6-Tetrachloro-2,3-dimethoxycyclohexane (VIII) and dl-(1245/36)-1,4,5,6-tetrachloro-2-methoxy-3-methylthiocyclohexane (IX)

Compound V (380 mg) was dissolved in a solution of the BF_3 methanol complex (3.2 ml) and abs. methanol (1 ml), then the mixture was heated 65~75°C for 3 hr. After being treated with alkali, the reaction mixture underwent extraction with ether. Evaporation and column chromatography (silicic acid, elution with $CHCl_3$) gave VI in an 82% yield (354 mg), mp 98~99°C. The PMR data for VI (60 MHz, in $CDCl_3$) δ: 2.7 (1H, s., OH), 3.55 (3H, s., OCH_3), 3.97 (1H, t., H-3) and 4.4~4.5 (4H, m., H-C-Cl).

The synthesis and physicochemical data for VII have been reported in Ref. 7).

The methylations of VI and VII were also carried out by the method of Kuhn *et al.* to give VIII (mp 89~90°C) and IX (mp 88~89°C), respectively, in 50~60% yields.

Anal. Found for VIII: C, 34.14; H, 4.30. Calcd. for $C_8H_{12}O_2Cl_4$: C, 34.07; H, 4.29. *Anal.* Found for IX: C, 32.20; H, 4.03. Calcd. for $C_8H_{12}SOCl_4$: C, 32.24; H, 4.06%.

dl-(1245/36)-2,3,4,5,6-Pentachloro-1-methylthiocyclohexane (XII)

A mixture of X (5 g), BF_3 etherate (47%, 30 ml) and dimethyl sulfide (100 ml) was heated at 70~80°C for 3 hr in a pressure bottle. This reaction mixture was neutralized with 0.5 N NaOH (300 ml), followed by ether extraction. Column chromatography (silicic acid, elution with $CHCl_3$) gave XI (4.4 g, 73%) almost exclusively, which was recrystallized from chloroform, mp 111°C.

The PMR data for XI (90 MHz, in $CDCl_3$) δ: 2.3 (3H, s., SCH_3), 2.82 (1H, s., OH), 3.24 (1H, d.d., H-2), 4.18 (1H, t., H-3), 4.75 (1H, t., H-6) and 4.4~4.6 (other protons).

Phosphorus pentachloride (1.2 g) was added gradually to a solution of XI (1 g) in phosphorus oxychloride (10 ml) under cooling to −1~−2°C. The reaction mixture was then poured into ice-water and subjected to extraction with ether. Evaporation and column chromatography (silicic acid, elution with *n*-hexane: chloroform=5: 1) gave XII (900 mg, 70%), which was recrystallized from *n*-hexane, mp 101~102°C.

Anal. Found for XII: C, 27.68; H, 3.00. Calcd. for

$C_7H_9SCl_5$: C, 27.80; H, 3.00%. The PMR data for XII (90 MHz, in $CDCl_3$) δ:2.34 (3H, s., SCH_3), 3.37 (1H, d.d., H-1) and 4.4~4.8 (other protons). The coupling constants ($J_{1,2}$=3.6, $J_{1,6}$=6.8 Hz) indicate that XII has the γ-configuration and interconverts between two conformers of about equal molar fractions.

dl-(1245/36)-2,3,4,5,6-Pentachlorocyclohexyl methyl sulfoxide (XIII)

The methylthio analog (XII) (100 mg) was added to a solution of $NaIO_4$ (90 mg) in water (0.6 ml) and methanol (0.2 ml) at 0°C. The solution was stirred overnight at room temperature. Ether extraction and evaporation afforded a sirupy product, which was chromatographed on a silicic acid column with chloroform as eluent. The sulfoxide (30 mg) was obtained as colorless crystals, mp 160°C.

Anal. Found for XIII: C, 26.63; H, 3.04. Calcd. for $C_7H_9SOCl_5$: C, 26.40; H, 2.85%.

dl-(1245/36)-2,3,4,5,6-Pentachlorocyclohexyl methyl sulfone (XIV)

To a solution of the methylthio analog (XII) (1 g) in CH_2Cl_2 (3.3 ml), *m*-chloroperbenzoic acid solution (1.0 g in 10 ml of CH_2Cl_2) was added dropwise with stirring at 40~50°C. After 4 hr, the solvent was carefully evaporated *in vacuo*, and the residue was extracted with ether. The ether extract was washed with saturated $NaHCO_3$ solution and water successively, and, after dried, was evaporated to dryness. Column chromatography on silicic acid with benzene/AcOEt (4: 1, v/v) as eluent afforded 250 mg of the sulfone (XIV) from the first fractions, and 400 mg of the sulfoxide (XIII) from the later fractions. The sulfone was recrystallized from benzene/AcOEt, mp 211~212°C.

Anal. Found for XIV: C, 25.71; H, 2.69. Calcd. for $C_7H_9SO_2Cl_5$: C, 25.14; H, 2.71%.

2-Chlorocyclohex-4-en-1-ol (XVII)

4,5-Epoxycyclohexene (XVI) was synthesized by the method of Md. Erfan Ali.[11] Conc. HCl (27.2 ml) was added dropwise under ice-cooling to a solution of XVI (8.5 g) in ether (200 ml). The reaction mixture was shaken for 30 min at room temperature, followed by the addition of water (200 ml). Ether extraction and evaporation gave XVII as a sirup (9.2 g, 78.5%), bp 53~54°C/11 mmHg.

The PMR data for XVII (100 MHz, in $CDCl_3$) δ: 1.9~3.0 (4H, m., methylenic), 2.85 (1H, s., OH), 3.70~3.95 (1H, octet, H-1), 3.87~4.15 (1H, sextet, H-2) and 5.4~5.75 (2H, m., H-4 and H-5). The coupling constants ($J_{1,6a}$=9.8, $J_{1,2}=J_{2,3b}$=9.0, and $J_{1,6b}=J_{2,3a}$=5.0 Hz) indicate that the conformer in which both Cl and OH are in equatorial conformation is dominant in $CDCl_3$ (a and b indicate the *cis* and *trans* configurations to the OH group, respectively).

cis-4,5-Dichlorocyclohexene (XVIII)

A mixture of XVII (500 mg) and dry DMF (5 ml) was added dropwise under ice-cooling to pure crystallized triphenyl phosphite dichloride (1.5 g). This reaction easily proceeded for several minutes. The reaction mixture was then poured into ice water and chloroform extraction followed. The extract was washed with alkali, dried and chromatographed. Elution with *n*-hexane: chloroform=5: 1 gave XVIII as a syrup (352 mg, 62% yield), bp 74°C/8 mmHg.

The PMR data for XVIII (90 MHz, in $CDCl_3$) δ: 2.5 (4H, m., methylenic), 4.3 (2H, m., H-4 and H-5) and 5.6 (2H, m., H-1 and H-2).

trans-4,5-Dichlorocyclohexene (XIX)

A solution of chlorine in CCl_4 was added dropwise at 0~5°C to a stirred solution of compound XV in chloroform. After additional stirring for 30 min, the reaction mixture underwent extraction with chloroform. All operations were carried out in the dark. This reaction proceeded very easily, giving XIX as colorless crystals, mp 41°C (Lit.[13] mp 42°C, Lit.[14] mp 43.1~43.6°C).

The PMR data for XIX (90 MHz, in $CDCl_3$) δ: 2.3 (2H, double-multiplet, methylenic), 2.8 (2H, double-multiplet, methylenic), 4.1 (2H, m., H-4 and H-5) and 5.5 (2H, m., olefinic).

(12/45)-4,5-Dichloro-1,2-epoxycyclohexane(XX)

A peroxytrifluoroacetic acid solution was prepared by reacting 90% hydrogen peroxide (0.4 ml) with trifluoroacetic anhydride (3 ml) in methylene chloride (3 ml). This solution was added dropwise under ice-cooling to a solution of XVIII (1 g) and Na_2HPO_4 (5.6 g) in methylene chloride. The reaction mixture was stirred for 1 hr at room temperature, then underwent extraction with chloroform. Evaporation and column chromatography on silicic acid gave XX as a single product (630 mg), which was recrystallized from *n*-hexane/chloroform, mp 38~39°C.

Anal. Found: C, 43.16; H, 4.99. Calcd. for $C_6H_8OCl_2$: C, 43.14; H, 4.83%. The PMR data for XX (60 MHz, in $CDCl_3$) δ: 2.35~2.65 (4H, m., methylenic), 3.15~3.25 (2H, m., H-1 and H-2) and 4.05~4.4 (2H, m., H-4 and H-5).

(124/5)-1,2,4-Trichlorocyclohexan-5-ol (XXI)

Conc. HCl (5.4 ml) was added dropwise under ice-cooling to a solution of XX (900 mg) in a minimum amount of ethanol. The reaction mixture was stirred for 1 hr at room temperature, then neutralized with alkali. Ether extraction and evaporation gave XXI (871 mg, 80% yield), which was recrystallized from *n*-hexane/chloroform, mp 57°C.

Anal. Found: C, 35.41; H, 4.46. Calcd. for $C_6H_7OCl_5$: C, 35.35; H, 4.67%. The PMR data for XXI (90 MHz, in $CDCl_3$) δ: 1.8 (1H, septet, H-6b), 2.35~2.8 (3H, m., H-3a, H-3b, H-6a and OH), 3.5~4.25 (3H, m., H-2, H-4 and H-5) and 4.45 (1H, q., H-1).

The structural determination of XX

The chlorohydrin, XXI, was acetylated with acetic anhydride and pyridine. In the PMR spectrum of this acetate, only H-5 shifted to δ 5.2 due to the anisotropic effect of the acetyl group. The decoupling of H-5 converted the septet pattern of H-6b ($J_{gem}=14$, $J_{5,6b}=11$ and $J_{1,6b}=3$ Hz) to the double-doublet pattern ($J_{gem}=14$, $J_{1,6b}=3$ Hz). This indicates that the acetate has the A, not B, structure (Fig. 4). From this, we concluded that the epoxide ring of XX is in *trans*-configuration to the chlorine atoms.

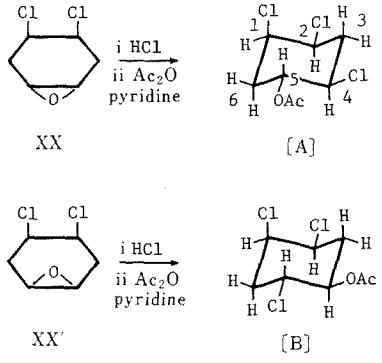

FIG. 4. Possible Conformers of XX.

meso-(1245)-1,2,4,5-Tetrachlorocyclohexane (XXII)

Crude crystals of triphenyl phosphite dichloride (4.5 g) were added under ice-cooling to a solution of XXI (600 mg) in dry DMF (3.5 ml). The reaction mixture was treated similar to that used in the chlorination of XVII to give XXII (255 mg, 37% yield), which was recrystallized from *n*-hexane/chloroform, mp 143~145°C (sublimation).

Anal. Found: C, 32.27; H, 3.34. Calcd. for $C_6H_8Cl_4$: C, 32.47; H, 3.63%. The PMR analysis of XXII was described in the section on synthetic methods.

(124/5)-1,2,4,5-Tetrachlorocyclohexane (XXV) and (34/6)-3,4,6-trichlorocyclohexene-1 (XXVI)

A solution of chlorine in CCl_4 was added dropwise under slight cooling to a solution of XVIII in CCl_4 in the dark. This reaction proceeded very easily to give XXV (43% yield) and XXVI (57% yield), mp 71.5~72.5°C for XXV and 65~66°C for XXVI.

Anal. Found for XXV: C, 32.59; H, 3.36. Calcd. for $C_6H_8Cl_4$: C, 32.47; H, 3.63%. *Anal.* Found for XXVI: C, 38.96; H, 3.82. Calcd. for $C_6H_7Cl_3$: C, 38.86; H, 3.78%.

The PMR data for XXVI (90 MHz, in $CDCl_3$) δ: 2.3 (1H, double-multiplet, methylenic), 2.65 (1H, octet, methylenic), 4.3~4.75 (3H, m., H-C-Cl) and 5.7~6.0 (2H, olefinic). The PMR data for XXV are shown in Fig. 2.

Acknowledgement. We are grateful to Miss Shigeko Yamashita for performing the 90 MHz PMR measurements. Microanalyses were carried out in the Research Laboratory for Organic Microelemental Analysis of this university.

REFERENCES

1) N. Kurihara, Y. Sanemitsu, M. Nakajima, G. E. McCasland and L. F. Johnson, *Agr. Biol. Chem.*, **35**, 71 (1971).
2) Y. Sanemitsu, N. Kurihara, M. Nakajima, G. E. McCasland, L. F. Johnson and L. C. Carey, *ibid.*, **36**, 845 (1972).
3) Y. Sanemitsu, Y. Minamite, N. Kurihara and M. Nakajima, *ibid.*, **39**, 223 (1975).
4) K. Tanaka, M. Kiso, M. Yoshida, N. Kurihara and M. Nakajima, *ibid.*, **39**, 229 (1975).
5) M. Kiso, K. Tanaka, Y. Sanemitsu, M. Yoshida, N. Kurihara, and M. Nakajima, *ibid.*, **39**, 443 (1975).
6) M. Kiso, Y. Irie, Y. Sanemitsu, N. Kurihara and M. Nakajima, *ibid.*, **39**, 451 (1975).
7) M. Kiso, M. Maeda, N. Kurihara and M. Nakajima, *ibid.*, **39**, 459 (1975).
8) M. Kiso, K. Tanaka, M. Nohta, N. Kurihara, T. Fujita and M. Nakajima, in preparation.
9) N. Kurihara, Y. Sanemitsu, T. Kimura, M. Kc-bayashi and M. Nakajima, *Agr. Biol. Chem.*, **34**, 784 (1970).
10) J. P. Wibaut and F. A. Haak, *Rec. Trav. Chim. Pays-Bas*, **67**, 85 (1948).
11) Md. Erfan Ali and L. N. Owen, *J. Chem. Soc.*, **1958**, 1066.
12) D. C. Goe, S. R. Landauer and H. N. Rydon, *ibid.*, **1954**, 2281.
13) O. Hassel, E. W. Lund and K. Lunde, *Acta Chem. Scand.*, **6**, 426 (1952).
14) K. Sakashita, *J. Chem. Soc. Japan* (Pure Chem. Sect.), **74**, 315 (1953).
15) M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2161 (1965).
16) R. Kuhn and H. Trischman, *Chem. Ber.*, **96**, 284 (1963).