1,1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane and Related Compounds[1]

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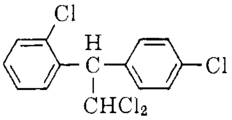
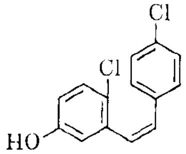
Aluminum amalgam in 90% ethanol reduces the trichloromethyl group in DDT-like compounds to dichloromethyl compounds. A number of 2,4'-dichlorostilbenes were synthesized as possibly physiologically active compounds.

The use of 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane, *o,p'*-DDD, I, in cases of cancer of the adrenals[2] suggested an investigation of isomers and hypothetical metabolites of this compound. The lack of functional groups in I together with the large dose in man (10–15 g. per day) might indicate that the drug undergoes *in vivo* conversion to an active material. We particularly wished to test the suggestion that *o,p'*-DDD might undergo *in vivo* hydroxylation and rearrangement to stilbenes such as II and III which may be regarded as being related to steroids in the sense that stilbesterol and coumesterol[3] are related to steroids. Finally, it was hoped that a more suitable source of *o,p'*-DDD might be made available by an improved synthesis of this compound.[4] The material employed clinically was obtained by an extensive and tedious purification of a by-product of insecticide manufacture.[2,5] The synthesis reported[6] gave *o,p'*-DDD in 39% yield by the condensation of IV with chlorobenzene. The necessary compound IV was obtained in 6% yield from *o*-chlorophenylmagnesium bromide and dichloroacetaldehyde.[6]



I



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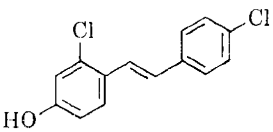

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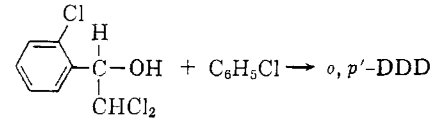

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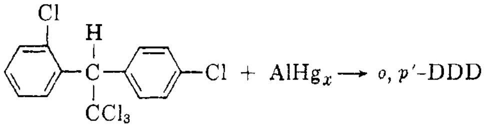
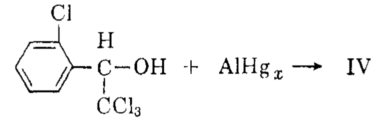


V

In our laboratory, we have found that the reduction of *o,p'*-DDT (V) with aluminum amalgam in 90% ethanol gave *o,p'*-DDD in 65% yield. The required V was made by the condensation of 2,2,2-trichloro-1-(*o*-chlorophenyl)ethanol VI with chlorobenzene in 64% yield as described.[6] This constitutes a preferable process due to the greater availability of the trichlorocarbinol VI.[6,7] The selective reducing action of aluminum amalgam–90% ethanol was further demonstrated by the conversion of VI to IV in 58% yield. This with chlorobenzene and boron trifluoride-saturated sulfuric acid gave *o,p'*-DDD in 47% yield. Other aluminum amalgam reductions of DDT-related compounds are summarized in Table I.



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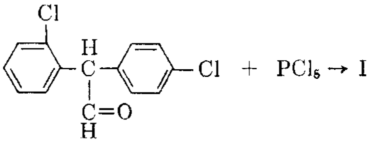
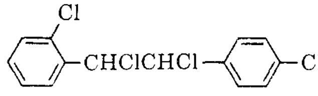


VII

In a proposed synthesis of *o,p'*-DDD according to the preceding equation a small amount (10%) of *meso*-α,α',2,4'-tetrachlorobibenzyl VIII was ob-



VIII

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[1] This investigation was supported by a Public Health Service Grant CY-5258 from the National Cancer Institute, Public Health Service.

[2] D. M. Bergenstal, M. B. Lipsett, R. H. Moy, and R. Hertz, *Trans. Assoc. Am. Physicians*, **72**, 341 (1959).

[3] L. Jurd, *J. Org. Chem.*, **24**, 1786 (1959); E. M. Bickoff, A. L. Livingston, and A. N. Booth, *Arch. Biochem. Biophys.*, **88**, 262 (1960).

[4] Such a synthesis would make available *o,p'*-DDD-C^{14} for metabolism studies.

[5] Private communication from D. C. West and M. J. Gortatowsky. We greatly appreciate the kindness of Dr. M. J. Gortatowsky in supplying us with a sample of purified *o,p'*-DDD derived from commercial material.

[6] H. L. Haller, *et al.*, *J. Am. Chem. Soc.*, **67**, 1591 (1945).

[7] J. W. Howard and I. Castle, *ibid.*, **57**, 376 (1935).

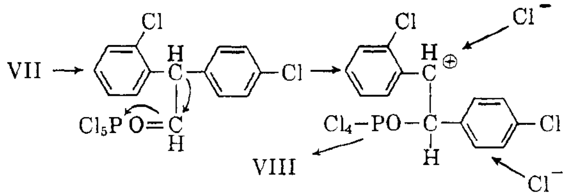
TABLE I

ALUMINUM AMALGAM REDUCTIONS OF DDT-RELATED COMPOUNDS[a]

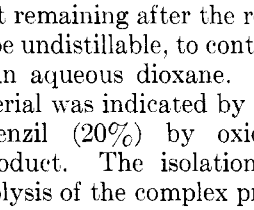
Product	Yield, %	M.p., °C.	Calcd. for	Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
m,p'-DDD	51	B.p. 178–180° (0.5 mm.)	$C_{14}H_{10}Cl_4$	52.54	3.15	44.3	53.08	3.16	44.2
p,p'-DDD	63	105.5–107.0[b,c]	$C_{14}H_{10}Cl_4$	52.54	3.15	44.3	52.62	3.02	43.9
1,1-Cl_2-2-phenyl-2-(*o*-Cl-phenyl)ethane[e]	85	B.p. 157–158 (0.5 mm.)	$C_{14}H_{11}Cl_3$[d]	58.87	3.88	37.2	58.01	4.34	38.3
1,1-Cl_2-2-phenyl-2-(*p*-Cl-phenyl)ethane	70	119.5–120.5[f]	$C_{14}H_{11}Cl_3$	58.87	3.88	37.2	59.08	4.10	37.1
1,1-Cl_2-2,2-diphenylethane	66	74.5–75.0[g]	$C_{14}H_{12}Cl_2$	66.95	4.82	28.2	67.05	4.81	27.9
1-(*o*-Cl-phenyl)-1-(*p*-Cl-phenyl)ethane[h]	62	B.p. 146–148 (1 mm.)	$C_{14}H_{12}Cl_2$	66.95	4.82	28.2	66.80	4.81	29.0

[a] Aluminum amalgam reduction of the corresponding 1,1,1-trichloro compound as previously described. [b] J. Forrest, O. Stephenson, and W. A. Waters, *J. Chem. Soc.*, 333 (1946). [c] Reference 6 reported m.p. 108.5–110°. [d] Distillation failed to remove the small amount of starting compound present. [e] The necessary 1,1,1-trichloro-2-(*o*-chlorophenyl)-2-phenylethane was obtained by condensation of VI with benzene using boron trifluororide–sulfuric acid (50% yield), m.p. 73.0–74.2°, from ethanol. *Anal.* Calcd. for $C_{14}H_{10}Cl_4$; C, 52.54; H, 3.15; Cl, 44.3. Found: C, 52.68; H, 3.31; Cl, 43.8. [f] λ_{max}^{alc} 229, 267 mμ (ε 16,100, 451). [g] λ_{max}^{alc} 221, 259 mμ (ε 11,150, 395). Reported m.p. 74°; R. Delaby and R. Barounet, *Bull. soc. chim. France*, 148 (1951). [h] By zinc dust reduction of *o,p'*-DDT according to ref. *b*; λ_{max}^{alc} 267.5 mμ (ε 1170).

tained, identical to material made by the addition of chlorine to *trans*-2,4'-dichlorostilbene. This is an additional example of the migration of a phenyl group in 1,1-diphenylethane compounds[8] visualized in terms of the proposed mechanism[9] as

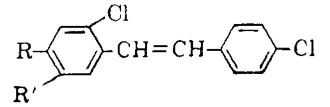


The product remaining after the removal of VIII was found to be undistillable, to contain phosphorus and to react in aqueous dioxane. Additional rearranged material was indicated by the isolation of 2,4'-dichlorobenzil (20%) by oxidation of the hydrolysis product. The isolation of VII after alkaline hydrolysis of the complex product suggests that the major pathway involves the formation of IX.

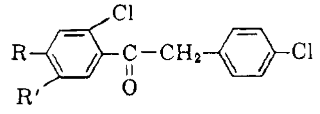


IX

The *trans*-stilbene X was obtained by the dehydration of the carbinol obtained by the addition of *p*-chlorobenzylmagnesium chloride to *o*-chlorobenzaldehyde. The ketone XIV was obtained by acylation of 4-chloroveratrole with *p*-chlorophenylacetic acid in polyphosphoric acid. Reduction to the carbinol and dehydration gave XI.



X. R,R' = H
XI. R,R' = OCH_3
XII. R = H; R' = OCH_3



XIII. R,R' = H
XIV. R,R' = OCH_3
XV. R = H; R' OCH_3

The stilbene XII required a lengthy synthesis from 3-methyl-4-chloroanisole. Reaction with N-bromosuccinimide gave 2-chloro-5-methoxybenzyl bromide which was converted to 2-chloro-5-methoxybenzaldehyde. The method described above for X then produced the desired stilbene XII. Attempts to demethylate XII to obtain the hydroxystilbene were not successful.

Experimental[10]

2,2-Dichloro-1-(*o*-chlorophenyl)ethanol(IV).—A mixture of 26 g. of VI,[6,7,11] 13.0 g. of amalgamated aluminum[12] and 260 ml. of 90% ethanol was refluxed gently for 3 hr. The mixture was filtered and the residue washed with hot ethanol. Distillation of the filtrate gave a fraction, b.p. 115–123° (0.5 mm.), 13.1 g. (58%); reported[6] b.p. 126–129° (3 mm.).

The *p*-nitrobenzoate melted at 119.2–120.0° after crystallization from ethanol.

Anal. Calcd. for $C_{15}H_{10}Cl_3NO_4$: C, 48.09; H, 2.69; Cl, 28.4. Found: C, 48.06; H, 2.83; Cl, 28.6.

***o,p'*-DDD I.**—(a) On refluxing a mixture containing 17.7 g. of V, 8.6 g. of amalgamated aluminum, and 175 ml. of 90% ethanol as above, the oil remaining after distillation of the ethanol gradually crystallized. Recrystallization from pentane and from 95% ethanol gave 10.5 g. (65.5%) of colorless needles, m.p. 75.5–76.5°; reported[6] m.p. 76–78°. It was identical by mixed melting point and ultraviolet

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(8) References are collected by A. Kaluszyner, *J. Org. Chem.*, **24**, 995 (1959).

(9) G. T. Barry and R. Boyer, *Can. J. Research*, **26B**, 518 (1948).

(10) Melting points of materials submitted for analysis are corrected.

(11) E. D. Bergmann, D. Ginsberg, and D. Lavie, *J. Am. Chem. Soc.*, **72**, 5012 (1950).

(12) W. W. Hartman and R. Phillips, "Organic Synthesis," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p. 233.

spectra with a sample isolated[5] from a by-product of insecticide manufacture. The ultraviolet absorption spectra gave bands at $\lambda_{\max}^{\text{alc}}$ 230, 267.5 mμ (ϵ 16,600, 590).

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.3. Found: C, 52.62; H, 3.02; Cl, 43.9.

(b) A mixture of 22.6 g. of IV, 12.4 g. of chlorobenzene, and 60 ml. of boron trifluoride-saturated sulfuric acid was stirred at 40° for 3 hr. The mixture was cooled and extracted directly with petroleum ether (b.p. 30–60°). The extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave an oily crystalline mass which deposited 15.0 g. (47%) of crystals, m.p. 75.5–76.5°, from pentane. This was identical by mixed melting point and by infrared spectra with the material prepared in (a).

1-(*o*-Chlorophenyl)-2-(*p*-chlorophenyl)ethanol.—*o*-Chlorobenzaldehyde (22.0 g.) was added dropwise over a 30-min. period to a Grignard reagent prepared from 41.0 g. of *p*-chlorobenzyl chloride, 6.1 g. of magnesium, and 200 ml. of ether. The reaction mixture was stirred and refluxed for 1 hr. The addition compound was decomposed with dilute hydrochloric acid and the product extracted with ether. After washing the extract with water and with saturated sodium bisulfite, the solid obtained on evaporation of the ether and recrystallization from petroleum ether (b.p. 30–60°) weighed 30.5 g. (74%) m.p. 93.5–94.5°.

Anal. Calcd. for $C_{14}H_{12}Cl_2O$: C, 62.94; H, 4.53; Cl, 26.5. Found: C, 63.16; H, 4.62; Cl, 26.5.

***trans*-2,4′-Dichlorostilbene(X).**—The above carbinol (7.0 g.) in 30 ml. of dry benzene was treated with 6 ml. of thionyl chloride and 5 drops of pyridine. The solution was refluxed for 1 hr. and the solvent and excess thionyl chloride were removed by distillation *in vacuo*. The residue was added to a solution of 12.0 g. of potassium hydroxide in 120 ml. of 95% ethanol, and the solution was refluxed for 2 hr. Evaporation of the ethanol followed by the addition of water and chilling gave solid which was recrystallized from petroleum ether (b.p. 30–60°). The colorless product weighed 5.3 g. (81%), m.p. 74.0–75.0°, unchanged when mixed with the material prepared below. The infrared spectra gave $\lambda_{\max}^{\text{CCl}_4}$ 10.4 μ (*trans*-CH═CH—) and was identical to the infrared spectra of the material prepared below at all points.

4′-Chloro-2-(*o*-chlorophenyl)acetophenone.—The acetylation of chlorobenzene with *o*-chlorophenylacetic acid gave the acetophenone in 68% yield m.p. 102–110°; reported[13] m.p. 103–107°.

The 2,4-dinitrophenylhydrazone from glacial acetic acid melted at 221–225° (Kofler).

Anal. Calcd. for $C_{20}H_{14}Cl_2N_4O_4$: C, 53.95; H, 3.17; Cl, 15.9. Found: C, 53.93; H, 3.39; Cl, 15.6.

Oxidation of 5.3 g. of this acetophenone with selenium dioxide[14] gave 4.49 g. of 2,4′-dichlorobenzil (80%), m.p. 96–99.5°. Further crystallization from absolute ethanol gave short thick prisms, m.p. 98.8–99.4°.

Anal. Calcd. for $C_{14}H_8Cl_2O_2$: C, 60.24; H, 2.89; Cl, 25.4. Found: C, 59.95; H, 3.11; Cl, 25.1.

The quinoxaline formed short hexagonal prisms from ethanol, m.p. 131.8–132.6°.

Anal. Calcd. for $C_{20}H_{12}Cl_2N_2$: C, 68.39; H, 3.45; Cl, 20.2. Found: C, 67.98; H, 3.57; Cl, 20.1.

A solution of 2.06 g. of 2,4′-dichlorobenzil and 0.85 g. of potassium hydroxide in 9 ml. of ethanol, after refluxing for 2 hr.[14] gave 2,4′-dichlorobenzilic acid (1.67 g. 76%), m.p. 177–187°. After six crystallizations from aqueous ethanol the colorless material melted at 185.7–187.9°.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_3$: C, 56.59; H, 3.39; Cl, 23.9. Found: C, 56.36; H, 3.62; Cl, 23.5.

1-(*p*-Chlorophenyl)-2-(*o*-chlorophenyl)ethanol.—A suspension of 1.2 g. of lithium aluminum hydride in 100 ml. of anhydrous ether was treated dropwise with a solution containing 6.63 g. of 4′-chloro-2-(*o*-chlorophenyl)acetophenone in 50 ml. of tetrahydrofuran. After refluxing for 15 min. on the steam bath and standing overnight, 1:1 hydrochloric acid was added and the product was obtained by extraction with ethyl acetate. The residue, on evaporation of the ethyl acetate, crystallized after chilling and rubbing with cold petroleum ether (b.p. 30–60°). The snow-white, woolly needles (5.44 g., 82%) melted at 57–61° and at 65.1–66.5° after repeated crystallization from petroleum ether (b.p. 60–72°).

Anal. Calcd. for $C_{14}H_{12}Cl_2O$: C, 62.94; H, 4.53; Cl, 26.5. Found: C, 63.04; H, 4.57; Cl, 26.5.

Three grams of this carbinol, treated with thionyl chloride and then potassium hydroxide as previously described gave 2.26 g. (81%) of *trans*-2,4′-dichlorostilbene (X), long thin rods, m.p. 75–77°. Further crystallization from ethanol gave material, m.p. 74.5–75.5°. The ultraviolet spectra gave $\lambda_{\max}^{\text{alc}}$ 228.5, 301.5 mμ (ϵ 15,200; 28,000).

Anal. Calcd. for $C_{14}H_{10}Cl_2$: C, 67.49; H, 4.05; Cl, 28.5. Found: C, 67.83; H, 4.23; Cl, 28.3.

***meso*-α,α′,2,4′-Tetrachlorobibenzyl(VIII).**—Chlorine gas was passed slowly into a solution of 2.26 g. of X in 135 ml. of anhydrous carbon tetrachloride for 1 hr. The solution was allowed to stand overnight. Distillation of the solvent gave a residue which crystallized when rubbed with ice-cold petroleum ether (b.p. 30–60°). The colorless powder melted at 141–142°, 1.1 g. (38%). The sample for analysis, crystallized from 95% ethanol, melted at 141.1–143.0°.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.3. Found: C, 52.58; H, 3.31; Cl, 43.9.

2-Chloro-5-methoxybenzyl Bromide.—A mixture of 62.0 g. of 4-chloro-3-methylanisole, 70.0 g. of *N*-bromosuccinimide, 0.5 g. of benzoyl peroxide, and 150 ml. of carbon tetrachloride was refluxed for 2 hr. and filtered. The residue was washed with carbon tetrachloride and the combined filtrate was distilled. The fraction, b.p. 125–128° (2 mm.), solidified, m.p. 58.0–58.6°; 80.0 g. (86%).

Anal. Calcd. for C_8H_8BrClO: C, 40.79; H, 3.42; total halogen, 49.0. Found: C, 41.09; H, 3.53; total halogen, 49.0.

Alkaline permanganate oxidation of this material gave 2-chloro-5-methoxybenzoic acid, m.p. 173.5–174.5°, unchanged when melted with authentic material.[15]

2-Chloro-5-methoxybenzaldehyde.—A solution of 10.4 g. of the above benzyl bromide and 5.6 g. of hexamethylenetetramine in 20 ml. of chloroform was refluxed for 1 hr. The precipitate obtained was filtered, washed with ether, and dissolved in 100 ml. of 50% aqueous acetic acid. After refluxing for 3 hr., 500 ml. of water was added and the product extracted with ether. The water-washed and dried ethereal extract gave, on evaporation of the ether, 4.8 g. (64%) of colorless needles, m.p. 62–64°; reported m.p. 62–63°.[16]

1-(2-Chloro-5-methoxyphenyl)-2-(*p*-chlorophenyl)ethanol.—The Grignard reagent from 14.5 g. of *p*-chlorobenzyl chloride, 2.34 g. of magnesium, and 50 ml. of ether was combined with 12.5 g. of the above aldehyde. The product, isolated as described above and recrystallized from 60% ethanol, weighed 17.0 g. (78%) m.p. 74.4–75.4°.

Anal. Calcd. for $C_{15}H_{14}Cl_2O_2$: C, 60.02; H, 4.75; Cl, 23.9. Found: C, 60.32; H, 4.53; Cl, 23.7.

***trans*-2,4′-Dichloro-5-methoxystilbene (XII).**—The above carbinol (7.0 g.) with thionyl chloride and pyridine as described for the previous case gave 5.4 g. (82%) of colorless needles m.p. 76.5–77.2°, $\lambda_{\max}^{\text{CCl}_4}$ 10.4 μ (*trans*-CH═CH—). $\lambda_{\max}^{\text{alc}}$ 215.5, 284 mμ (ϵ, 28600, 12800).

Anal. Calcd. for $C_{15}H_{12}Cl_2O$: C, 64.53; H, 4.34; Cl, 25.4. Found: C, 64.21; H, 4.53; Cl, 25.2.

2-Chloro-5-methoxyphenylacetic Acid.—(a) A solution of 17.6 g. of sodium cyanide in 4 ml. of water and 70 ml. of dimethylformamide at 70–75° was treated dropwise with

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[13] M. S. Newman and D. E. Reid, *J. Org. Chem.*, **23**, 665 (1958).

[14] H. Hatt, A. Pilgrim, and W. J. Hurran, *J. Chem. Soc.*, 93 (1936).

[15] W. J. Horton and D. E. Robertson, *J. Org. Chem.*, **25**, 1016 (1960).

[16] D. Ginsberg, *J. Am. Chem. Soc.*, **73**, 702 (1951).

70.7 g. of 2-chloro-5-methoxybenzyl bromide. The temperature was maintained at 75–80°. After stirring for 5 hr. at 70–75°, the filtered solution was concentrated *in vacuo.* The residue was combined with 150 ml. of water and extracted with ether. Distillation of the water-washed and dried extract gave 36.0 g. (76%) b.p. 143–145° (4 mm.). The material crystallized slowly, m.p. 60–63°, and after repeated crystallization from ethanol, melted at 63.8–64.8°.

Anal. Calcd. for C_9H_8ClNO: C, 59.51; H, 4.44; Cl, 19.5. Found: C, 58.64; H, 4.49; Cl, 19.6.

Hydrolysis of 31.8 g. of the crude nitrile by refluxing for 2 hr. in a solution made by combining 23 ml. each of water, acetic acid, and concentrated sulfuric acid gave small colorless needles after crystallization from water, m.p. 103.2–104.0°, 11.4 g. (47%).

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.88; H, 4.52; Cl, 17.7. Found: C, 53.74; H, 4.67; Cl, 17.7.

(b) 2-Chloro-5-methoxybenzoyl chloride, b.p. 122–125° (1 mm.) (14.5 g.), in 25 ml. of anhydrous ether, was added to an ice-cold solution of diazomethane prepared from 15.0 g. of nitrosomethylurea and 7.2 g. of triethylamine. After stirring in the cold for 7 hr., the triethylamine hydrochloride was filtered and washed with ether. Distillation of the solvent at reduced pressure gave 15.0 g. of crude diazo ketone. This, in 100 ml. of dioxane, was added dropwise with stirring to 1.8 g. of silver oxide, 4.5 g. of anhydrous sodium carbonate, and 2.7 g. of sodium thiosulfate in 200 ml. of water at 50–60°. Stirring was continued for 1 hr. and the temperature of the mixture finally raised to 85°. After addition of 20 ml. of 10% sodium hydroxide, the solution was filtered and diluted with 500 ml. of water. The filtrate was washed with benzene and acidified with dilute nitric acid. The cool mixture gave colorless material, 7.3 g. (52%), m.p. 97–100°, identical to the above by mixed melting point. Attempted acylation of chlorobenzene with 2-chloro-5-methoxyphenylacetylchloride failed.

2′-Chloro-2-(*p*-chlorophenyl)-4′,5′-dimethoxyacetophenone (XIV).—To polyphosphoric acid, prepared by the addition of 49 ml. of 85% phosphoric acid to 76.5 g. of phosphorus pentoxide, was added 8.5 g. of *p*-chlorophenylacetic acid and 8.6 g. of 4-chloroveratrole. The mixture was then heated on the steam bath for 2 hr. with occasional shaking. After decomposition of the complex with ice, the product was extracted with ether and the ether solution was washed with 10% sodium bicarbonate and with water. The dried ether solution gave 6.8 g. (42%) of product m.p. 57–61°. Repeated crystallization from cyclohexane gave material m.p. 84.9–86.1°. From the sodium bicarbonate washings, 4.8 g. of *p*-chlorophenylacetic acid was recovered.

Anal. Calcd. for $C_{16}H_{14}Cl_2O_3$: C, 59.01; H, 4.34; Cl, 21.8. Found: C, 58.86; H, 4.54; Cl, 21.5.

1-(2-Chloro-4,5-dimethoxyphenyl)-2-(*p*-chlorophenyl)ethanol.—(a) To a solution of 12.0 g. of the above ketone in 150 ml. of methanol was added slowly 1.4 g. of sodium borohydride in 50 ml. of methanol. After refluxing for 1 hr. the mixture was treated with 30 ml. of 15% hydrochloric acid. The resulting mixture was concentrated *in vacuo,* treated with water and extracted with ether. On evaporation of the ethereal extract, the residue was recrystallized from ethanol to give 8.5 g. (70%) of colorless material, m.p. 131.6–132.8°.

Anal. Calcd. for $C_{16}H_{16}Cl_2O_3$: C, 58.73; H, 4.93; Cl, 21.7. Found: C, 58.59; H, 5.09; Cl, 21.6.

(b) To a suspension of 10.0 g. of 6-chloroveratraldehyde[16] in 100 ml. of ether was added the Grignard reagent prepared from 8.5 g. of *p*-chlorobenzyl chloride, 1.2 g. of magnesium, and 50 ml. of ether. The reaction mixture was treated as described for 1-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethanol. The yield was 4.5 g. (27%), m.p. 130.6–132.0° unchanged when mixed with the material prepared above.

***trans*-2,4′-Dichloro-4,5-dimethoxystilbene(XI).**—Conversion of 4.5 g. of the above carbinol to the chloride and dehydrochlorination as described for 2,4′-dichlorostilbene gave 2.3 g. (54%) of colorless plates, m.p. 104.8–105.4°; λ_{max}^{alc} 212, 302, 332 mμ (ε 23,400; 30,100; 34,200); $\lambda_{max}^{CCl_4}$ 10.4 μ (*trans*-CH=CH—).

Anal. Calcd. for $C_{16}H_{14}Cl_2O_2$: C, 62.15; H, 4.56; Cl, 22.9. Found: C, 62.24; H, 4.73; Cl, 23.2.

2-(*o*-Chlorophenyl)-2-(*p*-chlorophenyl)acetaldehyde (VII).—A suspension of 63.6 g. of 2,4′-dichlorobenzophenone in 49.0 g. of ethyl chloroacetate was cooled in an ice–salt bath. The air was replaced by nitrogen and 10.0 g. of sodium hydride was added over a 4-hr. period. The reaction mixture was stirred continuously overnight and allowed to come to room temperature. It was then combined with ice and 1:1 hydrochloric acid and the product was extracted into benzene. After addition of 200 ml. of ethanol to the benzene solution, the solvents were distilled *in vacuo* and the residue, in a solution containing 40 g. of potassium hydroxide in 400 ml. of water, was refluxed for 2.5 hr. The alkaline solution was washed twice with benzene, acidified and the precipitated acid collected by benzene extraction. The washed and dried benzene solution was distilled *in vacuo* with carbon dioxide evolution at 120° (64 mm.). The fraction, b.p. 171–173° (0.2 mm.), weighed 41 g. (62%). The analyzed sample boiled at 155–156° (0.1 mm.).

Anal. Calcd. for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80; Cl, 26.7. Found: C, 63.46; H, 3.71; Cl, 26.8.

The 2,4-dinitrophenylhydrazone of VII, from ethyl acetate–ethanol melted at 177.5–178.0°.

Anal. Calcd. for $C_{20}H_{14}Cl_2N_4O_4$: C, 53.95; H, 3.17; Cl, 15.9. Found: C, 54.02; H, 3.27; Cl, 15.8.

Permanganate in dilute sulfuric acid oxidized the above aldehyde to 2,4′-dichlorodiphenylacetic acid (36%), m.p. 108.2–109.0° after crystallization from cyclohexane.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59. Found: C, 59.90; H, 3.67.

2-(*o*-Chlorophenyl)-2-(*p*-chlorophenyl)ethanol.—To a solution containing 1.3 g. of lithium aluminum hydride in 140 ml. of ether was added 12 g. of the above aldehyde in 60 ml. of ether. After refluxing for 3 hr. the product was isolated in the usual manner and distilled, b.p. 168–174° (0.4 mm.) (7 g. 58%).

Anal. Calcd. for $C_{14}H_{12}Cl_2O$: C, 62.94; H, 4.53. Found: C, 62.79; H, 4.46.

1-Chloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane.—The above alcohol (8.5 g.) in 16 ml. of anhydrous pyridine was treated with 7.8 ml. of thionyl chloride at 0° followed by heating for 5 min. on the steam bath. It was then allowed to stand for 0.5 hr. at room temperature. The reaction was then poured into ice water and the product was obtained by ether extraction. The ether solution was washed with water, dilute hydrochloric acid, and aqueous sodium bicarbonate in turn. On distillation, the fraction, b.p. 156–160° (0.2 mm.), weighed 6.3 g. (69%); λ_{max}^{alc} 221, 266 mμ (ε 18,300; 799).

Anal. Calcd. for $C_{14}H_{11}Cl_3$: C, 58.87; H, 3.88; Cl, 37.2. Found: C, 59.51; H, 3.91; Cl, 36.2.

Phosphorus Pentachloride on VII.—The aldehyde VII (19 g.) was added dropwise with mechanical stirring to 24.6 g. of phosphorus pentachloride without cooling. The mixture was then stirred and heated at 50° for 5 hr. Phosphorus oxychloride was then removed by distillation *in vacuo* and the residue, in benzene solution, was washed well with 10% aqueous sodium bicarbonate. The residue, after distillaiton of the benzene *in vacuo,* could not be distilled. Petroleum ether (b.p. 30–60°) was added and the material deposited crystals (2 g.) on standing in the refrigerator overnight. These melted at 141–143° after crystallization from ethanol and did not depress the melting point of VIII prepared as described previously. The infrared spectra of the two materials were found to be identical.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.54; H, 3.15; Cl, 44.3. Found: C, 52.82; H, 3.31; Cl, 43.9.

A portion of the material soluble in petroleum ether (4.6 g.) was refluxed for 4 hr. with a solution of 2.3 g. of potassium hydroxide in 40 ml. of ethanol. The cooled solution was filtered from a small amount of water-soluble phosphate salt and the diluted ethanol was extracted with benzene. The residue after distillation of the benzene was refluxed for 2 hr. with a solution containing 2 g. of chromic acid in 30 ml. of acetic acid. By benzene extraction 22.8 mg. of *p*-chlorobenzoic acid and 1.0 g. 2,4′-dichlorobenzil, m.p. 98.8–99.4°, was obtained. The latter did not depress the melting point of the 2,4′-dichlorobenzil previously prepared and the infrared spectra were identical.

Conformational Analysis. XXX. The Cyano Group[1,2]

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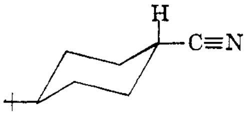
The standard free energy of a cyano group in the axial position on a cyclohexane ring (relative to the equatorial) has been determined by equilibrating the *cis* and *trans* isomers of 4-*t*-butylcyclohexyl cyanide at 66° and the experimental value is 0.25 kcal./mole.

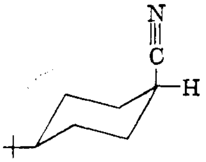
Conformational analysis has been put on an increasingly quantitative basis by the determination of the relative standard free energies of various groups in the axial and equatorial positions on a cyclohexane ring.[3] A group which has not been previously studied in this respect is the cyano group. Information on this group was of particular interest because it could be used to find a radius for carbon which would be suitable for calculations of the van der Waals type.

The experimental method was straightforward, and involved equilibrating the *cis* and *trans* isomers of 4-*t*-butylcyclohexyl cyanide (I). It can safely be assumed that the *t*-butyl group occupies an equatorial position and that the *cis* and *trans* isomers possess the conformations indicated in the figure.[4] The *cis* and *trans* isomers of 4-*t*-butylcyclohexyl cyanide were prepared from the known corresponding acids[5] by conversion of the acid to the acid chloride with thionyl chloride, reaction of the acid chloride with ammonia to give the amide, and dehydration of the latter with thionyl chloride. The nitrile obtained in each case was analyzed by gas phase chromatography on a Tide column, and it was noted that considerable epimerization had occurred and a mixture of the two nitriles was in fact obtained. The *trans* acid, however, led predominantly to one nitrile which was assigned the *trans* structure, while the *cis* acid led predominantly to the other nitrile, which was assigned the *cis* structure. Pure samples of the nitriles were obtained by vapor phase chromatography. When pure, both the *cis* and *trans* isomers proved to be crystalline and melted at 60° and 37°, respectively.

Equilibrium was established in tetrahydrofuran solvent at 66° using potassium *t*-butoxide as catalyst. The equilibrium was approached from both sides, and the mixture obtained in each case contained 59% of the *trans* isomer. The ΔF° for the cyano group moving from the equatorial to the axial position was thus +0.25 kcal./mole.



It



Ic

As an independent method for carrying out the determination of the conformational energy of the cyano group, the n.m.r. method introduced by Eliel[6] was considered. Compounds Ic and It must show nuclear resonance characteristic respectively of equatorial and axial protons attached to the cyano bearing carbon. The unsubstituted cyclohexyl cyanide must show the corresponding resonance at a field which is between these extremes, and which is a quantitative reflection of the relative concentrations of the axial and equatorial conformers.

Experimentally it was found that Ic showed a signal at 7.09 τ which corresponded in area to one proton and was assigned to the proton at C-1. With compound It, the corresponding proton showed a signal which was in the region of other resonance and could not be identified with certainty. The resonance definitely occurred above $\tau = 7.55$, however. For cyclohexyl cyanide itself, the signal was observed at 7.46 τ. These values indicate that there is at least 20% of axial cyanide in the latter compound, and although a quantitative value cannot be determined from these data, an upper limit for the energy of the cyano group can be set as 0.8 kcal./mole.

A theoretical approach to the energy of the axial cyano group can be made in the following way. Increasing the van der Waals radius in a series of

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(1) Paper XXIX, N. L. Allinger and S. Hu, *J. Org. Chem.*, **26**, 3417 (1962).

(2) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(3) For a recent tabulation of groups for which such determinations have been carried out, together with their free energies, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, 1962, p. 236.

(4) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(5) H. H. Lau and H. Hart, *ibid.*, **81**, 4897 (1959).

(6) E. L. Eliel, *Chem. Ind.* (London), 568 (1959).