Synthesis of Compounds Related to 2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-1,1-dichloroethane[1]

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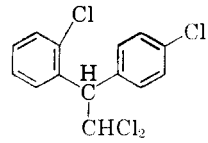
Received Feburary 19, 1962

A number of analogs of 2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-1,1-dichloroethane have been prepared by unambiguous synthetic methods for evaluation in the treatment of metastatic adrenal carcinoma.

Recent reports indicate that 2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-1,1-dichloroethane (*o,p'*-dichlorodiphenyldichloroethane, or *o,p'*-DDD, I) has produced favorable clinical responses and in some cases



I

complete regression of adrenocortical carcinoma in humans.[2] The toxicity of this compound, together with the damaging effect on the normal adrenal cortex, suggested the search for related compounds with better differentiating action between the normal and malignant cells of the adrenal cortex.

Up to the present time, *o,p'*-DDD (I) has generally been obtained from technical 2,2 - bis(*p* - chlorophenyl) - 1,1 - dichloroethane (*p,p'*-DDD) by fractional crystallization in 7–8% recovery.[3] The reported yield of synthetic *o,p'*-DDD, from chlorobenzene and 1-(*o*-chloro-

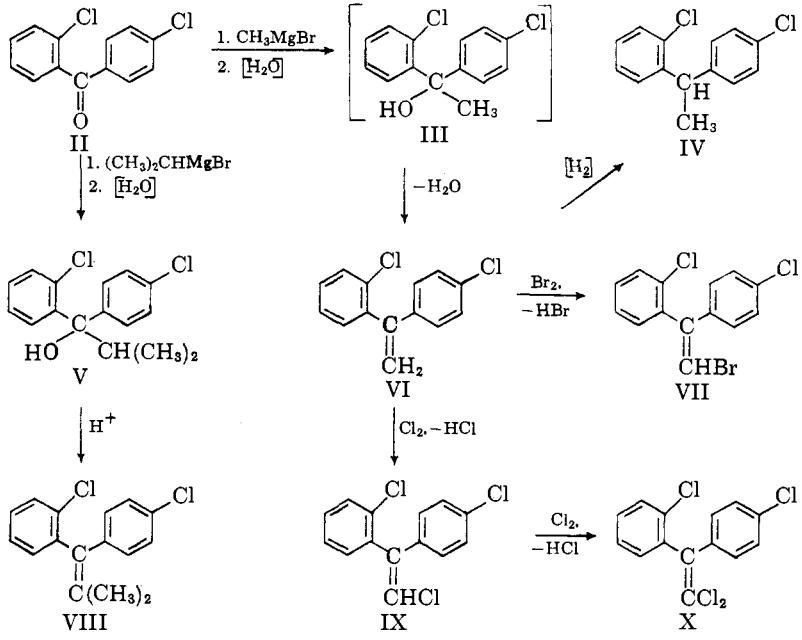
(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) J. Nichols and G. R. Henniger, *Exptl. Med. Surg.*, **15**, 310 (1957); (b) C. Cueto and J. H. U. Brown, *Endocrinology*, **62**, 224, 334 (1958); (c) L. F. Kumagai and C. D. West, *Clin. Res.*, **8**, 110 (1960); (d) L. F. Kumagai and C. D. West, *Proc. Am. Assoc. Cancer Res.*, **3**, 127 (1960); (e) T. Verdon, J. Bruton, R. H. Herman, and W. R. Beisel, *Clin. Res.*, **8**, 379 (1960); (f) D. M. Bergenstal, M. B. Lipsett, R. H. Moy and R. Herz, "Biological Activities of Steroids in Relation to Cancer," G. Pincus and E. P. Vollmer, ed., Academic Press, New York, 1960, p. 463; (g) D. M. Bergenstal, R. Herz, M. B. Lipsett and R. H. Moy, *Ann. Int. Med.*, **53**, 672 (1960); (h) R. H. Moy, *J. Lab. Clin. Med.*, **58**, 296 (1961); (i) R. Herz, "Canadian Cancer Conference," Vol. 4, R. W. Begg, ed., N. Y. Academic Press, 1961, p. 399; (j) M. E. Sears, in "Cancer Chemotherapy," R. L. Clark, ed., Charles C Thomas Co., Springfield, Ill., 1961, p. 175; (k) R. G. Rose, *ibid.*, p. 187.

(3) S. J. Cristol and H. L. Haller, *J. Am. Chem. Soc.*, **70**, 1323 (1948).

phenyl)-2,2-dichloroethanol, was less than 3%.[4] The compounds described in this paper have all been prepared by unequivocal synthetic methods and their yields are, in general, quite satisfactory.

Addition of methyl magnesium bromide to 2,4'-dichlorobenzophenone (II)[5] followed by hydrolysis gave an unstable tertiary alcohol (III), which was dehydrated spontaneously during distillation to give 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)ethylene (VI) in 85% yield.



Hydrogenation of VI readily yielded 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)ethane (IV).[6] Treatment of compound VI with chlorine or bromine in carbon tetrachloride followed by spontaneous dehydrohalogenation gave 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2-chloroethylene (IX) and 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2-bromoethylene (VII), respectively, in good yield. Compound IX was chlorinated and then dehydrohalogenated to yield 1-(*o*-chlorophenyl)-

(4) (a) H. L. Haller, P. D. Bartlett, N. L. Drake, M. S. Newman, S. J. Cristol, C. M. Eaker R. A. Hayes, G. W. Kilmer, B. Magerlein, G. P. Mueller, A. Schneider and W. Wheatly, *J. Am. Chem. Soc.*, **67**, 1591 (1945); (b) I. P. Tsukervanik and T. G. Garkovets, *Zhur. Obshchei Khim.*, **25**, 919 (1955).

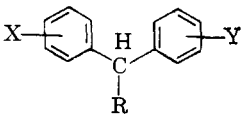
(5) (a) J. F. Norris and W. C. Twieg, *Am. Chem. J.*, **30**, 392 (1903); (b) R. F. Nystrom and C. R. A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).

(6) (a) This compound has been mentioned by R. B. March, R. L. Metcalf and L. L. Lewallen, *J. Econ. Entomology*, **45**, 851 (1952), but its preparative method was not given; (b) it has also been erroneously recorded in *C.A.*, **50**, 3347 (1956), *cf.* ref. 4(b).

1-(*p*-chlorophenyl)-2,2-dichloroethylene (X),[4] m.p. 77–78°. The presence of four negatively substituted groups on both sides of the carbon-carbon double bond caused resistance to hydrogenation[7] under various conditions.

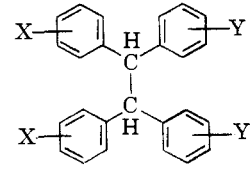
The addition of isopropylmagnesium bromide to 2,4′-dichlorobenzophenone (II) and subsequent hydrolysis gave the corresponding tertiary alcohol (V) in 70% yield. This compound appeared to be more stable than the corresponding methyl derivative (III). Hyperconjugation is presumed to be responsible for the difference of stability between these two compounds. Dehydration of V was effected by treatment with concentrated sulfuric acid or potassium hydrogen sulfate at elevated temperature. The resulting compound, 1-(*o*-chlorophenyl) - 1 - (*p* - chlorophenyl) - 2,2 - dimethylethylene (VIII), unlike compound VI, absorbed hydrogen very slowly in the presence of various catalysts and resulted in the loss of chlorine atoms from the phenyl rings. This probably could be explained by the weakening of the C-Cl bond through the conjugated system by the two methyl groups.

Addition of substituted phenylmagnesium bromides to substituted benzaldehydes followed by hydrolysis yielded the corresponding benzhydrols (XI). Thionyl chloride converted the secondary alcohol to the corresponding halide (XII). Compound XII then was converted into a Grignard compound and treated with ethyl orthoformate to give a mixture of aldehyde (XIV) and a dimeric compound, 1,1,2,2-tetra(substituted-phenyl)ethane (XVIII). When the Grignard compound of XII was allowed to react with carbon dioxide, the corresponding di(substituted-phenyl)acetic acid (XV) was formed together with a good yield of the dimeric compound XVIII. Thionyl chloride readily converted the acid (XV) into the acid chloride (XVI), which gave the corresponding amide (XVII) in good yield.



XI, R = OH
XII, R = Cl
XIII, R = OCH_3
XIV, R = CHO
XV, R = COOH
XVI, R = COCl
XVII, R = $CONH_2$

(a) X = *o*-Cl, Y = *p*-Cl
(b) X = *o*-Cl, Y = H
(c) X = *p*-Cl, Y = H



XVIII

(7) (a) A. Mailhe and A. Sabrou, *Bull. Soc. Chim.*, **47**, 350 (1930); (b) A. Mailhe, *Tech. moderne*, **23**, 373, 460 (1931).

The methyl ethers (XIII) were prepared either from the benzhydrols (XI) with concentrated hydrochloric acid in methanol or from the halides (XII) and sodium methoxide. The second method is preferred because the product isolated was obtained in good yield and very high purity.

Preliminary endocrinological studies showed that compounds IV, V, VI, VII, IX, XIa, XIb, XIc, XIIa, and XIIc failed to affect the secretion of 17-hydroxycorticoids (Porter-Silber)[8] by the adrenal gland in the dog.[9] However, one of the compounds, 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)ethane [NSC-60813] (IV), alone in the series affected adrenal histology, there being substantial lipoid accumulation in the *zona fasciculata* and the *zona reticularis*. Such an effect resembles the activity of a compound like Amphenone B[10] rather than that of *o,p'*-DDD, which tends to cause breakdown of the cells of the *zona fasciculata*.

Experimental[11]

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)ethylene (VI).[12]—To 150 ml. of a stirred ether solution of methylmagnesium iodide (prepared from 7.5 g. of magnesium and 44 g. of methyl iodide) was added, dropwise, during 1 hr., a solution of 50 g. (0.2 mole) of 2,4'-dichlorobenzophenone (II)[5] in 150 ml. of dry ether. The mixture was refluxed for 1 hr., cooled, and decomposed cautiously with 150 ml. of 10% hydrochloric acid. The layers were separated. The aqueous phase was extracted with ether (3 × 60 ml.) and the combined ether layers were washed successively with water, 5% sodium bicarbonate and water. The dried (Na_2SO_4), filtered ether solution was distilled to give 43 g. (85%) of colorless oil, b.p. 142–144° (3 mm.); $\lambda_{max}^{ethanol}$ 238 mμ (ε 13,300), 252 mμ (ε 14,100).

Anal. Calcd. for $C_{14}H_{10}Cl_2$: C, 67.6; H, 4.0. Found: C, 67.2; H, 4.3.

1,1-Di(*o*-chlorophenyl)ethylene.—Ethyl acetate (22 g.) in 100 ml. of dry ether was added dropwise to an ethereal solution of *o*-chlorophenylmagnesium bromide (prepared from 96 g. of *o*-bromochlorobenzene and 13.2 g. of magnesium in 250 ml. of dry ether). The mixture was refluxed for 6 hr. and decomposed with 10% hydrochloric acid. The ether layer was worked up as described previously and distilled to give 19 g. of the product, b.p. 140–145° (1.8 mm.).

Anal. Calcd. for $C_{14}H_{10}Cl_2$: C, 67.6; H, 4.0. Found: C, 67.3; H, 3.9.

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)ethane (IV).[8]—A solution of 25 g. of VI in 100 ml. of absolute ethanol in the presence of 2.5 g. of 5% palladium on charcoal

(8) C. C. Porter and R. H. Silber, *J. Biol. Chem.*, **185**, 201 (1950).

(9) Information kindly supplied by Drs. Erwin P. Vollmer and W. W. Tullner of the National Cancer Institute, Bethesda 14, Maryland.

(10) (a) J. J. Chart and H. Sheppard, *J. Med. Pharm. Chem.*, **1**, 407 (1959); (b) J. Nichols, "The Adrenal Cortex," H. D. Moon, ed., Paul B. Hoeber, Inc., N. Y., 1961, p. 84.

(11) All melting points were taken on a Thomas-Hoover melting point apparatus. The infrared spectra were determined on the Perkin-Elmer Infracord and the ultraviolet absorption on the Beckman DK-2.

(12) This compound has been reported by G. T. Barry and R. Boyer, *Canad. J. Research*, **26B**, 511 (1948), as a minor product of a reaction, with no details of preparation.

was hydrogenated at room temperature. The theoretical amount of hydrogen was absorbed within 5 min. The catalyst was filtered and the solvent evaporated. The oily residue was distilled *in vacuo* to give 21 g. (84%) of colorless oil, b.p. 127–129° (1.5 mm.).

Anal. Calcd. for $C_{14}H_{12}Cl_2$: C, 67.2; H, 4.8. Found: C, 67.1; H, 4.9.

2-Bromo-1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)ethylene (VII).—To a stirred solution of 25 g. of VI in 100 ml. of carbon tetrachloride was added dropwise a solution of 16 g. of bromine in 50 ml. of carbon tetrachloride at room temperature. After 2 hr. gaseous hydrogen bromide started to escape slowly through the condenser. Stirring was continued for 2 days. The solvent was removed and the residue distilled to give 24 g. (74%) of VII, b.p. 154–157° (1.5 mm.); $\lambda_{max}^{ethanol}$ 261 mμ (ε 18,000).

Anal. Calcd. for $C_{14}H_9BrCl_2$: C, 51.4; H, 2.8. Found: C, 51.2; H, 2.8.

2-Chloro-1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)ethylene (IX) was similarly prepared from 16 g. of chlorine, 50 g. of VI and 500 ml. of carbon tetrachloride to give 50 g. (89%) of IX, b.p. 152–154° (1.7 mm.); $\lambda_{max}^{ethanol}$ 255 mμ (ε 16,700).

Anal. Calcd. for $C_{14}H_9Cl_3$: C, 59.4; H, 3.2. Found: C, 59.1; H, 3.4.

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethylene (X).—To a stirred solution of 12 g. of chlorine in 150 ml. of carbon tetrachloride was added 34 g. of IX dissolved in 80 ml. of the same solvent. The reaction mixture was stirred for 2 days and worked up similarly to give 34 g. (89%) of viscous oil, b.p. 178–180° (3.8 mm.). The product solidified upon standing. Recrystallization from ethanol yielded white crystals, m.p. 77–78° (lit., m.p. 78.4–79.5°,[4a] m.p. 77–78°[4b]); $\lambda_{max}^{ethanol}$ 246 mμ (ε 14,000).

Anal. Calcd. for $C_{14}H_8Cl_4$: C, 53.2; H, 2.5. Found: C, 53.1; H, 2.7.

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2-methyl-1-propanol (V).—A solution of 200 g. of 2,4′-dichlorobenzophenone (0.8 mole) in 500 ml. of dry ether was slowly added to the isopropyl Grignard reagent, prepared from 185 g. (1.5 mole) of 2-bromopropane and 37 g. of magnesium in 500 ml. of ether. The reaction mixture was refluxed for 5 hr., decomposed with acid and extracted with ether. The product, 148 g. (62%), was obtained as a pale yellow oil, b.p. 179–182° (3.5 mm.); $\lambda_{max}^{ethanol}$ 258 mμ (ε 4,500). The compound possesses a strong hydroxyl band in the infrared region at 2.88 μ.

Anal. Calcd. for $C_{16}H_{16}Cl_2O$: C, 65.3; H, 5.4. Found: C, 64.9; H, 5.1.

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2-methylpropene (VIII).—A mixture of 55 g. (0.15 mole) of V and 1.5 ml. of concd. sulfuric acid was heated at 160° for 3 hr., cooled, and extracted with ether. The ether extract was washed, dried, and distilled to give 25 g. of VIII (60%), b.p. 151° (3 mm.); $\lambda_{max}^{ethanol}$ 249 mμ (ε 12,000).

Anal. Calcd. for $C_{16}H_{14}Cl_2$: C, 69.5; H, 5.1. Found: C, 69.3; H, 5.1.

This compound was also prepared in 53% yield using 5 g. of potassium hydrogen sulfate instead of sulfuric acid.

Benzhydrols (XI) were prepared according to the method of Faith, *et al.*[13] The use of more ether (2–3 times) and a longer reflux time (3–4 hr.) gave considerably better yields (see Table I).

Diphenylchloromethanes (XII) were prepared by refluxing the corresponding benzhydrol in thionyl chloride (1:4 by weight) for 1 hr. The product was then fractionally distilled after removal of the excess thionyl chloride (see Table I).

Reaction between (*o*-Chlorophenyl)-phenylmethylmagnesium Chloride and

(13) H. E. Faith, M. E. Bahler and H. J. Florestano, *J. Am. Chem. Soc.*, **77**, 543 (1955).

Ethyl Orthoformate.—To a suspension of 3.8 g. of magnesium and several crystals of iodine in 100 ml. of dry ether was added, dropwise with stirring, 36 g. (0.15 mole) of XIIb. The mixture was refluxed for 1 hr. and cooled. To this was added, in the course of 10 min., 18 g. (0.12 mole) of ethyl orthoformate. The solution was refluxed for 6 hr. with stirring. It was then decomposed with acid and the organic layer was separated. After evaporation of the ether the residual syrup was triturated with 60 ml. ethanol to yield 12 g. (39%) of **1,2-di(*o*-chlorophenyl)-1,2-diphenylethane** (XVIIIb) as a white solid, m.p. 179–181° (from ethanol).

Anal. Calcd. for $C_{26}H_{20}Cl_2$: C, 77.5; H, 5.0. Found: C, 77.5; H, 5.1.

The filtrate from the triturated mixture was evaporated and the residue was distilled to give 1.5 g. (5%) of (*o*-chlorophenyl)phenylacetaldehyde (XIVb), b.p. 133° (1 mm.). No ultraviolet absorption was observed.

Anal. Calcd. for $C_{14}H_{11}ClO$: C, 73.0; H, 4.8; Cl, 15.5. Found: C, 73.2; H, 5.1; Cl, 15.8.

(*o*-Chlorophenyl)-(*p*-chlorophenyl)methoxymethane (XIIIa).—A solution of 27.2 g. (0.1 mole) of XIIa in 100 ml. of methanol was added to a sodium methoxide solution (prepared from 3.5 g. of sodium and 100 ml. of methanol). The mixture was refluxed for 4 hr., cooled and filtered. The filtrate was evaporated, the resulting residue was poured into water and the aqueous solution extracted with ether to give, by distillation, 23.5 g. of XIVa (other analogs were similarly prepared, see Table I).

This compound was also obtained in 77% yield by refluxing (4 hr.) 25.3 g. of XIa in 100 ml. of methanol containing 10 ml. of concd. hydrochloric acid. The product, b.p. 136–139° (1.9 mm.), however, still contained a trace of XIa (detected by the infrared absorption spectra).

2-(*o*-Chlorophenyl)-2-(*p*-chlorophenyl)acetic acid (XVa).—To a suspension of 3.2 g. of magnesium and 0.5 ml. of ethyl bromide in 50 ml. of dry ether was slowly added 27.1 g. of XIIa dissolved in 100 ml. of ether. The mixture was refluxed for 30 min. To this mixture was added, in 20 min., 80 g. of solid carbon dioxide. After stirring for 1 hr. the reaction mixture was decomposed with 200 ml. of 10% hydrochloric acid. The layers were separated and the aqueous portion extracted with ether. The combined organic solution was extracted with 10% of sodium hydroxide and the alkaline extraction acidified with acid. The oily product was then extracted with 3 × 50 ml. of ether. The evaporated ether extract gave 4.2 g. (15%) of white solid, m.p. 95–98°. This solid was washed with petroleum ether and recrystallized from a mixture of water and ethanol to give pure XVa, m.p. 106–108°.[16] This compound transmits ultraviolet light completely. It possesses a strong carbonyl band at 5.81μ in the infrared region.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_2$: C, 59.8; H, 3.6; Cl, 25.3. Found: C, 59.1; H, 3.6; Cl, 25.2.

The portion remaining in ether after sodium hydroxide extraction was evaporated and the residue was recrystallized from ethanol to give 3.5 g. of 1,2-bis(*o*-chlorophenyl)-1,2-bis(*p*-chlorophenyl)ethane (XVIIIa), m.p. 209–211°; $\lambda_{max}^{ethanol}$ 230 mμ (ϵ 30,800).

Anal. Calcd. for $C_{26}H_{18}Cl_4$: C, 66.2; H, 3.8. Found: C, 66.2; H, 3.9.

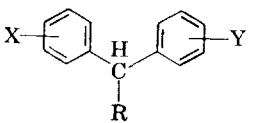
(14) (a) M. P. J. Montagne and J. M. V. Charante, *Rec. Trav. Chim.*, **31**, 298 (1912); (b) M. P. J. Montagne, *ibid.*, **26**, 253 (1907).

(15) J. F. Norris and C. Banta, *J. Am. Chem. Soc.*, **50**, 1804 (1928).

(16) Prepared by S. J. Cristol and H. L. Haller, *J. Am. Chem. Soc.*, **67**, 2222 (1945) in low yield from *o,p'*-DDT.

TABLE I

DERIVATIVES OF DIPHENYLMETHANE



X	Y	R	Molecular Formula	B.p. (mm.)	Yield %	U.v. Absorption [Ethanol] λ_{max} mμ	ϵ	Analyses —Calcd.— C	H	—Found— C	H
o-Cl	*p*-Cl	OH	$C_{13}H_{10}Cl_2O$	146–148 (4)[a]	86	219	18,500	61.7	4.0	61.4	4.0
						265	1,000				
o-Cl	H	OH	$C_{13}H_{11}ClO$	138–140 (2)[b]	80	[c]	—	71.5	5.1	71.7	5.1
p-Cl	H	OH	$C_{13}H_{11}ClO$	150–151 (2.6)[d]	78	224	16,200	71.5	5.1	71.2	5.2
						260	880				
o-Cl	*p*-Cl	Cl	$C_{13}H_9Cl_3$	145–156 (1.9)	96	230	19,300	57.5	3.3	57.3	3.4
o-Cl	H	Cl	$C_{13}H_{10}Cl_2$	125–156 (2)[e]	95	260	2,400	65.8	4.2	65.5	4.4
p-Cl	H	Cl	$C_{13}H_{10}Cl_2$	124–125 (1.2)[f]	93	218	21,300	65.8	4.2	65.7	4.3
o-Cl	*p*-Cl	CH_3O	$C_{14}H_{12}Cl_2O$	129–130 (1.3)	88	[c]	—	62.9	4.5	62.5	4.6
o-Cl	H	CH_3O	$C_{14}H_{13}ClO$[g]	110–112 (1.2)	88	[c]	—	72.3	5.6	71.8	5.6
p-Cl	H	CH_3O	$C_{14}H_{13}ClO$[h]	110–112 (1)	95	224	17,500	72.3	5.6	72.2	5.7

[a] M.p. 76–78° (from hexane), lit.[13] m.p. 74–76°. [b] M.p. 65–67° (from hexane), lit.[14a] m.p. 65°. [c] Does not possess absorption spectra in the ultraviolet region. [d] M.p. 60–62° (from hexane), lit.[14b] m.p. 62°. [e] Lit.[15] dec. 90°. [f] Lit.[15] b.p. 172–173° (6 mm.). [g] Calcd.: Cl, 15.2. Found: Cl, 14.9. [h] Calcd.: Cl, 15.2. Found: Cl, 15.0.

The filtrate from the base-insoluble portion was distilled *in vacuo* to give 2.8 g. of (*o*-chlorophenyl)-(*p*-chlorophenyl)methane, b.p. 144–145° (3.5 mm.).

Anal. Calcd. for $C_{13}H_{10}Cl_2$: C, 65.8; H, 4.2; mol. wt., 237. Found: C, 65.6; H, 4.5; mol. wt., 241.

2-(*o*-Chlorophenyl)-2-phenylacetic acid (XVb) was similarly prepared from 36 g. (0.15 mole) of XIIb. Recrystallization from water gave 15 g. (40% yield) of XVb as white crystals, m.p. 106–108°.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.2; H, 4.5. Found: C, 68.4; H, 4.6.

The corresponding 1,2-bis(*o*-chlorophenyl)-1,2-diphenylethane (XVIIIb) was similarly isolated (6.2 g.) from the base-insoluble ethereal layer, m.p. 179–180°. This compound is identical with that prepared from XIIb and ethyl orthoformate, as described previously.

2-(*o*-Chlorophenyl)-2-phenylacetamide (XVIIb).—A mixture of 12 g. of XVb and 100 ml. of thionyl chloride was refluxed for 1 hr. The excess thionyl chloride was evaporated *in vacuo* and the residual syrup distilled to give 10.6 g. (82%) of the acid chloride (XVIb), b.p. 150–154° (2.8 mm.).

Seven grams of this acid chloride was added dropwise, with stirring, to 80 ml. of 10% ethanolic ammonia. The mixture was then boiled gently for 10 min., filtered (ammonium chloride), and evaporated to a syrup. This syrup was triturated with heptane to give 6.2 g. (95% yield) of solid, m.p. 102–105°. Recrystallization from a mixture of heptane and benzene gave XVIIb as white needles, m.p. 105–106°. This compound does not absorb light in the ultraviolet region.

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.5; H, 4.9; N, 5.7. Found: C, 68.8; H, 5.0; N, 5.6.

Acknowledgment:—The authors wish to express their appreciation to Drs. John Nichols, Roland K. Robins, Ronald B. Ross, Erwin P. Vollmer, and Harry B. Wood, Jr., for their information and encouragement and to Mr. Wayne H. Nyberg, Miss Phyllis G. Shaul and Mrs. Carol R. Tuttle for their valuable assistance in performing analytical and instrumental measurements.