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Research Articles

Synthesis of ^{14}C-Labeled Isomers of Dichlorodiphenyldichloroethanes (DDD)

By R. E. COUNSELL and ROBERT E. WILLETTE

1,1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl-^{14}C)ethane (*o,p'*-DDD-^{14}C), 1,1-dichloro-2-(*m*-chlorophenyl)-2-(*p*-chlorophenyl-^{14}C)ethane (*m,p'*-DDD-^{14}C), and 1,1-dichloro-2,2-bis-(*p*-chlorophenyl-^{14}C)ethane (*p, p'*-DDD-^{14}C) were synthesized by acid catalyzed condensation of chlorobenzene-^{14}C with excess 2,2-dichloro-1-(*o*-, *m*-, and *p*-chlorophenyl)ethanols. The carbinols were prepared in good yields by reverse addition of the chlorophenyl Grignard reagent to dichloroacetaldehyde. Purity was determined by thin-layer and gas chromatography. The I.R., U.V., and NMR spectra of these compounds are discussed.

INTEREST in the development of radiopharmaceuticals suitable for adrenal photoscanning prompted the present study. For this purpose, an agent that selectively concentrated in the adrenal and could be labeled with a γ-emitting radionuclide was necessary. This paper describes the synthesis of ^{14}C labeled isomers of 1,1-dichloro-2,2-bis-(chlorophenyl)ethane (DDD) to be utilized in tissue distribution studies. The synthesis of other DDD isomers and ^{125}I and ^{131}I isomers will be reported elsewhere.

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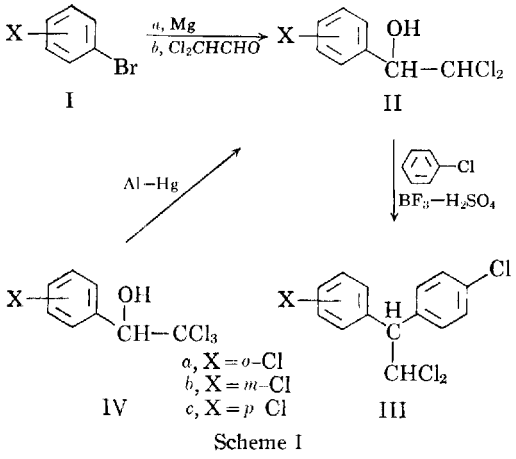
TABLE I.—2,2-DICHLORO-1-(CHLOROPHENYL)ETHANOLS

Isomer	moles (n)	Yield, %	B.p., °C./mm.
ortho	0.2	35	105–120/0.4[a]
meta	0.13	53	81–84/0.04[b]
para	0.4	63	118–123/1.2[c]

[a] Lit. b.p. 126–129°/3 mm. (12) and 115–123°/0.5 mm. (13). [b] Lit. b.p. 115–118°/3 mm. (14). [c] Lit. b.p. 140–145°/2 mm. (12).



Scheme I

Isomers of DDD were chosen for this study because they have been shown to have a predilection for adrenal tissue. During an investigation of the toxicological properties of various insecticides, Nelson and Woodard (1) observed that *p,p'*-DDD (III*c*) caused extensive necrosis and atrophy of the adrenal cortex in dogs. This observation led to unsuccessful attempts to utilize this substance clinically to produce a chemical adrenalectomy (2). Cueto and Brown (3) demonstrated, however, that the adrenocorticolytic activity ascribed to *p,p'*-DDD was actually due to the *o,p'*-isomer (III*a*) which was present as a contaminant. They also showed that *o,p'*-DDD concentrated to a greater extent than *p,p'*-DDD in the adrenals of dogs.

Several reports concerning the actions of *o,p'*-DDD have appeared recently. Studies have shown it to produce tumor regression in cases of metastatic adrenal cortical carcinoma (4) and to cause remissions of symptoms in patients with Cushing's syndrome (5, 6). It was found ineffective, however, for the treatment of mammary carcinoma (7). *o,p'*-DDD has also been found to have an effect on steroid metabolism and this aspect has received considerable attention. These studies have shown it to stimulate cortisol metabolism (8), to alter the extra-adrenal metabolism of cortisol (9), and to inhibit specific enzymes (10).

Although *o,p'*-DDD has been studied to a considerable extent, Nichols *et al.* (11) indicated that the *m,p'*-isomer (III*b*) was more effective in causing regression of adrenal carcinoma with fewer side effects. Despite the interest in *o,p'*-DDD and its isomers, tissue distribution studies with labeled compounds have not been reported. The first synthesis of these labeled DDD isomers is reported here.

EXPERIMENTAL[1]

Synthesis of Isomeric 2,2-Dichloro-1-(chlorophenyl)ethanols (II).—The Grignard reagent, prepared from the appropriate bromochlorobenzene (n mole), magnesium (n mole), and ether in a three-necked flask provided with a stopcock-fitted outlet on the bottom, was added over 1 hr. to a well-stirred solution of dichloroacetaldehyde[2] (n mole) in ether (total $n \times 200$ ml.) with ice cooling under a nitrogen atmosphere. After stirring an additional 30 min. at room temperature, 6 *N* sulfuric acid or concentrated ammonium chloride solution was added and the mixture separated and extracted with ether. The combined organic layers were dried ($MgSO_4$) and the ether removed at atmospheric pressure. The residue was distilled under reduced pressure. (See Table I.)

1,1 - Dichloro - 2 - (o - chlorophenyl) - 2 - (p-chlorophenyl-^{14}C)ethane.—A mixture of 2.26 Gm. (0.01 mole) of 2,2-dichloro-1-(*o*-chlorophenyl)ethanol, 29.7 mg of chlorobenzene-^{14}C (uniformly labeled, 0.50 mc.),[3] and 530.3 mg. (total 0.005 mole) of chlorobenzene was stirred at 40° and 6 ml. of boron trifluoride-saturated sulfuric acid added dropwise over 5 min. The mixture was heated at 40° with vigorous stirring for 3 hr. and then extracted with petroleum ether (b.p. 30–40°, 3 × 25 ml.). The combined extract was washed with water (2 × 25 ml.) and dried ($MgSO_4$ and charcoal). The filtered extract was concentrated under vacuum and the residue chromatographed on a column of 35 Gm. of silicic acid, prepared and developed with benzene–hexane (1:1). The eluate was monitored with a Geiger survey meter and the radioactive fraction collected and evaporated. The oily residue was taken up in methanol and refrigerated to give,

[1] Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Infrared spectra were taken in KBr disks on a Perkin-Elmer 337 spectrophotometer. Ultraviolet spectra were recorded on a Beckman DK2A spectrophotometer in 95% ethanol. The NMR spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ at a concentration of 10%, with tetramethylsilane as internal reference. Thin-layer chromatograms (TLC) were run with 1 in. wide Eastman Chromagrams, type K301R with fluorescence indicator, developed with benzene, and spots detected with U.V. light and iodine vapor. Chromagrams of ^{14}C-labeled compounds were scanned with an Atomic Associates RCS-363 Radiochromatogram Scanner. Gas-liquid chromatography (GLC) was carried out with a F&M, model 400, gas chromatograph equipped with an electron-capture detector; column, 122 cm. × 3 mm. i.d. glass tube; packing, 3.8% by wt. silicone rubber SE-30 on 80–100 mesh Diatoport S, prepared according to Horning *et al.* (21); column temperature, 185°; detector temperature, 210°; flash heater, 230°; inlet pressure, 40 p.s.i.; flow rate, about 70 ml./min. Radioactivity measurements were made with an Atomic Associates FC-72A gas-flow planchet counter and Baird-Atomic 146 scaler. Silicic acid used in the column chromatography was Baker and Adamson reagent grade, dried at 105° for 1 hr. just prior to its use.

[2] Columbia Organic Chemicals Co., Columbia, S. C.

[3] Purchased from New England Nuclear Corp., Boston, Mass.

in two crops, 656 mg. (41%) of colorless needles, m.p. 75–76° [lit. m.p. 76–78° (12) and 75.5–76.5° (13)]; specific activity 99.5 μc./mmole. It showed one spot (R_f 0.67) on a TLC strip, which scanned as a homogeneous radioactive area. $\nu_{max.}$ 3070, 3050 (Ar—H); 2980, 2930 (CH); 1480, 1465 (C=C); 1100, 1051, 1029, 770 (1,2-disubstituted Ar—H); 1083, 1040, 1010, 810 (1,4-disubstituted Ar—H); 757 (CCl_2); 608; and 509 cm.$^{-1}$. $\lambda_{max.}$ 229.5 (ε 16,970) and 267.5 mμ (ε 640). The NMR spectrum showed doublets at 5.21 δ (benzylic proton) and 6.38 δ (—$CHCl_2$) with J = 8.5 c.p.s., and a single aromatic-proton peak at 7.35 δ.

1,1 - Dichloro - 2 - (m - chlorophenyl) - 2 - (p-chlorophenyl-^{14}C)ethane.—A mixture of 2.26 Gm. (0.01 mole) of 2,2-dichloro-1-(*m*-chlorophenyl)ethanol, 29.7 mg. of chlorobenzene-^{14}C (uniformly labeled, 0.50 mc.)[3] and 530.3 mg. (total 0.005 mole) of chlorobenzene was stirred at 40° and 6 ml. of boron trifluoride-saturated sulfuric acid added dropwise over 1 hr. After heating at 40° with vigorous stirring for 1 hr., 2 ml. of cyclohexane was added. After heating 2 hr. longer, the mixture was worked up as above and chromatographed with benzene–hexane (1:4). The radioactive fraction was dissolved in an equal volume of 95% ethanol and after allowing to stand in the refrigerator 3 weeks gave 490 mg. (31%), m.p. 51–52°, which was recrystallized from ethanol to give 388 mg., m.p. 53–54° [lit. m.p. 54° (14)], specific activity 89.3 μc./mmole. TLC showed one spot (R_f 0.67), which was the only radioactive area on scanning. $\nu_{max.}$ 3050 (Ar—H); 2995, 2910 (CH); 1580, 1565, 1480, 1470 (C=C); 1090, 1072, 836, 785 (1,3-disubstituted Ar—H); 1085, 1040, 1009, 808 (1,4-disubstituted Ar—H); 759 (CCl_2); 615; and 502 cm.$^{-1}$. $\lambda_{max.}$ 219 (ε 19,770), sh. 226.5 (ε 16,700), and 268.5 mμ (ε 800). The NMR spectrum showed doublets at 4.57 δ (benzylic proton) and 6.31 δ (—$CHCl_2$) with J = 8.0 c.p.s., and an aromatic peak split at 7.26 and 7.29 δ.

1,1 - Dichloro - 2,2 - bis - (p - chlorophenyl - ^{14}C)-ethane.—A mixture of 2.26 Gm. (0.01 mole) of 2,2-dichloro-1-(*p*-chlorophenyl)ethanol, 107 mg. of chlorobenzene-^{14}C (uniformly labeled, 0.50 mc.),[4] and 456 mg. (total 0.005 mole) of chlorobenzene was stirred at 40° and 6 ml. of boron trifluoride-saturated sulfuric acid added dropwise over 30 min. The reaction was conducted and worked up as described for the *meta* isomer above.

The radioactive fraction afforded from methanol 694 mg., m.p. 107–110°, which was recrystallized from methanol to give 602 mg. (43%), m.p. 109–110° [lit. m.p. 109.5–110° (12)], specific activity 106.9 μc./mmole. TLC showed one spot which corresponded to the only radioactive area on scanning (R_f 0.72). $\nu_{max.}$ 3050, 3020 (Ar—H); 2970, 2910 (C—H); 1580, 1490, sh. 1475 (C=C); 1087, 1040, 1010, 803 (1,4-disubstituted Ar—H); 763 (CCl_2); 532; and 499 cm.$^{-1}$ $\lambda_{max.}$ sh. at 211.5 (ε 17,060), 217.5 (ε 15,910), 231 (ε 19,710), and 268 mμ (ε 713). The NMR spectrum showed doublets at 4.58 δ (benzylic proton) and 6.33 δ (—$CHCl_2$) with J = 8.0 c.p.s., and a single aromatic peak at 7.33 δ.

DISCUSSION

The syntheses of these three DDD isomers have been reported previously. After initial isolation of *o,p'*- (III*a*) and *p,p'*-DDD (III*c*) from technical "DDT,"[5] Haller *et al.* (12) synthesized them in 39 and 63% yields, respectively, by the Friedel-Crafts alkylation of chlorobenzene with the appropriate carbinol (II) in the presence of 100% sulfuric acid. They obtained the *ortho* carbinol (II*a*) in only 6% yield by the addition of dichloroacetaldehyde to the Grignard reagent prepared from *o*-bromochlorobenzene (I*a*). The *para* carbinol (II*c*) was prepared in good yields by this method [67% (12)] or by reduction of 2,2,4'-trichloroacetophenone [96% (15)]. (See Scheme I.)

In an approach to the synthesis of the more biologically interesting *o,p'*-DDD, Inoi, Gericke, and Horton (13) obtained the *ortho* carbinol (II*a*) by reduction of the more readily available 2,2,2-trichloro-1-(*o*-chlorophenyl)ethanol (IV*a*) with aluminum amalgam in 90% ethanol. They synthesized several diphenyldichloroethanes by this method, including *o,p'*-, *m,p'*-, and *p,p'*-DDD (III*a*, *b*, and *c*), all in good yield. They also improved on the condensation of carbinol (II*a*) with chlorobenzene by using boron trifluoride-saturated sulfuric acid (47% yield).

Although the biological properties of *m,p'*-DDD (III*b*) have been mentioned several times in the literature, reports of the synthesis and physical properties have been limited. It was prepared by the reduction outlined above, being reported as an oil, b.p. 178–180°/0.5 mm. (13). Synthesis of the *meta* carbinol (II*b*) by the Grignard procedure was reported in 32% yield and *m,p'*-DDD (III*b*), using sulfuric acid in the Friedel-Crafts reaction and a laborious work-up, in 19% yield (14).

With the specific intention of preparing the ^{14}C labeled compounds, interest centered on the Friedel-Crafts route since this enabled incorporation of the labeled precursor at the last step. In preliminary investigations on the synthesis of the carbinol intermediates, the authors were unable to repeat the aluminum amalgam reduction of the trichloroethanol (IV*a*) [prepared according to Haller *et al.* (12) and Bergmann *et al.* (16)]. Attention turned to the Grignard synthesis. It was anticipated that slow addition of the Grignard reagent prepared from the bromobenzenes (I) to a cold ethereal solution of the unstable dichloroacetaldehyde would give an improvement in the yields. In this manner, yields of 35, 53, and 63% were obtained for the *o*-, *m*-, and *p*-carbinols (II), respectively.

The condensation reaction was studied extensively in an effort to maximize the radioactive yield. It is usual in Friedel-Crafts alkylations of benzene and its readily available derivatives to have them in excess relative to the alkylating agent, and to serve as solvent. As the chlorobenzene to be used was the labeled precursor and it seemed likely that the carbinols (II) would exhibit some instability with possible decomposition, trial reactions were run with varying proportions of chlorobenzene and carbinols and a twofold excess of the latter was found to give maximum yields. These varied from 56 to 75%, depending somewhat on the isolation procedure used. It was found most convenient to chromato-

[4] Purchased from Tracer Lab, Waltham, Mass.

[5] DDT, of various grades, is the product obtained from the condensation of chloral with chlorobenzene in the presence of sulfuric acid, and usually contains about 70% 1,1,1-trichloro-2,2,-bis-(*p*-chlorophenyl)ethane.

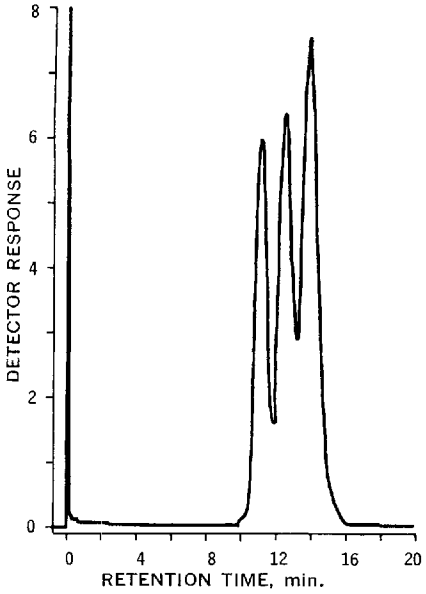


Fig. 1.—GLC tracing of 2.5 ng. each of *o,p'*-, *m,p'*-, and *p,p'*-DDD-^{14}C, injected in 6 μl. of benzene.

graph the crude product on activated silicic acid with benzene–hexane (1:4). In all three cases, an aromatic by-product was eluted before the DDD isomers. Since heterogeneous reactions tend to give variable results, tetrachloroethane and cyclohexane were tried as solvents. Yields were lower with the former and unaffected by the latter, although it did facilitate stirring. The labeled compounds were obtained in about 40% yields following recrystallization.

It has been pointed out frequently (17) that special purity analyses are required for radiochemicals intended for biological distribution studies. In this investigation the labeled isomers were checked for purity by thin-layer (TLC) and gas-liquid chromatography (GLC). With TLC, chemical purity was established by spot detection with ultraviolet light and iodine vapor, and radioactive purity by means of a radiochromatogram scanner. GLC was found to be the most effective analytical tool for assessment of purity. The type of column and conditions employed have been used extensively for detection of pesticide residues (18) and gave satisfactory separation of the three isomers (Fig. 1). The electron-capture detector used was capable of detecting trace impurities. This made it possible to show that each was isomerically pure. This was necessary as the condensation of *o*-, *m*-, and *p*-carbinols (II) with chlorobenzene can occur at both the *ortho* and *para* positions. Of most concern was the complete elimination of *o,p'*-DDD from *p,p'*-DDD, as the former is known to localize to a much greater extent in various tissues. This was readily seen as the gas chromatogram of *p,p'*-DDD-^{14}C showed a single peak even when 25 ng. (10 times that used in obtaining Fig. 1) was injected. It is curious to note that their order of retention does not correspond to their melting points, the lower melting *m,p'*-DDD following the sterically hindered *o,p'*-DDD. Additional isomers are being prepared to study this and other properties.

We examined the I.R., U.V., and NMR spectra of the three DDD isomers for possible use in assessing purity. Reports on spectral data for these compounds have been limited. McDonald and Watson (19) employed I.R. spectroscopy for differential analysis of *o,p'*-, and *p,p'*-DDD and used the distinguishing bands at 685 and 765 cm.$^{-1}$, respectively. In addition, *o,p'*-DDD has been observed to exhibit a strong characteristic band at 608 cm.$^{-1}$.

Inoi *et al.* (13) reported on the U.V. spectra of *o,p'*-DDD and some related compounds but made no comparisons. In the studies reported here, comparison of the *o,p'*-, *m,p'*-, and *p,p'*-isomers showed them to have similar but distinguishable U.V. absorption spectra.

The NMR spectra showed the greatest distinctions. In contrast with *m,p'*- and *p,p'*-DDD, the benzylic proton of *o,p'*-DDD showed a shift to lower field of 38 c.p.s. due to the deshielding effect of the *o*-chloro substituent. A similar downfield shift has been reported for the benzylic proton of benzhydryl derivatives possessing *o*-methyl groups (20). In addition, whereas the *o,p'*- and *p,p'*-isomers showed a single strong peak at approximately 7.34 δ for the aromatic protons, the *m,p'*-isomer displayed two major peaks at 7.26 and 7.29 δ.

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