N-(3-Dimethylaminopropyl)-3-azatrispiro[5.2.2.5.2.2]heneicosane Dihydrochloride (4).—The acid **15** (0.4 g, 0.001 mole) was refluxed with 15 ml of Ac_2O for 15 min; the excess Ac_2O was vacuum-distilled. The crude trispiro anhydride was heated at 200° for 1 hr with 0.5 g of $Me_2N(CH_2)_3NH_2$. Excess amine was removed *in vacuo*. The remaining, crude imide in 100 ml of dry Et_2O was added slowly to a stirred solution of $LiAlH_4$ (1 g) in 100 ml of dry Et_2O. After 2 hr, the mixture was decomposed with H_2O and filtered. The filtrate was dried (Na_2SO_4), and the solvent was distilled. The residual oil in alcohol was treated with HCl gas. The product was recrystallized from EtOH–Et_2O, mp 330–332°, yield 0.35 g, 77% (based upon **15**). *Anal.* ($C_{25}H_{48}N_2Cl_2$) C, H, N, Cl.

Tumor Localizing Agents. IV. Radioiodinated Analogs of 1,1-Dichloro-2,2-di(chlorophenyl)ethane

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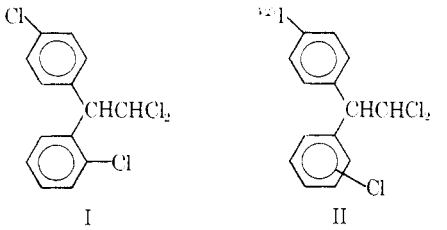
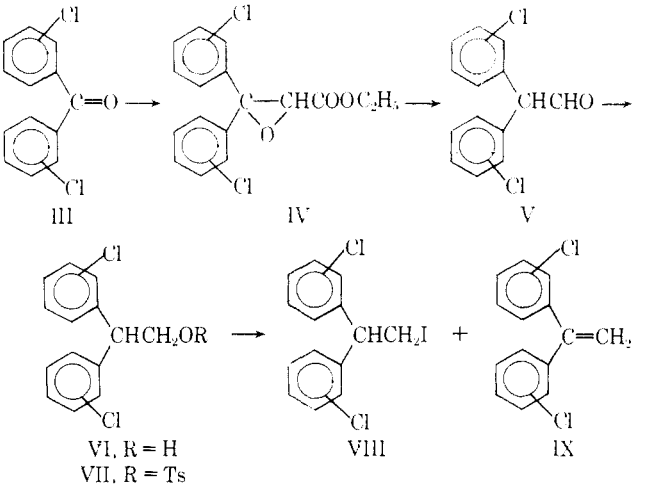
A previous paper[1] in this series indicated the clinical need for an agent which could be employed for photoscanning the adrenal gland and associated tumors. In an attempt to meet this need, several radioiodinated analogs of 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (*o,p'*-DDD, I) were described in which one of the aromatic chlorines had been replaced by radioiodine (II). The synthesis of these compounds was prompted by the fact that *o,p'*-DDD is currently the only effective agent used for the treatment of adrenocortical carcinoma,[2] and apparently exerts its action by concentrating in adrenal tissue.[3] Preliminary animal studies with the radioiodinated compounds have indicated that they may be useful for adrenal photoscanning in humans[4] and larger quantities of one of the isomers is currently in preparation for clinical investigation. As part of a continuation of the synthetic studies in this area, this paper describes the preparation of radioiodinated DDD analogs in which the aliphatic chlorines have been replaced with radioiodine (VIII).



The synthetic approach to the appropriately substituted 2,2-diphenylethyl iodides involved a study of the nucleophilic displacement of the corresponding tosylates (VII) with iodide. As shown in Scheme I, the required tosylates were obtained in two steps from the substituted diphenylacetaldehydes (V). The aldehydes were either obtained commercially or synthesized from the appropriate benzophenone (III) by Darzen's synthesis.

Scheme I

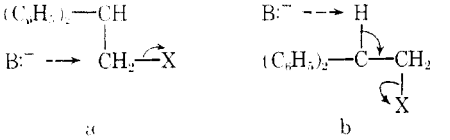


a, *o'p'*; b, *p,p'*; c, *o,o'*

During the course of these studies it was noted that Riemschneider and co-workers[5] had reported isolating *p,p'*-dichlorodiphenylacetaldehyde (Vb) as a solid, mp 147°, following acid hydrolysis of the corresponding ethylene glycol acetal. They had obtained the acetal by refluxing *p,p'*-DDD with alkaline ethylene glycol. The aldehyde obtained in our studies, however, was a high-boiling liquid (bp 158–162° at 0.35 mm) which resisted crystallization from a variety of solvents. Moreover, elemental analysis and the nmr spectra of our aldehyde were in agreement with the assigned structure. Studies[6] in our laboratory subsequently demonstrated that the high-melting solid obtained by the earlier investigators was *p,p'*-dichlorobenzophenone (IIIb), lit.[7] mp 147–148°.

Horton and co-workers[8] previously prepared the alcohol VIa by $LiAlH_4$ reduction of the aldehyde in 58% yield. We found, however, that $NaBH_4$ reduction in ethanol was more convenient and afforded the desired alcohols in over 80% yield in each case. These alcohols were readily converted to the tosylates using the general procedure of Tipson.[9]

Previous studies by Hamrick and Hauser[10] had shown that 2,2-diphenylethyltosylate afforded unrearranged elimination and/or substitution products when treated with various nucleophiles. In such cases, nucleophilic displacement (a) and elimination (b) are competing reactions and the amounts of each product depend on the relative rates of the two reactions.



In our studies, the ratio of displacement to elimination product was found to depend on the structure of

(1) R. E. Counsell, R. E. Willette, and W. DiGuilio, *J. Med. Chem.*, **10**, 975 (1967).

(2) D. A. Karnofsky in "Drugs of Choice 1966–1967," W. Modell, Ed., C. V. Mosby Co., St. Louis, Mo., 1966, p 617.

(3) C. Cueto and J. H. V. Brown, *Endocrinology*, **62**, 326 (1958).

(4) W. DiGuilio, Chief of the Radioisotope Unit, V. A. Hospital, Ann Arbor, Mich., personal communication.

(5) R. Riemschneider, I. Abrle, W. Cohnen, and E. Heilmann, *Chem. Ber.*, **92**, 900 (1959).

(6) Manuscript in preparation.

(7) J. Böeseken and W. D. Cohen, *Chem. Zentr.*, **1**, 1376 (1915).

(8) T. Inoi, P. Gericke, and W. J. Horton, *J. Org. Chem.*, **27**, 4597 (1962).

(9) R. S. Tipson, *ibid.*, **9**, 235 (1944).

(10) P. J. Hamrick and C. R. Hauser, *ibid.*, **26**, 4199 (1961).

the starting tosylate. In the case of the *o,p'*-tosylate (VIIa), reaction with potassium iodide in refluxing acetone, aqueous acetone or 2-propanol resulted in the recovery of starting material in each case. When the displacement was carried out in DMF or DMSO at 140°, the corresponding olefin, 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)ethylene (IXa), was isolated as the sole product. The desired iodo compound (VIIIa) was obtained, however, when the displacement was performed in refluxing acetonitrile over a 4-day period. Nmr analysis of the crude reaction product showed a ratio of displacement to elimination product of 2:1. On the other hand, all attempts to carry out the same displacement with the *p,p'*-tosylate (VIIb) under identical conditions gave only the elimination product IXb. Although halide ions are not usually considered to be strong bases, iodide has been noted to cause dehydrohalogenation in dipolar aprotic solvents.[11]

Steric factors are known to play an important role in bimolecular elimination reactions.[12] Molecular models of VIIa clearly illustrate the steric hindrance imposed by the *o*-chlorine on the β-hydrogen and undoubtedly accounted for the isolation of substitution product in this case. This consideration prompted a study of the *o,o'*-tosylate (VIIc), and in this instance no elimination occurred and the iodide (VIIIc) was isolated in essentially quantitative yield.

Radioiodine-labeled VIIIa and c were obtained by isotope exchange with $Na^{125}I$ in refluxing acetone and acetonitrile, respectively. With the former, isotope exchange was accompanied by elimination and necessitated purification of the radioiodinated product by column chromatography. This complication was not encountered with VIIIc.

Preliminary tissue distribution studies with the radioiodinated compounds have been carried out in rats, and tissues were analyzed 4 and 24 hr after intravenous administration.[13] For VIIIa, most of the radioactivity was found in the thyroid after 4 hr with little radioactivity appearing in other tissues. Considerable thyroidal radioactivity was also noted 4 hr following the administration of VIIIc. In this case, however, high concentrations of radioactivity were also found in fat tissue and whole blood. Twenty-four hours after the administration of VIIIc, the concentration of radioactivity decreased slightly in fat, increased slightly in blood, and increased to a considerable degree in thyroid. Only low concentrations of radioactivity were found in the adrenals which is in contrast with the results obtained with ring-iodinated DDD analogs.[1] These data are consistent with the premise that these compounds are metabolized in a manner similar to DDT[14] giving rise to substituted diphenylacetic acids and inorganic iodide. The apparent slower metabolism of VIIIc could be accounted for on steric grounds similar to those discussed above.

Experimental Section[15]

Ethyl β,β-Di(*p*-chlorophenyl)glycidate (IVb).—To a solution of ethyl chloroacetate (13.6 ml) and *p,p'*-dichlorobenzophenone (20 g) in anhydrous C_6H_6 (20 ml) was added NaH (54% dispersion, 6.4 g) in portions with stirring. The addition was carried out under N_2 over a period of 4 hr. The addition flask was rinsed with anhydrous C_6H_6 (20 ml) which was added to the reaction mixture. Stirring at room temperature was continued overnight and the reaction mixture was poured onto ice water–HCl (1:1). The mixture was extracted (C_6H_6) and the dried extract (Na_2SO_4) was concentrated to dryness. The yellowish, solid residue was recrystallized from MeOH to afford crude IVb (22 g), mp 95–105°. Recrystallization from ether–cyclohexane furnished pure IVb (18.5 g, 69%): mp 110–112°; nmr peaks, 1.02 (CH_3, triplet, J_{AX} = 7 cps), 3.97 (CH), 4.03 (CH_2, quartet, J_{AX} = 7 cps), 7.32, and 7.41 ppm (aromatic). *Anal.* ($C_{17}H_{14}Cl_2O_3$) C, H.

2,2-Bis(*p*-chlorophenyl)acetaldehyde (Vb).—A solution of IVb (15.0 g) in EtOH (100 ml) and 20% aqueous KOH (25 ml) was refluxed with stirring for 8 hr. The EtOH was removed by evaporation, H_2O (50 ml) was added, and the mixture was extracted with ether (two 25-ml portions). The aqueous phase was warmed on the steam bath to remove residual ether, allowed to cool, and acidified by the addition of dilute HCl. The mixture was extracted (Et_2O) and the extract was washed (H_2O) and dried (Na_2SO_4). The solvent was removed and the residue was heated in an oil bath at 150° under reduced pressure (aspiration). Distillation of the crude decarboxylated product (11.5 g) afforded pure Vb (9.4 g, 80%): bp 158–162° (0.35 mm); ν_{max} 1720 cm^{-1} (C=O); nmr peaks at 4.83 (doublet, benzylic H, J_{AX} = 2 cps), 6.85–7.68 (aromatic), and 9.90 ppm (doublet, aldehyde H, J_{AX} = 2 cps). *Anal.* ($C_{14}H_{10}Cl_2O$) C, H.

The 2,4-dinitrophenylhydrazone was recrystallized from EtOH–EtOAc, mp 178–180°. *Anal.* ($C_{26}H_{14}Cl_2N_4O_2$) C, H.

Borohydride Reduction of Bis(chlorophenyl)acetaldehydes.—The aldehyde (V)[16] was added with external cooling to a solution containing $NaBH_4$ (1.0 g) in EtOH (20 ml). The solution was allowed to stand at room temperature overnight and poured into 10% NH_4Cl solution (100 ml). The mixture was extracted (Et_2O) and the extract was washed (H_2O), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting crude alcohol was purified by distillation or recrystallization (see Table I).

Tosylation of Bis(chlorophenyl)ethanols.—*p*-Toluenesulfonyl chloride (2.4 g) was added to a solution of the alcohol (VI, 2.0 g) in pyridine (20 ml). The mixture was cooled in an ice–salt bath and stirred until all of the acid chloride had dissolved. The solution was kept below 0° for an additional 2 hr and then refrigerated for 17 hr. Water (1 ml) was added dropwise maintaining the temperature below 15° and the solution was poured into cold water (20 ml) with stirring. The crude product was collected by filtration, washed well with water, and recrystallized (see Table I).

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2-iodoethane (VIIIa).—To a solution of VIIa (4.0 g) in freshly distilled MeCN (100 ml) was added KI (4.0 g) and the mixture refluxed for 4 days. The solvent was removed *in vacuo* and the residue was shaken with H_2O and $CHCl_3$. The organic phase was separated and dried (Na_2SO_4), and the solvent was removed. The residual oil was fractionally distilled to give two constant-boiling fractions. The first (0.43 g), bp 110–114° (0.15 mm), proved to be identical with an authentic sample of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-ethylene (IXa) prepared according to Zee-Cheng and Cheng.[17] The higher boiling fraction (1.5 g), bp 164–166° (0.15 mm), was the desired product VIIIa (see Table I). Nmr analysis of the

(11) A. J. Parker, *Quart. Rev.* (London), **16**, 183 (1962).

(12) *Cf.* D. J. Cram in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 333.

(13) The authors are grateful to Dr. Walter DiGuilio and Mr. Scott Skinner of the Radioisotope Unit, V. A. Hospital, Ann Arbor, Mich., for furnishing this information.

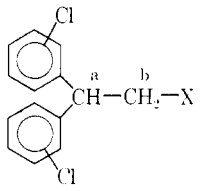
(14) W. J. Hayes, Jr., *Ann. Rev. Pharmacol.*, **5**, 27 (1965).

(15) 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. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were taken on a Perkin-Elmer 337 spectrophotometer. The nmr spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ at a concentration of 10%, with TMS as internal reference. Thin layer chromatograms (tlc) were run with 1-in. wide Eastman chromagrams, Type K301R, with fluorescence indicator and spots detected with uv light. Chromatograms of radioiodinated compounds were scanned with an Atomic Associates RCS-363 radiochromatogram scanner. The specific activities were determined with an Atomic Associates well-scintillation counter Model 810C and scintillation spectrometer Model 530. Silicic acid used in the column chromatography was Baker and Adamson reagent grade.

(16) The *o,p'*-aldehyde (Va) was prepared according to Horton, *et al.*,[8] and the *o,o'*-aldehyde (Vc) was obtained from Aldrich Chemical Co., Milwaukee, Wis. 53210.

(17) K. Y. Zee-Cheng and C. C. Cheng, *J. Med. Pharm. Chem.*, **5**, 1008 (1962).

TABLE I



Compd	X	Mp, °C	Yield, %	Analyses	Chemical shifts, ppm H_a	H_b
VIa	OH	*a*	82		4.67	4.06
b	OH	97–98[b,c]	98		4.10[d]	4.10
c	OH	65–67[c,e]	85	C, H	5.02	4.02
VIIa	OTs	112.5–113.5[a]	86	C, H	4.72	4.40
b	OTs	119–120[c]	83	C, H	(4.16–4.38)[f]	
c	OTs	112–114[c]	88	C, H	5.06	4.43
VIIIa	I	*h*	55	C, H	4.83	3.60
c	I	126–128[c]	87	C, H	5.20	3.60

[a] Bp 157–158.5° (0.125 mm), lit.[8] 168–174° (0.4 mm). [b] O. Grummitt, A. A. Arters, and J. A. Stearns [*J. Am. Chem. Soc.*, **73**, 1856 (1951)] reported mp 98.5–99.5°. [c] Recrystallized from MeOH–H_2O. [d] The deshielding effect of *ortho*-substituted chlorine on benzylic protons has been noted previously: R. E. Counsell and R. E. Willette, *J. Pharm. Sci.*, **55**, 1012 (1966). [e] Recrystallized from Me_2CO–H_2O. [f] Bp 172–174° (0.7 mm). [g] Recrystallized from Me_2CO–cyclohexane. [h] Bp 164–166° (0.15 mm). [i] Multiplet.

crude product prior to distillation showed the ratio of VIIIa to IXa to be approximately 2:1.

1,1-Bis(*o*-chlorophenyl)-2-iodoethane (VIIIc).—A mixture of VIIc (1.6 g), KI (1.8 g), and MeCN (40 ml) was heated to reflux and sufficient H_2O was added to effect homogeneity. Gentle reflux was continued for 5 days, whereupon the solvent was removed by distillation *in vacuo*. The resulting solid was washed (H_2O) and recrystallized from Me_2CO–H_2O to afford pure VIIIc (1.2 g), mp 126–128° (see Table I).

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2-iodoethane-^{125}I.—A solution of VIIIa (0.20 g) and $Na^{125}I$ (2 mCi)[18] in Me_2CO (10 ml) was stirred at the reflux temperature for 12 hr. The Me_2CO was evaporated and the residue was dissolved in ether. The ether solution was washed (H_2O, two 20-ml portions) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was dissolved in hexane and chromatographed on silica gel (20 g). The column was eluted with hexane–benzene (9:1) and the radioactive fractions were collected. Removal of the solvent afforded radioiodinated VIIIa (58.4 mg) as a colorless oil with a specific activity of 0.4 μCi/mg. Chemical and radiochemical purity was established by tlc using hexane as the eluent. Analysis under uv light revealed a single spot (R_f 0.62) coincident with the single radioactive area shown on a radiochromatogram scan.

1,1-Bis(*o*-chlorophenyl)-2-iodoethane-^{125}I.—A solution of VIIIc (0.1 g) and $Na^{125}I$ (1 mCi)[18] in Me_2CO (7 ml) was stirred and gently refluxed for 5 hr. The solution was allowed to cool and poured into H_2O (25 ml), and the resulting precipitate was collected by filtration. The product was washed well (H_2O) and dried to give 91 mg, specific activity 0.89 μCi/mg. Tlc as above gave a single spot (R_f 0.38) coincident with the single radioactive area shown on a radiochromatogram scan.

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[18] Obtained from New England Nuclear Corp., Boston, Mass. 02118.

Phosphorus–Nitrogen Compounds. IX.[1,2] Hydroxylamine Derivatives

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In the course of continuing study on oncolytic properties of compounds containing PNO and PNHCONO groups[2,3] it was thought that certain of these derivatives might lead to interesting CNS activities.

An examination of **3c–g** structures reveals the presence of both hypnotic–anticonvulsant pharmacophores and the weak central depressant, urethan. This suggests that the derivatives may be bioisosteric with, and possess mild depressant properties similar to, those of acyclic ureides. These compounds were consequently tested for reduction in locomotor activity and protective action against electroshock (Table I). The former screening included the phosphorous triamides (**4a**, **b**) and triethyl phosphinylidynetricarbamate (**3g**).

TABLE I

LOCOMOTOR ACTIVITY EFFECTS AND ANTICONVULSANT PROPERTIES

Compound	Dose, mg/kg	% decrease in motor activity[a] 30 min	60 min	Anti-electroshock,[b] % block
3c	400	83	31	...
	800	18	7	...
3d	800	55	48	...
3e	100	...	...	10[c]
	200	67	67	40[d]
3f	400	94	74	20[d]
	800	34	36	30[c]
3g	800	24	12	...
4a	200	40	44	...
	400	36	34	...
4b	200	50	46	...

[a] Expressed as the percentage decrease in activity from the controls. [b] All control mice convulsed, 2/10 deaths. [c] 0/10 deaths. [d] 1/10 deaths.

Estimations of toxicities[4] gave LD_{50} values of 550 (**3e**, **4b**), 800 (**4a**), and >1600 (**3c**, **d**, **f**) mg/kg. The anticipated greater toxicity of phosphorous over phosphoric triamides, and chlorinated carbamate over urethan derivatives, was realized.

The greatest motor activity reduction occurred with the most toxic derivatives (**4a**, **b**, **3e**) at about 25–50% LD_{50}. A comparison between equidoses of **3c**, **f**, and **g** indicates that two or three urethan moieties produce a greater reduction in activity than one such group. In addition, **3c** and **g** were the only derivatives showing appreciable induction latency. Preliminary screening using five animals showed anticonvulsant activity in all four phosphoric triamides containing urethan and methoxyurea moieties. The two most active, **3e** and

(1) This investigation was supported by Grant CA-08711 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper, see L. A. Cates and J. A. Nelson, *J. Pharm. Sci.*, in press.

(3) L. A. Cates, *J. Med. Chem.*, **10**, 924 (1967).

(4) C. S. Weil, *Biometrics*, **8**, 249 (1952).