Experimental Section[10]

1-Hydroxy-10a-methyl-3-pentyl-6b,7,8,9,10,10a,11,12-octahydro-6H-benzo[*b*]naphtho[1,2-*d*]-6-pyrone (VI).—$POCl_3$ (3 ml) was added to a mixture of 4.5 g (0.025 mole) of olivetol (IV) and 5.6 g (0.025 mole) of 10-methyl-1-carbomethoxy-*trans*-2-decalone[6] (V) in C_6H_6, and the mixture was heated under reflux. After 5 hr the volatile material was removed *in vacuo* and the residue was crystallized from MeOH to give 4.5 g (51%) of colorless crystals of VI, mp 220–222°. Absorption bands of spectrum (uv, ir, nmr) were as expected.

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.82; H, 8.48.

6b,7,8,9,10,10a,11,12-Octahydro-3-pentyl-6,6,10a-trimethyl-6H-benzo[*b*]naphtho[1,2-*d*]pyran-1-ol Acetate (III).—A mixture of 2.36 g (0.0066 mole) of pyrone VI and 60 ml of MeLi (2.4 *M* in hexane) was refluxed for 48 hr. After decomposition of the mixture with dilute H_2SO_4, the organic layer was separated. It was washed, dried, and evaporated to leave a residue which was heated under reflux for 1 hr in dry heptane to which a few drops of 48% HBr had been added. After cooling, the heptane solution was washed ($NaHCO_3$, H_2O) and then dried and evaporated. The dark greenish blue residue thus obtained was heated under reflux in excess Ac_2O containing 1 g of NaOAc. After 1.5 hr the volatile material was removed *in vacuo*, water was added, and the mixture was extracted (C_6H_6). The organic layer was washed, dried, and evaporated to leave a reddish brown gum. This gum was chromatographed on silicic acid (100 mesh) with C_6H_6 and finally purified by preparative tlc (C_6H_6) to give 90 mg of III as a brownish gum: *m/e* 410, 395 ($M^+ - CH_3$), 368 ($M^+ - 42$), 367 ($M^+ - C_2H_3O$), 353 ($M^+ - C_4H_9$). Absorption bands of spectra (uv, ir, nmr) were as expected.

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.69; H, 9.41.

Acknowledgment.—We wish to thank Dr. P. L. Levins for his assistance in the interpretation of spectra and Arthur D. Little, Inc., for supporting this work.

(10) All melting points are uncorrected; mass spectrum was determined with a CEC 21-110B instrument (direct introduction probe at 110°).

Spirans. XIV. Azatrispirans[1]

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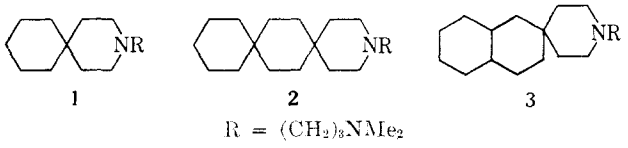
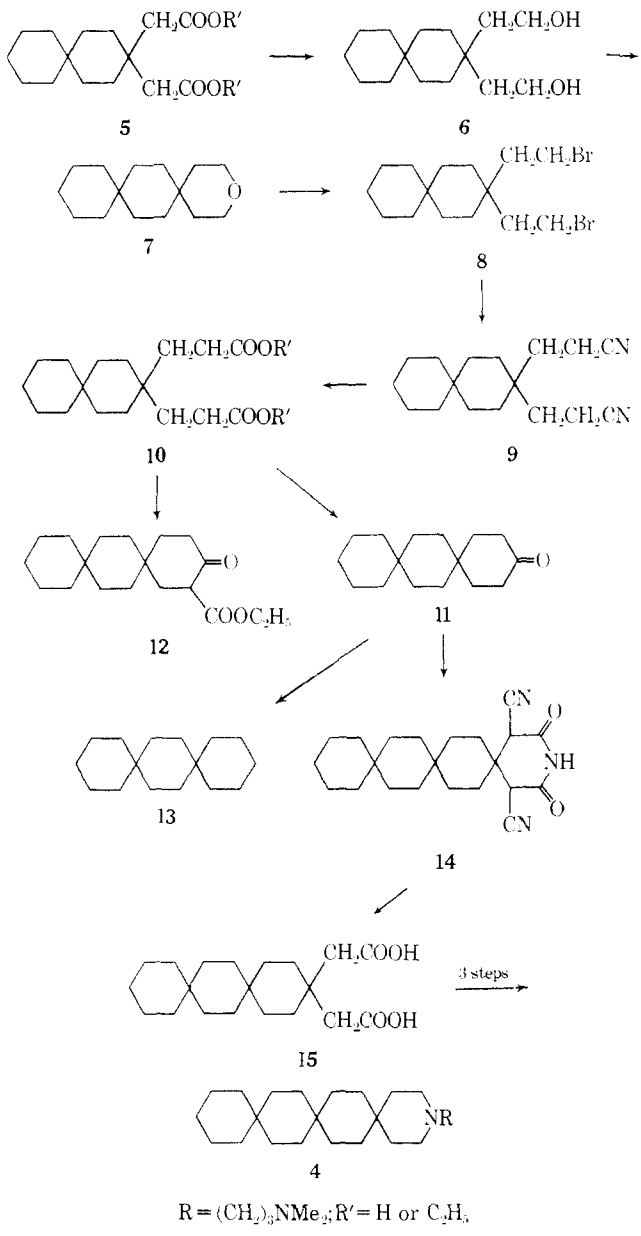
In previous papers[2,3] we described the synthesis of azaspiro (**1**) and azadispiro compounds (**2**). These compounds were of interest to us as a part of a broad program concerning the structure–activity relationships of spiro compounds on tissue culture cells. It was also of interest to study the effect, on the testes, of some of these compounds which may be related to structure **3** that had shown a profound effect on the testes of experimental animals.[4] This paper is concerned with the extension of the synthesis of the dispiro compounds (**2**) to the corresponding trispiro compounds (**4**).



1 2 3

R = $(CH_2)_3NMe_2$

CHART I



R = $(CH_2)_3NMe_2$; R' = H or C_2H_5

In the preparation of dispiro[5.2.5.2]hexadecan-3-one (**11**), considerable difficulty was experienced. For example, spiro[5.5]undecane-3,3-dipropionic ester (**10**, R = C_2H_5) was cyclized by means of potassium *t*-

(1) Part XIII: L. M. Rice and K. R. Scott, *J. Org. Chem.*, **32**, 1966 (1967).

(2) L. M. Rice, M. E. Freed, and C. H. Grogan, *ibid.*, **29**, 2637 (1964).

(3) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.*, **6** 388 (1963).

(4) C. F. Geschickter, 8th Annual Clinical Conference on Cancer, University of Texas, M. D. Anderson and Tumor Institute, Houston, Texas, 1963.

butoxide to the keto ester **12**. Hydrolysis and decarboxylation of **12** with 20% sulfuric acid in a limited number of trials gave only a small amount of impure ketone **11**. The ketone was eventually obtained by pyrolysis of the acid **10** with barium hydroxide. Wolff–Kishner reduction of the dispiro ketone **11**, employing the procedure used by deJongh and Wynberg,[5] gave the dispiro hydrocarbon **13**, identical (spectra and melting point) with dispiro[5.2.5.2]hexadecane.[5]

Reaction of the ketone with ethyl cyanoacetate and saturated alcoholic ammonia gave the Guareschi imide **14**, a new trispiroheneicosane ring system. The hydrolysis of **14** to dispiro[5.2.5.2]hexadecane-3,3-diacetic acid (**15**) proved to be extremely disappointing. In many trials with various concentrations of acid and reaction periods, only a very small amount of the desired acid (at best, less than 10% yield) could be obtained.

Because of the limited amount of acid **15**, it was decided to prepare the desired N-substituted trispiro base **4**, without isolation of the intermediate anhydride and imide. This was readily accomplished. The acid was treated with acetic anhydride to produce the anhydride. The crude anhydride was treated with 3-dimethylaminopropylamine, and the product was thermally cyclized to the crude imide, which on reaction with lithium aluminum hydride yielded the desired base **4**. This was converted directly to the dihydrochloride.

When compound **4** was screened for cytotoxicity in KB tissue culture cells, it showed inhibition at about 0.3 μg/ml which is of the same order of activity as **2** and **3**, each of which is effective in the range of 0.5–1 μg/ml. These multiring compounds are thus more active than the corresponding spiro[5.5]undecane derivative **1** which is active at 5 μg/ml.

Experimental Section

All melting points (Thomas–Hoover capillary-type apparatus) are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The infrared spectra of all compounds corresponded with assigned structures. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Diethyl Spiro[5.5]undecane-3,3-diacetate (5, R′ = C_2H_5).—The ester was prepared by refluxing a C_6H_6–alcohol–H_2SO_4 mixture with the acid **5** (R′ = H)[2] in the usual manner; the product was obtained in 91% yield, bp 136–146° (0.15 mm). *Anal.* ($C_{19}H_{32}O_4$) C, H.

3,3-Bis(β-hydroxyethyl)spiro[5.5]undecane (6).—A solution of 23 g (0.08 mole) of **5** in absolute Et_2O was slowly added with stirring to 0.3 mole of ethereal $LiAlH_4$ in 1 l. of anhydrous Et_2O. After stirring and refluxing for 4 hr, the reaction mixture was decomposed with 48 ml of H_2O, stirred an additional 4 hr, and filtered, and the filter cake was extracted twice with alcohol, then C_6H_6. The extracts were combined with the original filtrate and dried (Na_2SO_4). Removal of the solvents, *in vacuo*, gave a residue, 17 g (90%), which on two recrystallizations from C_6H_6 melted at 101–102°. *Anal.* ($C_{15}H_{28}O_2$) C, H.

3-Oxadispiro[5.2.5.2]hexadecane (7).—The glycol **6** (15 g, 0.06 mole) was treated with 100 ml (0.06 mole) of 48% HBr, and the mixture was heated on a steam bath overnight. After cooling, it was poured into 100 ml of H_2O, neutralized with Na_2CO_3, and extracted (three times with Et_2O). The ethereal extracts were combined and washed (dilute HCl, H_2O, saturated NaCl). After drying (Na_2SO_4), the ether was removed *in vacuo*, and the residue was recrystallized from EtOH–H_2O; 10.9 g (79%), mp 72–73°. An additional recrystallization raised the melting point to 73–74°. *Anal.* ($C_{15}H_{26}O$) C, H.

3,3-Bis(β-bromoethyl)spiro[5.5]undecane (8).—A mixture of 17 g (0.08 mole) of **7** and 150 ml (0.90 mole) of HBr was cooled to 10°, and 75 ml of concentrated H_2SO_4 was added in small portions with shaking and cooling. The resultant mixture was heated at 100° for 24 hr, cooled, diluted with 500 ml of H_2O, and extracted (three 100-ml portions of Et_2O). The Et_2O solution was washed (H_2O, saturated $NaHCO_3$, NaCl), then dried (Na_2SO_4). The Et_2O was removed *in vacuo*, and the residue was distilled to yield one fraction (3 g) collected to 165° (0.3 mm) (impure starting material), and a second fraction, bp 175–185° (0.3 mm). The latter was dissolved in EtOH–C_6H_6 and was twice treated with charcoal. After filtration, the solvents were removed *in vacuo*. Recrystallization from MeOH yielded pure **8**, 14.2 g (52%), mp 67–68°. *Anal.* ($C_{15}H_{26}Br_2$) C, H, Br.

3,3-Bis(β-cyanoethyl)spiro[5.5]undecane (9).—A solution of 14 g (0.04 mole) of **8** in 200 ml of EtOH was mixed with 20 g (0.30 mole) of KCN in 100 ml of 80% EtOH. The mixture was refluxed overnight, cooled, and poured into 2 l. of cold H_2O. The crude product which crystallized was filtered, washed thoroughly with H_2O, and air dried (9 g). After recrystallization from C_6H_6–petroleum ether (bp 37–54°), it melted at 78–80°. An additional recrystallization was made by dissolving the product in absolute EtOH and adding a few drops of H_2O; mp 80–80.5°, 8 g, 78%. *Anal.* ($C_{17}H_{26}N_2$) C, H, N.

Spiro[5.5]undecane-3,3-dipropionic Acid (10, R′ = H).—Compound **9** (17 g, 0.07 mole) and 200 ml of concentrated HCl were refluxed for 24 hr. After adding 200 ml of H_2O and cooling, 17 g (89%) of **10**, R′ = H, was obtained; mp 173–175° (173–174° after one recrystallization from MeOH). *Anal.* ($C_{17}H_{28}O_4$) C, H.

Diethyl Spiro[5.5]undecane-3,3-dipropionate (10, R′ = C_2H_5) was prepared as described for **5** (R′ = C_2H_5) from 16 g (0.05 mole) of acid; bp 165–175° (0.15 mm), 15.5 g, 88%. *Anal.* ($C_{21}H_{36}O_4$) C, H.

2-Carboethoxydispiro[5.2.5.2]hexadecan-3-one (12).—The diester **10** (R′ = C_2H_5) (19 g, 0.05 mole) was added to a refluxing solution of 20 g (0.17 mole) of KO-*t*-Bu in 1 l. of C_6H_6. After 4 hr of refluxing, the mixture was cooled, acidified with 10% HCl, and washed with H_2O. The C_6H_6 was washed ($NaHCO_3$ solution, saturated NaCl) and dried (Na_2SO_4). The C_6H_6 was removed *in vacuo;* the remaining oil (which gave a strong enol test with $FeCl_3$) had bp 158–160° (0.35 mm), yield 9.1 g (60%). *Anal.* ($C_{19}H_{30}O_3$) C, H.

Dispiro[5.2.5.2]hexadecan-3-one (11).—Compound **10** (R′ = H) (25 g, 0.09 mole) was mixed with 2.5 g of $Ba(OH)_2$ in a 100-ml flask equipped with a small column. On heating, some H_2O distilled above the melting point of the acid, and active pyrolysis started at 275–300°. The pressure was gradually reduced to 10 mm as the reaction proceeded. Toward the end of the reaction, the pressure was reduced to less than 0.5 mm and kept constant until no more distillate was obtained. The distillate was dissolved in Et_2O and washed with H_2O, saturated $NaHCO_3$, and saturated NaCl. After drying (Na_2SO_4), the Et_2O was removed, *in vacuo*, and the residue was distilled; bp 120–125° (0.12 mm). The distillate, 6 g (43%), on recrystallization from MeOH then from ligroin, had mp 85–85.5°. *Anal.* ($C_{16}H_{26}O$) C, H.

The **2,4-dinitrophenylhydrazone,** when prepared in the usual way and recrystallized from EtOH, melted at 156–157°. *Anal.* ($C_{22}H_{30}N_4O_4$) N.

1,5-Dicyano-3-azatrispiro[5.2.2.5.2.2]heneicosane-2,4-dione (14).—Compound 11 (6 g, 0.03 mole) and 5.7 g (0.06 mole) of ethyl cyanoacetate were dissolved in 50 ml of absolute EtOH and cooled to 0°. EtOH (75 ml), saturated with NH_3 at 0°, was added, and the mixture was stored at 0–5° for 1 week. The precipitated ammonium salt was filtered, dissolved in 2 l. of boiling H_2O, filtered, and acidified with HCl. The free imide was filtered, washed with H_2O, and dried; 5 g (45%), mp 297–299°, after recrystallization from EtOH. *Anal.* ($C_{22}H_{29}N_3O_2$) C, H, N.

Dispiro[5.2.5.2]hexadecane-3,3-diacetic Acid (15).—Compound **14** (4.5 g, 0.01 mole) was refluxed with 100 ml of 72% H_2SO_4 for 16 hr. After diluting with 300 ml of H_2O, the black reaction mixture was filtered, and the solid was boiled with 1 l. of saturated $KHCO_3$. Only a small amount of the solid dissolved. The solution was treated with charcoal, filtered, and treated with HCl. The product was allowed to settle. It was filtered and recrystallized from EtOH; yield 0.4 g (12%), mp 233–234°. *Anal.* ($C_{20}H_{32}O_4$) C, H.

(5) H. A. P. deJongh and H. Wynberg, *Tetrahedron*, **20**, 2553 (1964).

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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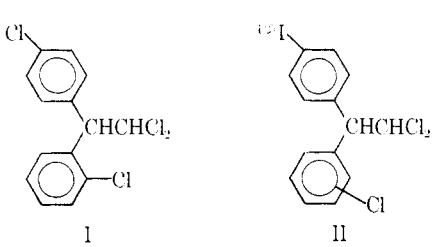
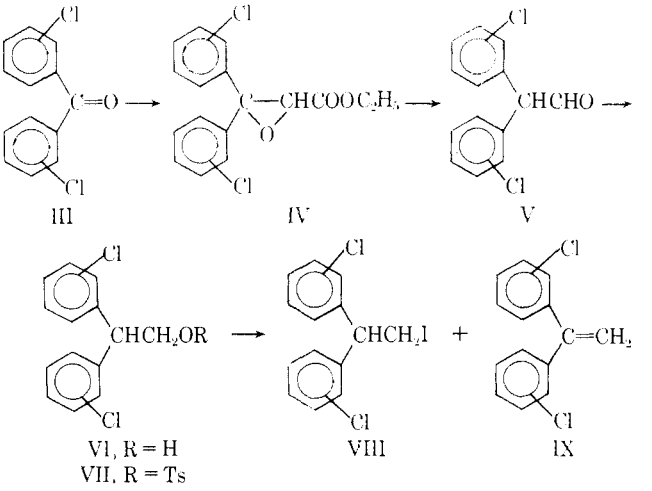
A previous paper[1] in this series indicated the clinical need for an agent which could be employed for photoscanning the adrenal gland and associated tumors. In an attempt to meet this need, several radioiodinated analogs of 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (*o,p'*-DDD, I) 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

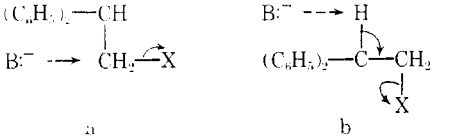


a, *o,p'*; b, *p,p'*; c, *o,o'*

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

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(6) Manuscript in preparation.

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