Antifertility Agents. 12. Structure-Activity Relationship of 3,4-Diphenylchromenes and -chromans[1]

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Synthesis and antiimplantation activity of variously substituted 2,2-dialkyl-3,4-diphenylchromenes and 3,4-*cis*- and *trans*-chromans derived from them are described. Pregnancy-inhibiting activity in rats was exhibited by a number of these compounds, which was particularly marked in the case of 3,4-*trans*-3-phenyl-4-*p*-(β-pyrrolidinoethoxy)-phenyl-7-methoxychroman (**32**), the corresponding 2,2-dimethyl analog **34**, and 3-phenyl-4-*p*-(β-pyrrolidinoethoxy)phenyl-7-methoxychromene (**26**). The structure–activity relationship of these compounds is discussed.

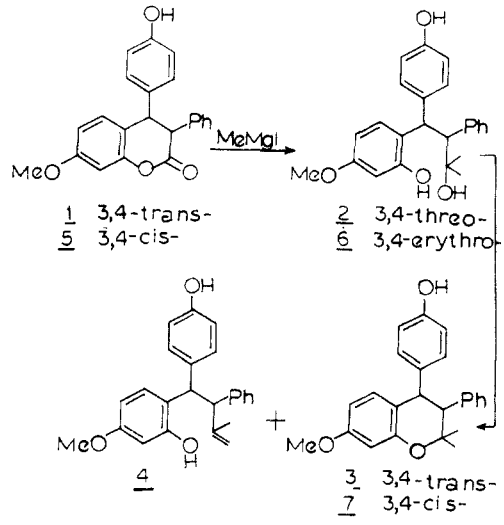
In a continuing search for nonsteroidal pregnancy-inhibiting agents,[2] the synthesis and antiimplantation activity of 2,3-diphenylbenzofurans, having an ω-*tert*-aminoethoxy chain at an appropriate position, were reported earlier.[2a] This led to a detailed study of 2,2-dialkyl-3,4-diphenylchromenes and 2,2-dialkyl-3,4-*cis*- and -*trans*-3,4-diphenylchromans as possible antifertility agents. Their syntheses and biological evaluation are reported in this communication. During the course of this work Carney et al.[3a] reported the preparation of *trans*-3-phenyl-4-*p*-(β-pyrrolidinoethoxy)phenyl-7-methoxychroman by Friedel–Crafts alkylation of phenol with 3-phenyl-7-methoxy-4-chromanol. The preparation of substituted 3,4-diphenylchromans and -chromenes and their estrogenic and antifertility activity were also reported by Carney et al.[3b]

cis- and *trans*-3,4-diphenylchromans were synthesized by acid-catalyzed cyclization of *erythro*- and *threo*-2,3-diphenyl-4-(*o*-hydroxy)phenyl-1-propanols, respectively, following the method described earlier.[2d] The synthesis of 2,2-dialkyl-3,4-diphenylchromans was first attempted through the reaction of alkylmagnesium halides on 3,4-diphenyldihydrocoumarins[4] (Scheme I), prepared in turn from the corresponding coumarins by treatment with Raney nickel alloy in alkali. *trans*-3-Phenyl-4-(*p*-hydroxyphenyl)-7-methoxy-3,4-dihydrocoumarin (**1**) on treatment with methylmagnesium iodide gave the *threo*-carbinol **2** in good yield. Treatment of **2** with MeOH–HCl or polyphosphoric acid gave the required *trans*-chroman **3** in only 15 and 25% yields, respectively, and the corresponding butene **4** was formed as the major product. This butene **4** could not be converted to the chroman under different conditions tried.

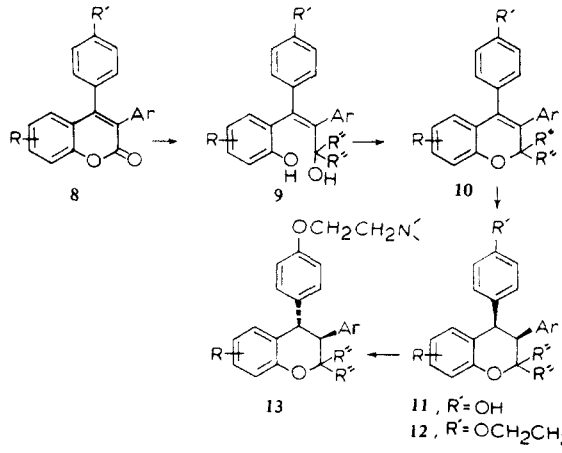
The *erythro*-butan-2-ol **6**, obtained in a similar manner from *cis*-dihydrocoumarin **5**, was found to be still more recalcitrant to cyclization, giving only about 4% yield of the required *cis*-chroman **7**. In the rotamer population of the *erythro*-carbinol **6**, the conformer shown in Figure 1 would be the most predominant as this would have the least gauche interactions of all the possible rotamers. The spatial geometry of this rotamer would be unfavorable for cyclization which is the likely reason for the poor yield obtained in the cyclization of the *erythro*-carbinol **6** to the *cis*-chroman **7**.

In view of the difficulty experienced in preparing chromans **3** and **7** by cyclization of carbinols **2** and **6**, the alternative route shown in Scheme II, starting from 2,-2-dialkyl-3,4-diphenylchromenes **10**, was next investigated. The chromenes **10** were very conveniently synthesized by the reaction of 3,4-diphenylcoumarins with excess Grignard reagents[5] when the corresponding diols **9** were obtained, which cyclized very readily to the required chromenes **10** by treatment with mineral acids or heating; this cyclization was particularly facile when electron-releasing groups were present in the phenyl rings in conjugation with the $\Delta^{3,4}$ in the starting coumarin, when even during work-up of the

Scheme I



Scheme II

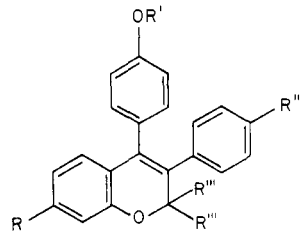


Grignard reaction product the chromenes were formed. The use of limiting quantities of Grignard reagent gave a mixture of products including the corresponding 2,3-diphenylbenzofurans.[6]

The chromenes **10** on catalytic hydrogenation gave the *cis*-chromans **11** in excellent yield and were converted to the corresponding β-*tert*-aminoethoxy ethers **12** by standard methods. **12** when treated with BuLi in Me_2SO isomerized almost quantitatively to the thermodynamically more stable *trans*-chromans **13**. This method thus provides a convenient route for the synthesis of both *cis*- and *trans*-chromans from a common intermediate.

In the NMR spectrum of the chromene **16** both the CH_3 groups resonate at 84 Hz ($CDCl_3$), while in chromans the CH_3 signals appear as two peaks at 74 and 98 Hz in the *cis*-chroman **33** and at 74 and 82 Hz in the *trans*-chroman **34**. The CH_3 signals thus appearing at 98 and 82 Hz were diagnostic for cis and trans diastereomers and were helpful

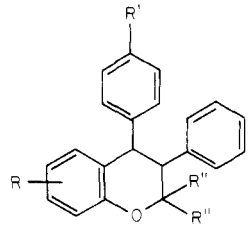
Table I



Compd no.	R	R'	R''	R'''	Mp, °C	Yield, %	Mol formula	Analyses	Antifertility ED_{100} (rat), mg/kg
14	OMe	H	H	Me	172	78	$C_{24}H_{22}O_3$	C, H	Inactive
15	OMe	$CH_2CH_2N(Et)_2$	H	Me	215	87	$C_{30}H_{35}NO_3 \cdot HCl$	C, H, N	10
16	OMe	CH_2CH_2-c-NC_4H_8	H	Me	216	85	$C_{30}H_{33}NO_3 \cdot HCl$	C, H, N	5
17	H	H	H	Me	152	73	$C_{23}H_{20}O_2$	C, H	Inactive
18	H	CH_2CH_2-c-NC_4H_8	H	Me	224	69	$C_{29}H_{31}NO_2 \cdot HCl$	C, H, N	10
19	OH	Me	H	Me	145	75	$C_{24}H_{22}O_3$	C, H	Inactive
20	OCH_2CH_2-c-NC_4H_8	Me	H	Me	118	76	$C_{30}H_{33}NO_3 \cdot HCl$	C, H, N	10
21	OMe	H	Cl	Me	205	70	$C_{24}H_{21}ClO_3$	C, H	Inactive
22	OMe	CH_2CH_2-c-NC_4H_8	Cl	Me	258	82	$C_{30}H_{32}ClNO_3 \cdot HCl$	C, H, N	5
23	OMe	Me	OMe	Me	133	78	$C_{26}H_{26}O_4$	C, H	Inactive
24	OMe	H	H	Et	96	45	$C_{26}H_{26}O_3$	C, H	Inactive
25	OMe	CH_2CH_2-c-NC_4H_8	H	Et	202	85	$C_{32}H_{37}NO_3 \cdot HCl$	C, H, N	10
26[a]	OMe	CH_2CH_2-c-NC_4H_8	H	H					0.15

[a] This compound was supplied by E. Merk, Darmstadt, for comparison of biological activity.

Table II



Compd no.	R	R'	R''	Isomer	Antifertility ED_{100} (rat), mg/kg
28	6-Me	H	H	Cis	Inactive
30	6-Me	H	H	Trans	Inactive
31	7-OMe	OCH_2CH_2-c-NC_4H_8	H	Cis	1
32	7-OMe	OCH_2CH_2-c-NC_4H_8	H	Trans	0.25
7	7-OMe	OH	Me	Cis	Inactive
33	7-OMe	OCH_2CH_2-c-NC_4H_8	Me	Cis	Inactive
3	7-OMe	OH	Me	Trans	Inactive
34	7-OMe	OCH_2CH_2-c-NC_4H_8	Me	Trans	0.25
35	7-OMe	OH	Et	Cis	Inactive
36	7-OMe	OCH_2CH_2-c-NC_4H_8	Et	Cis	Inactive
37	7-OMe	OCH_2CH_2-c-NC_4H_8	Et	Trans	5.0

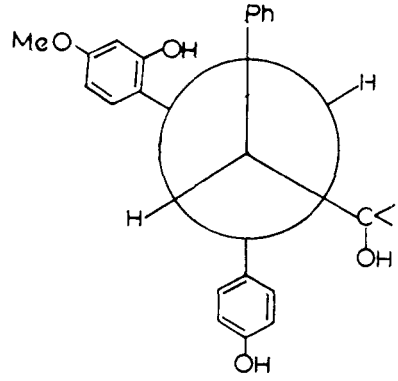


Figure 1.

in monitoring the stereochemical purity of the samples.

The compounds thus prepared are listed in Tables I and II.

Biological Activity. The compounds were tested for their antifertility activity in pregnant female albino rats of proven fertility. The day on which the vaginal smears showed the presence of spermatozoa was considered day 1 of pregnancy. In the primary screening the compounds were fed for 5 days from days 1–5 of pregnancy using five animals in each group. The compounds were macerated with gum acacia and administered orally to animals. The results were scored as positive only if implantations were totally absent in both uterine horns, examined on day 10 of pregnancy; control animals had an average of seven implants. The initial dose for each compound was 20 mg/kg/day unless otherwise mentioned. Compounds inactive at this dose level were dropped. Results of antifertility screening are given in Tables I and II.

Table III

Compd no.	Dose, mg/kg	Uterotrophic act.[a]	Vaginal opening	Vaginal smear
Control		13.6 ± 0.8 (6)	–	
Estrogen	1 μg/rat[b]	74.5 ± 3.0 (6)	+	+++
14	10	49.2 ± 4.2 (5)	+	+ to ++
15	10	42.0 ± 2.0 (6)	+	– to +
24	10	39.2 ± 2.4 (8)	+	–
25	10	35.4 ± 2.8 (7)	+	–
26[c]	10	37.4 ± 1.8 (7)	+	–
31	10	50.6 ± 2.0 (7)	+	++
31	5	43.7 ± 2.3 (7)	+	– to ++
32	10	48.3 ± 3.9 (7)	+	– to +
33	10	20.5 ± 1.3 (6)	–	
34	10	48.3 ± 3.1 (7)	+	++ to +++
35	10	14.6 ± 0.4 (7)	–	
36	10	16.5 ± 1.1 (6)	–	
37	10	46.6 ± 2.0 (7)	+	+ to +++

[a] Uterine weight in mg, mean ± SE; number of animals in parentheses. [b] Immature rats of 25–30-g weight. [c] Compound **26** is reported to be positive in the Allen-Doisy test according to E. Merck, Darmstadt.

Estrogenic activity of the compounds was tested in immature female rats weighing 25–30 g by increase in uterine weight[7] and vaginal cornification[8] and compared with estrone as standard, and the results are described in Table III. The compounds were administered orally twice

daily for 3 days and the animals killed on the fourth day. The uteri were separated from uterotubal and cervical junctions and weighed fresh after pressing out the uterine fluid between folds of a blotting paper. Vaginal smears were examined before autopsy and scored as −, diestrus smear, leucocytes only; +, mixture of leucocytes and epithelial cells; ++, proestrus smear, nucleated or nucleated and cornified cells; and +++, estrus smear cornified cells only.

Failure to induce vaginal opening[9] by any particular compound was considered as complete absence of estrogenic activity.

Most of the compounds showed weak estrogenic activity as compared to estrone. The antifertility potential of the compounds does not seem to be due to estrogenicity alone since compound **34**[2b] (under detailed investigation) showed estrogenic, antiestrogenic, and antiprogestational property.

In conformity with earlier results only compounds with a basic side chain showed antiimplantation activity and pyrrolidine residues in the side chain yielded more active compounds than the diethylamino moiety.[10] Introduction of a chloro radical in the para position of the 3-phenyl group as in **22** did not materially increase the activity in chromenes while removal of the 7-OMe radical as in **18** decreased the activity. It is of note that deletion of the substituents at the 2 position of chromenes (compound **26**) markedly increased activity.

In the chroman series the trans basic ether **32** showed activity approaching that of the most active chromene. The corresponding cis isomer **31** shows but one-fourth the activity of the trans compound. Substitution of the methyl group at the 2 position (compound **34**) has no influence on the activity of the trans isomer. The dimethyl cis isomer **33**, on the other hand, is inactive. Substitution of the 2 position of the trans compound by the larger ethyl group, compound **37**, decreases potency by a factor of 20. The corresponding cis isomer **36** is again inactive. Examination of Dreiding models of the isomeric chromans suggests that the trans isomers retain considerable planarity even when substituted at position 2; the same substitution induces considerable distortion in the cis isomers.

Experimental Section

All melting points were determined in a sulfuric acid bath and are uncorrected. The structure of the products was checked routinely by ir, uv, and NMR spectroscopy run on Perkin-Elmer Infracord 137, Unicam, and Varian A-60D spectrometers, respectively.

The following experiments represent typical experimental procedures employed in the preparation of the above-mentioned compounds.

2,2-Dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychromene (14). A solution of 3-phenyl-4-*p*-hydroxyphenyl-7-methoxycoumarin[4] (2.2 g, 0.006 mol) in tetrahydrofuran (40 ml) was gradually added to methylmagnesium iodide [from 8.5 g (0.05 mol) of CH_3I and 1.2 g (0.049 g-atom) of Mg] in dry ether (30 ml). The mixture was heated under reflux for 4 hr and poured over crushed ice containing ammonium chloride (10 g) and hydrochloric acid (5 ml). The reaction mixture was extracted with ethyl acetate, the extract was washed with water to neutrality and dried (Na_2SO_4), the solvent distilled off, and the syrup crystallized from benzene–petroleum ether: yield 1.8 g (78%); mp 172°C.

2,2-Dimethyl-3-phenyl-4-*p*-(β-pyrrolidinoethoxyphenyl)-7-methoxychromene (16). A mixture of **14** (0.5 g, 0.0016 mol), pyrrolidinoethyl chloride hydrochloride (0.5 g, 0.0029 mol), anhydrous potassium carbonate (2.0 g), and dry acetone (50 ml) was heated under reflux for 15 hr. The solvent was removed, the residue extracted with benzene, and the extract washed with water to neutrality and dried (Na_2SO_4). The benzene extract was passed through a short column of basic alumina; the solvent distilled off and the residue was converted to its hydrochloride and crystallized from ethanol–ether: yield 0.60 g (76%); mp 216°.

erythro-**2,3-Diphenyl-3-(2-tosyloxy-5-methyl)phenyl-1-*O*-tosylpropanol (27).** A mixture of *erythro*-2,3-diphenyl-3-(2-hydroxy-5-methyl)phenylpropan-1-ol[11] (2 g, 0.006 mol) and *p*-toluenesulfonyl chloride (3.4 g, 0.018 mol) in dry pyridine (15 ml) was heated on a steam bath for 3 hr, poured over ice, and extracted with benzene. The organic layer was washed with 3 *N* HCl and then with water to neutrality, dried (Na_2SO_4), and concentrated and the residue was crystallized from methanol: yield 2 g (53%); mp 140°. Anal. ($C_{36}H_{34}O_6S_2$) C, H.

cis-**3,4-Diphenyl-6-methylchroman (28).** A mixture of the ditosylate **27** (1.8 g, 0.0028 mol) in alcoholic KOH (KOH, 10 g in 200 ml of ethanol) was refluxed for 3 hr, the solvent distilled off, and residue extracted with benzene. The benzene extract was washed with water to neutrality, dried (Na_2SO_4), and concentrated and the residue was crystallized from benzene–methanol: yield 0.9 g (93%); mp 117°. Anal. ($C_{22}H_{20}O$) C, H.

threo-**2,3-Diphenyl-3-(2-tosyloxy-5-methyl)phenyl-1-*O*-tosylpropanol (29).** This was similarly prepared from the corresponding *threo*-2,3-diphenyl-3-(2-hydroxy-5-methyl)-phenylpropan-1-ol[11] in 56% yield and crystallized from benzene–hexane: mp 195°. Anal. ($C_{36}H_{34}O_6S_2$) C, H.

trans-**3,4-Diphenyl-6-methylchroman (30).** Cyclization of **16** by treatment with ethanolic KOH as described for **28** gave **30** in 91% yield which was crystallized from benzene–hexane: mp 117°. Anal. ($C_{22}H_{20}O$) C, H.

erythro-**2-Methyl-3-phenyl-4-(*p*-hydroxyphenyl)-4-(2-hydroxy-4-methoxy)phenylbutan-2-ol (6).** A 3 *M* solution of MeMgCl (6.5 ml) in THF was added to a solution of *cis*-3-phenyl-4-*p*-acetoxyphenyl-7-methoxy-3,4-dihydrocoumarin (1.5 g, 0.004 mol) in anisole (25 ml) and the reaction mixture stirred at 100° for 24 hr. The reaction mixture was then cooled, treated with ammonium chloride solution, and extracted with ether, the extract was washed with water and dried (Na_2SO_4), the solvent distilled off, and the residue was crystallized from THF–benzene, yield 1.22 g (80%), and recrystallized from THF–benzene: mp 192°. Anal. ($C_{24}H_{26}O_4$) C, H.

cis-**2,2-Dimethyl-3-phenyl-4-*p*-hydroxyphenyl-7-methoxychroman (7).** (a) A solution of the butanol **6** (1 g) in PPA (15 g) was heated at 75–80° for 0.5 hr. The reaction mixture was treated with water and the solid which separated was crystallized from benzene: yield 0.04 g (4%); mp 180°. Anal. ($C_{24}H_{24}O_3$) C, H.

(b) Hydrogenation of **14** (23.1 g) in 300 ml of THF in the presence of Pd/C catalyst [4.5 g of dry, 5% Pd/C and 12.8 g of 5% Pd/C (w/w 50/50)] at 60° and 100 psi of pressure gave 19.5 g (84%) of **7**.

cis-**2,2-Dimethyl-3-phenyl-4-*p*-(β-pyrrolidinoethoxy)-phenyl-7-methoxychroman (33).** β-Pyrrolidinoethyl chloride hydrochloride (9.8 g, 0.57 mol) was added to a warm solution of **7** (20.74 g, 0.058 mol) in NaOH (5.8 g, 0.145 mol), water (16.5 ml), and 2-propanol (104 ml) and the mixture was heated at 50° for 4 hr under vigorous stirring. The reaction solution was cooled and diluted with cold water (200 ml) and the solid which separated was collected by filtration, washed successively with 30% 2-propanol (10 ml) and cold water (40 ml), and dried: yield 23.7 g (90%); mp 118–121°.

The hydrochloride of **33** crystallized from ethanol–ether: mp 196°. Anal. ($C_{30}H_{36}ClNO_3$) C, H, N.

trans-**2,2-Dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman (3).** (a) A solution of *trans*-3-phenyl-4-*p*-hydroxyphenyl-7-methoxy-3,4-dihydrocoumarin[4] (3.46 g, 0.01 mol) in dry THF was added under stirring to CH_3MgI prepared from CH_3I (7.10 g, 0.05 mol) and Mg (1.33 g, 0.05 g-atom) in dry ether. The reaction mixture was refluxed for 6 hr and then worked up as described above for **6**. The oily product thus obtained was found to be a complex mixture (five spots) on TLC. Chromatography of this mixture on silica gel using increasing proportions of chloroform in benzene as eluent gave **3** in 15% yield (0.55 g) which was crystallized from benzene: mp 264°. Anal. ($C_{24}H_{24}O_3$) C, H.

Further development of the column gave *threo*-2-methyl-3-phenyl-4-(*p*-hydroxyphenyl)-4-(2-hydroxy-4-methoxy)phenylbutan-2-ol (**2**) in 20% yield (0.75 g) which was crystallized from benzene–hexane: mp 180°. Anal. ($C_{24}H_{26}O_4$) C, H.

(b) A solution of the butanol **33** (1 g) in PPA (15 g) was heated

at 75–80° for 0.5 hr. The reaction mixture was decomposed with water and the separated solid was crystallized from benzene: yield 0.22 g (25%).

(c) The butanol **2** when heated under reflux with EtOH–HCl (4%) gave **3** in 15% yield.

***trans*-2,2-Dimethyl-3-phenyl-4-*p*-(β-pyrrolidinoethoxyphenyl)-7-methoxychroman (34).** (a) Alkylation of **3** with β-pyrrolidinoethyl chloride hydrochloride as mentioned above for **7** gave **34** in 92% yield which was converted to its HCl salt and crystallized from ethanol–ether: mp 164°. Anal. ($C_{30}H_{36}ClNO_3$) C, H, N.

(b) BuLi (35 ml of 19.85%) in THF was added to a suspension of **33** (23.6 g, 0.05 mol) in 250 ml of anhydrous Me_2SO at room temperature under nitrogen atmosphere under good stirring. The resulting red solution was stirred for further 3 hr and then decomposed with 50 ml of cold water. The reaction mixture was then poured over 1.5 l. of an ice–water mixture and extracted with ether. The organic layer was washed well with water and dried (Na_2SO_4), the solvent distilled off, and the residue converted to its HCl salt and crystallized from ethanol–ether: yield 24.8 g (97.4%); mp 164°.

***cis*-2,2-Diethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman (35).** High-pressure hydrogenation of **24** following the procedure used for **7** yielded **35** in 68% yield. The solid was recrystallized from benzene–hexane: mp 186°. Anal. ($C_{26}H_{28}O_3$) C, H.

***cis*-2,2-Diethyl-3-phenyl-4-*p*-(β-pyrrolidinoethoxy)-phenyl-7-methoxychroman (36).** Alkylation of **35** with β-pyrrolidinoethyl chloride hydrochloride as mentioned above for **33** gave a 93% yield of **36** as a solid compound which was recrystallized from benzene–hexane: mp 133–133.5°. Anal. ($C_{32}H_{39}NO_3$) C, H, N.

***trans*-2,2-Diethyl-3-phenyl-4-*p*-(β-pyrrolidinoethoxy)-phenyl-7-methoxychroman (37).** Isomerization of **36** using BuLi in Me_2SO as mentioned for **34** yielded 81.3% of **37** which was converted to its HCl salt and crystallized from 2-propanol: mp 227°. Anal. ($C_{32}H_{40}ClNO_3$) C, H, N.

Acknowledgment. We are thankful to Dr. Jim Bolger for his help in the reduction of chromene **14** and its subsequent isomerization which greatly facilitated the preparation of **34**.

References and Notes

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Relationship of Molecular Structure to in Vivo Scintigraphic Distribution Patterns of Carbon-11 Labeled Compounds. 3. [11C]Hydantoins

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The preparation and γ-scintigraphic evaluation of the in vivo distribution patterns in dogs of a series of structurally related hydantoins labeled with the positron emitting, 20.4 min half-life radionuclide, carbon-11 are described. Carbon-11 labeled HCN was collected in water or aqueous Me_2SO containing carrier KCN following cyclotron bombardment of 99% N_2–1% H_2 gas mixture with 22 MeV protons for 1 hr at 25–35 μA. Five ^{11}C-labeled 5,5-dialkylhydantoins, three [^{11}C]diarylhydantoins, five [^{11}C]-5-alkyl-5-phenylhydantoins, and five [^{11}C]spirohydantoins were prepared by heating, generally under pressure, a mixture of ^{11}C-labeled KCN, which was produced by isotopic exchange with carrier KCN, the corresponding aldehyde or ketone, and excess $(NH_4)_2CO_3$ in aqueous ethanol or Me_2SO solvent. The ^{11}C-labeled hydantoins were dissolved in 1–1.5% aqueous NaOH for intravenous administration to dogs. Total synthesis time was 70–106 min and 1–59 mCi of final product was available for conducting serial in vivo imaging for up to 2 hr or more with the γ-scintillation camera. Carbon-11 activity from all compounds showed initial blood-pool distribution with variable concentration of activity in the brain, lungs, liver, and kidney. All of the ^{11}C-labeled diarylhydantoins, and most having one phenyl substituent, and one having a hexamethylene moiety showed initial accumulation of ^{11}C activity in brain. Carbon-11 labeled 5,5-diphenylhydantoin (dilantin) showed the greatest qualitative accumulation of activity in the brain. Those ^{11}C-labeled hydantoins having a carboxyl substituent showed prominent renal concentration and urinary excretion of activity. Most ^{11}C-labeled hydantoins showed a progressive homogenous whole body distribution of activity in all cellular tissues of the body. The relatively uniform distribution of activity in cellular tissues and slow excretion from the body support the thesis that the pharmacologic action of the hydantoins is related to physical effects on biomembranes rather than to specific chemical interactions with cell constituents.

Data presently available from experiments using ^{14}C-labeled compounds are insufficient to predict adequately the relationship between molecular structure of an organic compound and its in vivo distribution pattern as studied by scintigraphic techniques. This is so for several reasons. The inherent low specific activity of ^{14}C-labeled compounds makes ^{14}C an unsuitable label for evaluation of in vivo distribution patterns of molecules whose in vivo distribution demonstrates a strong "carrier" effect in the range of the quantity of ^{14}C-labeled material