

Animals were randomly distributed into groups of six animals. A modification⁵¹ of the uterotrophic assay described above was used. Estradiol was dissolved in sesame oil (0.1 µg/mL). The test compounds were dissolved in IPM and diluted with IPM to achieve desired concentrations. The solutions were periodically checked by TLC to insure homogeneity. Injections were made in the nape of the neck for 3 consecutive days. The unstimulated control group received vehicles alone (0.05 mL of IPM and 0.1 mL of sesame oil each day), while the stimulated control group received 0.1 mL of the estradiol solution (total dose 0.03 µg). All test groups received 0.1 mL of the stimulating dose of estradiol (0.01 µg) plus 0.05 mL of the test compound solutions each day. The IPM and oil injections were made at separate sites to minimize possible physical or chemical interactions or reduced absorption of either compound. Antiestrogenic activity was measured as a decrease from the estradiol-induced increase in uterine weight seen in the test compound groups versus the estradiol-stimulated group alone.

Cell Culture. MCF-7 human breast cancer cells (obtained from the Michigan Cancer Foundation, Detroit) were grown as monolayer cultures at 37 °C in T-75 flasks in RPMI 1640 medium (without phenol red) supplemented with 2 mM L-glutamine, gentamicin (50 µg/mL), penicillin (100 units/mL), streptomycin

(100 µg/mL), and calf serum (5%). Cultures were grown in a humid 5% CO₂ atmosphere and fed on alternate days. Exponential growth was maintained by subculturing at intervals when a level of (10–12) × 10⁶ cells/T-75 flask was reached (8 days). Cells were trypsinized and plated in multiwell plates at a density of 7.5 × 10⁴ cells/well in 3 mL of medium. The cells were allowed to attach for 2 days in the growth medium. The test compounds were dissolved in 11:9 PEG 400–EtOH and added to the culture medium on alternate days. The final concentration of vehicle was 0.1%. Control samples received vehicle alone at the same concentration. Cell growth was measured on day 4 by hemocytometric trypan blue exclusion. Percent inhibition was calculated as the ratio of the control mean cell count per well minus the treatment group mean cell count per well to the control mean cell count per well, multiplied by 100.

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Synthesis and Biological Activity of *D*₃-Trishomocubyl-4-amines

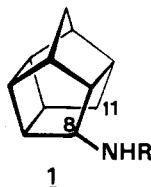
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The *D*₃-trishomocubyl system was prepared from tertiary pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ols **5** in one step by using a modified Ritter reaction yielding only one of the possible two geometrical isomers of 4-amino-3-alkyl (or aryl)-*D*₃-trishomocubane (**8**). Promising antagonism of reserpine-induced catalepsy was exhibited by these compounds which compared favorably with that of amantadine. Weak to mild anticholinergic properties were observed during the reduction of oxotremorine induced tremor and salivation procedure. Acute toxicities similar to that of amantadine were observed for some of these compounds. *D*₃-Trishomocubyl-4-amines appeared as a promising new class of anti-Parkinson agents.

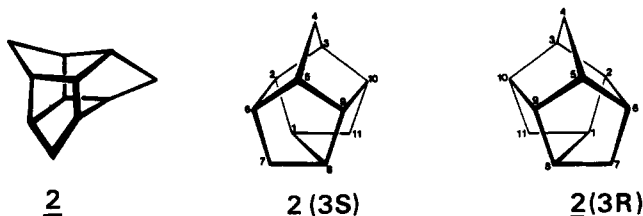
Introduction

The tricyclic amantadine (1-aminoadamantane) is well-known for its clinical applications since the discoveries of its antiviral¹ and anti-Parkinson² properties. Numerous studies on the chemistry of various novel polycyclic hydrocarbons have been conducted the past half-century.^{3–6} However, research on the biological activities of these compounds have to a large extent been neglected. We recently reported the synthesis and pharmacological properties of a series of novel pentacyclic amines, namely pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl-8-amines (**1**).⁷



Promising anticataleptic activities were observed for some members in the series, while only weak to mild anticholinergic activities were noted. It was concluded that potential anti-parkinson properties of these pentacycloundecylamines were attributed by their effects on the dopaminergic system.⁷ *D*₃-Trishomocubane (**2**), i.e. pentacyclo[6.3.0.2⁶.0^{3,10}.0^{5,9}]undecane, the most thermodynamically stable member⁸ of all the possible pentacyclo-

undecanes, has drawn the attention of many researchers because of its unique *D*₃ stereochemistry. Various authors^{9–19} have reported the synthesis of *D*₃-trishomocubane and its derivatives during the past 20 years. This unique carbon skeleton, having chiral point group *D*₃ symmetry, intrinsic gyrochirality, and the stereoisomerism of *D*₃-trishomocubane have significant stereochemical implications, resulting in 3*R* and 3*S* stereoisomers for the racemic



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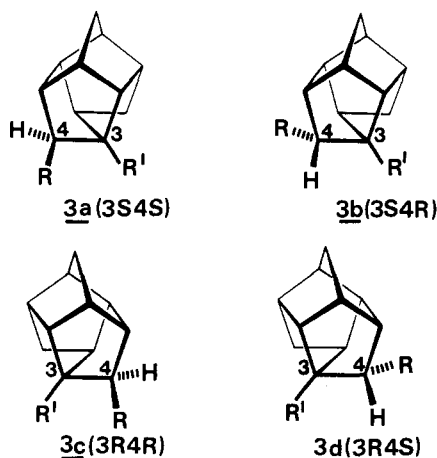
[†] Noristan Ltd.

Table I. 3-Substituted 4-Amino-*D*₃-trishomocubanes **8a-h**

substrate	reagent	product	yield %	mp, °C	formula ^d	¹³ C NMR (CDCl ₃)
5: R ¹ = CH ₃	CH ₃ CN-H ₂ SO ₄ ^a	8a: R ¹ = CH ₃	62	315 dec	C ₁₂ H ₁₈ NCl	60.4, 55.3, 49.4, 48.9, 47.4, 46.6, 46.2, 45.6, 42.0, 33.6, 31.5, 15.0 (CH ₃)
5: R ¹ = C ₆ H ₅	CH ₃ CN-H ₂ SO ₄ ^a	8b: R ¹ = C ₆ H ₅	55	308 dec	C ₁₇ H ₂₆ NCl	138.0, 128.0, (2 × C), 127.7, 126.2 (2 × C), 63.5, 59.3, 50.9, 49.2, 47.0, 46.5, 44.7, 43.9, 40.6, 33.1, 30.9
5: R ¹ = CH ₃	CH ₃ CN-H ₂ SO ₄ ^b	8c: R ¹ = CH ₃ , R = C ₂ H ₅	92	279-281	C ₁₄ H ₂₂ NCl	65.3, 55.0, 49.3, 47.0, 46.7, 46.4 (2 × C), 45.2, 41.5, 41.3, 33.4, 31.0, 15.2 (CH ₃), 10.7 (CH ₃)
5: R ¹ = CH ₃	C ₃ H ₇ CN-H ₂ SO ₄ ^b	8d: R ¹ = CH ₃ , R = C ₄ H ₉	85	199-201	C ₁₆ H ₂₆ NCl	65.6, 55.1, 49.3, 47.0, 46.9, 46.4 (3 × C), 45.3, 41.3, 33.4, 31.0, 26.9, 20.1, 15.3 (CH ₃), 13.3 (CH ₃)
5: R ¹ = CH ₃	C ₆ H ₅ CN-H ₂ SO ₄ ^b	8e: R ¹ = CH ₃ , R = CH ₂ C ₆ H ₅	88	174-175	C ₁₉ H ₂₄ NCl	130.5, 130.2 (2 × C), 128.6 (3 × C), 64.2, 55.1, 49.4, 49.0, 47.1, 46.4 (2 × C), 45.3, 41.3, 33.3, 30.9, 15.4 (CH ₃)
5: R ¹ = CH ₃	C ₆ H ₅ CH ₂ CN-H ₂ SO ₄ ^b	8f: R ¹ = CH ₃ , R = C ₂ H ₄ C ₆ H ₅	86	210-212	C ₂₀ H ₂₆ NCl	137.2, 128.7 (4 × C), 126.8, 66.3, 55.5, 49.6, 48.2, 47.3, 47.1, 46.7, 45.5, 41.6, 36.1, 33.7, 31.9, 31.3, 15.6 (CH ₃)
5: R ¹ = C ₂ H ₅	CH ₃ CN-H ₂ SO ₄ ^b	8g: R ¹ = C ₂ H ₅ , R = C ₂ H ₅	87	195-197	C ₁₅ H ₂₄ NCl	60.9, 59.4, 46.6, 46.5 (2 × C), 46.2, 44.2, 44.1, 41.1, 40.5, 32.8, 30.3, 19.6, 10.2 (CH ₃), 8.8 (CH ₃)
5: R ¹ = C ₆ H ₅	CH ₃ CN-H ₂ SO ₄ ^b	8h: R ¹ = C ₆ H ₅ , R = C ₂ H ₅	74	298 dec	C ₁₉ H ₂₄ NCl	137.9, 128.6 (4 × C), 126.8, 66.9, 63.6, 50.3, 49.6, 47.4, 47.0, 46.0, 44.3, 42.0, 40.7, 35.5, 31.3, 10.6 (CH ₃)

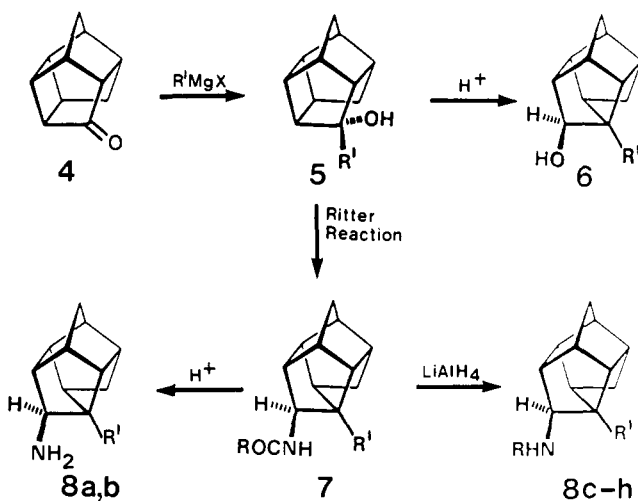
^a Ritter reaction followed by hydrolysis. ^b Ritter reaction followed by LiAlH₄ reduction. ^c Isolated yield based on starting alcohol (5). ^d All compounds gave satisfactory microanalytical data in accordance with the proposed formulae.

mixture of unsubstituted *D*₃-trishomocubane. The various routes reported for the synthesis of the *D*₃-trishomocubyl system all afforded the racemic mixture **2** (3*R* and 3*S*).⁹⁻¹⁹ Additionally, several geometrical isomers are subsequently possible for substituted *D*₃-trishomocubanes (see structures **3a-d**).²⁰ No attention has to date been paid to the



pharmacological properties of amino derivatives of *D*₃-trishomocubanes. This paper reports the synthesis of 4-amino-*D*₃-trishomocubanes and their anticataleptic and anticholinergic properties in order to test their potential as anti-Parkinson agents. Their therapeutic indices were also derived through evaluation of their acute toxicities.

Scheme I



Chemistry

We reported¹⁹ that 8-methylpentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ol (**5**; R¹ = CH₃) rearranges smoothly and stereoselectively to 3-methyl-*D*₃-trishomocuban-4-ol (**6**; R¹ = CH₃) (Scheme I). It was stated that this rearrangement may find general application in the synthesis of 4-X-3-alkyl (or aryl)-*D*₃-trishomocubanes from **5**, where X is an appropriate nucleophile present in carbocationic generation medium. In the present study a number of tertiary alcohols of type **5** were prepared (Scheme I) by reaction of monoketone **4**^{18,19} with the appropriate Grignard reagents. A modified Ritter reaction^{21,22} provided the base for a facile synthesis of 4-amino derivatives of 3-alkyl (or aryl)-*D*₃-trishomocubanes (**8**; Scheme I, Table I). The Ritter reaction was carried out by treatment of a tertiary alcohol **5** with a nitrile in concentrated sulfuric acid at -10°. 3-Substituted *D*₃-trishomocuban-4-amide **7** was obtained in good yield by quenching the reaction mixture with alkaline ice water. The amide was subsequently either hydrolyzed to the primary amine **8a,b** or reduced with lithium aluminium hydride to the corresponding secondary amine **8c-h** (Scheme I). The ¹³C NMR spectra (Table I) of the amines **8a-h** prepared via the Ritter reaction show on ¹³C signal per carbon atom,

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Table II. Acute Toxicity (LD₅₀), Anticataleptic Activity (ED₅₀), and Therapeutic Index of 3-Substituted 4-Amino-*D*₃-trishomocubanes **8a-h**

no.	substituent		LD ₅₀ , mg/kg (24 h)	ED ₅₀ , mg/kg	therapeutic index: LD ₅₀ /ED ₅₀
	R	R ¹			
8a	H	CH ₃	>1000	145	6.9
8b	H	C ₆ H ₅	681	16	42.5
8c	C ₂ H ₅	CH ₃	315	10	31.5
8d	(CH ₂) ₃ CH ₃	CH ₃	150	15	10.0
8e	CH ₂ C ₆ H ₅	CH ₃	>1000	34	>29.4
8f	(CH ₂) ₂ C ₆ H ₅	CH ₃	>1000	150	>6.6
8g	C ₂ H ₅	C ₂ H ₅	462	17	27.2
8h	C ₂ H ₅	C ₆ H ₅	261	14	18.6
amantadine			1000	17	58.8

indicating that only one of the possible two geometrical isomers were obtained. The Ritter reaction therefore proceeds highly stereospecifically to yield the geometrical isomer with the proposed 3*S*4*S*/3*R*4*R* stereochemistry.²³

Biological Evaluation

3-Substituted-4-amino-*D*₃-trishomocubanes **8a-h** were screened for their anticataleptic and anticholinergic activities and acute oral toxicity in mice.⁷ The ED₅₀ values for reversing the reserpine-induced catalepsy were determined in order to rank the relative potencies of *D*₃-trishomocubanes^{24,25} (Table II). An Irwin-dose range behavioral screen²⁶ indicated the approximate acute toxicity of the test compound (Table II). The reduction of the oxotremorine-induced salivation and tremor²⁶ indicated the anticholinergic activity of the test compounds (Table III). Amantidine hydrochloride and atropine sulfate were used as reference drugs. The therapeutic indices (LD₅₀/ED₅₀) were calculated and appear in Table II.

Discussion and Conclusion

Behavioral patterns, i.e. central nervous system stimulation, increased locomotor activity, and convulsions, were observed for these *D*₃-trishomocubanes similar to those previously noted for the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl series⁷ and amantidine.²⁷ Stereotyped behaviour induced by the *D*₃-trishomocubanyl-4-amines included head flicking and uncontrolled licking. Deaths occurred only during the first 24 h (Table II).

Comparing the ED₅₀ values of the *D*₃-trishomocubylamines with that of amantidine in reversing the reserpine-induced catalepsy indicate that several *D*₃-trishomocubanes exhibit promising anticataleptic activities (10–34 mg/kg) which compare with that of amantidine (17 mg/kg). Two compounds, i.e. the primary amine **8a** (145 mg/kg) and *N*-ethylphenyl **8f** (150 mg/kg) are considerably less active than amantidine and the other *D*₃-trishomocubyl derivatives. Contrary to the low activity of the primary amine **8a**, the primary amine **8b** is approximately 10 times more active than **8a**. It is interesting to note that **8b** has at carbon C-3 a phenyl substituent compared to the methyl group at C-3 of **8a**. Approximate equipotency was observed for the secondary amine **8h** (*N*-ethyl; 14 mg/kg) and the corresponding primary amine **8b** (16 mg/kg) that may suggest the importance of a C-3 phenyl substituent. The secondary amines **8c** (*N*-ethyl; 10 mg/kg), **8d** (*N*-butyl; 15 mg/kg), and **8e** (*N*-benzyl; 34 mg/kg) are signifi-

Table III. Anti-Oxotremorine Activity Reduction of Tremor and Salivation of 3-Substituted 4-Amino-*D*₃-trishomocubanes **8a-h**

no.	substituent		dose, ^a mg/kg	mean score (±SEM) ^b	
	R	R ¹		tremor	salivation
vehicle				2.0 ± 0.1	2.6 ± 0.1
amantadine			100	1.7 ± 0.1	1.1 ± 0.4
atropine			3	0.5 ± 0.1	0.0 ± 0.0
8a	H	CH ₃	100	1.7 ± 0.2	1.3 ± 0.2
8b	H	C ₆ H ₅	30	1.6 ± 0.2	1.2 ± 0.3
8c	C ₂ H ₅	CH ₃	10	1.7 ± 0.2	1.4 ± 0.2
8d	(CH ₂) ₃ CH ₃	CH ₃	10	1.2 ± 0.1	1.2 ± 0.2
8e	CH ₂ C ₆ H ₅	CH ₃	30	1.5 ± 0.2	1.5 ± 0.2
8f	(CH ₂) ₂ C ₆ H ₅	CH ₃	30	1.3 ± 0.3	1.3 ± 0.2
8g	C ₂ H ₅	C ₂ H ₅	30	1.6 ± 0.2	2.5 ± 0.2
8h	C ₂ H ₅	C ₆ H ₅	10	1.3 ± 0.3	1.0 ± 0.2

^aDose which exhibited the highest activity. ^bThirty minutes postdose.

cantly more potent than the primary amine **8a**. Diethyl groups (*N*-ethyl; 3-ethyl) afforded *D*₃-trishomocubane **8g** that exhibited equipotency to amantidine. In general, hydrophobicity seems to be important for the anticataleptic properties of these *D*₃-trishomocubanes. Comparing the acute toxicities of the *D*₃-trishomocubanes, the more hydrophilic primary amines (**8a,b**), as well as the compounds containing aromatic moieties (**8b,e,f**), are considerably less toxic than the other members of this series. However, compound **8h** which also contains an aromatic moiety, exhibited much higher toxicity. The increased hydrophobicity due to *N*-substitution could account for the higher toxicity of **8h**. The remaining alkyl substituted compounds **8c**, **8d**, and **8g** exhibited higher toxicities, supporting the suggestion that the toxicities of the *D*₃-trishomocubanes may be related to their hydrophobicities. The rank order of the most promising *D*₃-trishomocubyl-4-amines based on therapeutic indices is as follows: **8b** (42.5), **8c** (31.5), **8e** (29.4), and **8g** (27.2). The primary amine 3-phenyl-*D*₃-trishomocubyl-4-amine (**8b**) appears to be the most promising compound (TI = 42.5) when compared with amantidine (TI = 58.8).

The anticholinergic activities of the *D*₃-trishomocubyl-4-amines as tested in the anti-oxotremorine test are throughout significantly lower than the activity of the classical anticholinergic drug atropine but comparable with that of amantidine in both the reduction of the induced tremor and salivation. Although the induced salivation is reduced more than the induced tremor, the *D*₃-trishomocubylamines possess in general only weak to mild anticholinergic activities (Table III), similar to those previously reported for the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl-8-amines.⁷

A series of *D*₃-trishomocubyl-4-amines was prepared via a stereospecific Ritter rearrangement of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ol compounds. These *D*₃-trishomocubylamines were found to possess anticataleptic and anticholinergic activities comparable to that of amantidine. Hydrophobicity and the presence of aromatic moieties seem to play an important role in both the activity and toxicity of these *D*₃-trishomocubyl-4-amines. These results indicate that *D*₃-trishomocubyl-4-amines have promising potential as anti-Parkinson agents.

Experimental Section

Chemistry. Melting points were determined on a Gallenkamp apparatus (design no. 889339) and are uncorrected. A Pye Unicam 104 instrument was used for G.L.C. analysis (2% Carbowax on Celite). Mass spectra were recorded at 70 eV on a A.R.I. MS 12 spectrometer, using direct insertion. Elemental analyses were performed on a Perkin-Elmer Model 240 analyzer and data were within about 0.4% of the theoretical values. NMR spectra were recorded on Varian spectrometers (T60, EM-390, HA-100, and CFT-20) and on a Bruker WM-300 spectrometer using TMS as

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internal standard with CDCl_3 and D_2O as solvents. Infrared spectra were obtained with a Beckmann Acculab 4 spectrometer with carbon tetrachloride and KBr disks.

3-Alkyl(or Aryl)-4-amino- D_3 -trishomocubanes 8a-h
General Procedure. Concentrated sulfuric acid (12 mL) was added slowly to a well-stirred nitrile (40 mL) (Table I) at 0°C . The stirred mixture was cooled to -10°C and the tertiary alcohol 5 (0.5 g) was added slowly to keep the reaction temperature at -10°C . The reaction mixture was allowed to reach room temperature, stirred for another 3 h, and then poured onto ice, whereupon the mixture was made alkaline with aqueous sodium hydroxide (10%). Precipitated amide 7 was filtered, dried, and either hydrolyzed or reduced without further purification. The amide was reduced with LiAlH_4 in anhydrous ether under reflux for 2 h to the desired 4-amino- D_3 -trishomocubane 8c-h. The excess LiAlH_4 was decomposed with ice-cold water, and the amine was extracted with ether (3×50 mL). The organic layer was dried (sodium sulfate) and evaporated (20 mbar), yielding 4-amino- D_3 -trishomocubanes 8c-H. The amine was dissolved in anhydrous ether, and hydrogen chloride was bubbled through the solution, whereupon the hydrochloride salts of the 4-amino- D_3 -trishomocubanes (Table I) crystallized. Amide 7 was hydrolyzed under reflux conditions in concentrated hydrochloric acid (72 h) to yield the corresponding primary 4-amino- D_3 -trishomocubane 8a,b. The reaction mixture was made alkaline, whereupon the amine was extracted with ether (3×50 mL). The organic layer was then treated as described above, yielding the hydrochloride salt of the primary 4-amino- D_3 -trishomocubane 8a,b (Table I).

Pharmacology. Irwin Dose-Range Study/Acute Toxicity in Mice. Male CD-1 mice were deprived of food for 18 h prior to the experiment, but water was available ad libitum except during the observation period. The test compounds were prepared in 1% tragacanth and administered orally to groups of four mice. The test compound were tested at 1000, 464, 214, and 100 mg/kg;

the dose volume remained constant at 10 mL/kg. The animals were observed daily for 7 days postdose and any mortalities noted. The LD_{50} values were estimated by using the method of Horn.²⁸

Anti-Oxotremorine Test in Mice. Male CD-1 mice were deprived of food for 18 h prior to the experiment, but water was available ad libitum except during the observation period. The test compounds were prepared in 1% tragacanth and administered orally to groups of 10 mice. The test compounds were tested at doses of 100, 30, and 10 mg/kg at a constant dose volume of 10 mL/kg. Thirty minutes after administration of the test compound, vehicle, or reference standard, the mouse received an intraperitoneal injection of oxotremorine (0.4 mg/kg). The intensity of salivation and tremor was scored for all mice on a 0-3 scale, at 10, 20, and 30 min post-oxotremorine. Only the concentrations of the test compounds exhibiting the most promising anti-oxotremorine activity appear in Table III.

Antagonism of Reserpine-Induced Catalepsy in Mice. Male CD-1 mice were deprived of food for 18 h prior to the experiment, but water was available ad libitum except during the observation period. The test compounds were prepared in 1% tragacanth and administered orally to groups of five mice. Four hours prior to the administration of the test compounds or vehicle, each mouse received an intraperitoneal dose of reserpine (5 mg/kg). Forty-five minutes after the administration of the test compounds or vehicle, each mouse was placed with its forepaws on a 5-cm high cork, in order to assess the presence or absence of catalepsy. Mice which remain in this position for 5 min were considered cataleptic. The ED_{50} (i.e. the dose of the test compound causing a reduction of the catalepsy score to 50% of that of the control group) values were determined. Each test compound was tested at doses 100, 30, and 10 mg/kg. A constant dose volume of 10 mL/kg was employed.

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Synthesis, Receptor Binding, and Tissue Distribution of 7α - and 11β -Substituted ($17\alpha,20E$)- and ($17\alpha,20Z$)-21- ^{125}I Iodo-19-norpregna-1,3,5(10),20-tetraene-3,17-diols[†]

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The 11β -methoxy, 11β -ethoxy, and 7α -methyl derivatives of the isomeric ($17\alpha,20E$)- and ($17\alpha,20Z$)-(iodovinyl)estradiols 3 and 6, and their no-carrier-added [^{125}I]iodovinyl analogues, were evaluated for their relative target-tissue retention and binding affinity for the estrogen receptor. The isomeric iodovinyl and [^{125}I]iodovinyl derivatives were prepared via destannylation of the corresponding tributylstannyl precursors in the presence of H_2O_2 or chloroamine-T, with retention of configuration. The $20Z$ isomers 6 exhibited slightly higher receptor binding affinities than the $20E$ isomers 3, with all eight isomeric products giving relative binding affinity values in the 20-50 range. The 11β - and 7α -substituted (iodovinyl)estradiols gave substantially higher estrogen receptor-mediated uterus uptake as compared to the nonsubstituted parent molecule. Synergism between the effect of 11β - or 7α -substituents and the configuration of the iodovinyl group was evident from the in vivo distribution pattern of [^{125}I]-3 and -6. The best uterus uptake was observed, at 2 h postinjection, with the $20E$ isomer of 11β -methoxy derivative 3b. However, at 5 h postinjection the $20Z$ isomer 6b reached higher uterus concentrations than the $20E$ isomer 3b, and furthermore, these values are now comparable to those observed with the $20Z$ isomer of the 11β -ethoxy derivative 6c. In the case of the 7α -methyl derivatives the differences in in vivo stability between the $20E$ and $20Z$ isomers was less pronounced, whereas the $20Z$ isomer 6d reached somewhat higher uterus to blood as well as nontarget ratios.

A radiolabeled estrogen analogue with high binding affinity for estrogen receptors could play an important role in the characterization, delineation, as well as management of breast cancer. Among the many radiolabeled estrogens advanced to this end,¹ the 17α -iodovinyl derivatives of substituted estradiols are particularly promising.² Comparative studies with such derivatives in transplanted tumors containing various concentration of receptor proteins suggested that their level of tissue uptake qualitatively relates to the estrogen receptor concentration.^{3,4} The

3-methyl ether derivatives (e.g. 3b) have also been suggested as a potential imaging agents;^{2d} however, their insignificant receptor-binding affinity and high lipid solubility render these derivatives unsuitable for imaging of small receptor-containing tumors.⁵ Most studies to data

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