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Synthetic Fibrinolytic Agents. 2. Selected *N*-Monosubstituted Bis(tetrahydroisoquinolines) Designed to Possess Enhanced Bioavailability

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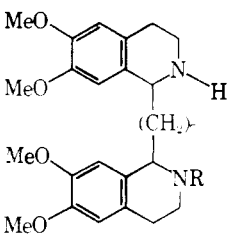
Certain N-monosubstituted analogs (1) of the bis(tetrahydroisoquinoline) 1a were specifically designed and synthesized in an attempt to enhance the oral absorption characteristics of this class of fibrinolytic agents. A number of latentiated derivatives were prepared, wherein the N-substituents were potentially susceptible to enzymatic or hydrolytic cleavage to the parent drug 1a. A selection of anionic side chains was also incorporated, and a group of miscellaneous derivatives was prepared. Many of the analogs had parenteral activity comparable to the parent drug 1a in the dilute blood clot lysis assay in rats, but none possessed a useful level of oral activity.

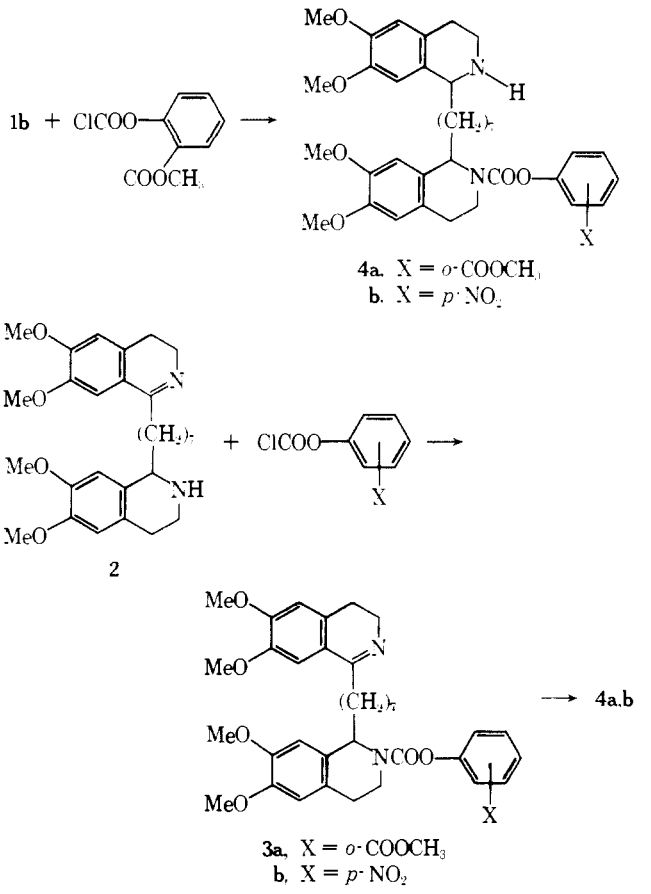
A preceding paper[1] described the rationale for synthesizing monosubstituted bis(tetrahydroisoquinolines) of general structure 1 as potential orally effective fibrinolytic agents. Two general syntheses were developed, and a series of mono-*N*-acyl, *N*-alkyl, and *N*-sulfonyl analogs was prepared, primarily from the mono-Boc intermediate **1b**. Although a number of compounds possessed comparable activity to that of the parent drug **1a**[2] upon parenteral administration to rats in the dilute blood clot lysis assay, no significant oral activity was seen. This paper reports the continuation of our work in this series, describing the synthesis of a variety of compounds of type 1 where R represents a moiety more specifically designed to enhance oral absorption, either by latentiation of the amine function or by otherwise altering the chemical nature and lipid solubility of the molecule.



1a, R = H
b, R = Boc

Carbamate Ester Latentiation. In searching for lipophilic amphetamine derivatives that would more readily penetrate the blood–brain barrier, Verbiscar and Abood[3] discovered that nitrophenyl and *o*-carbomethoxyphenyl carbamate esters of α-[^{14}C]amphetamine rapidly enter the mouse brain where they are readily hydrolyzed to the free amine. By analogy, we hoped that similar carbamates in our series would be better absorbed from the gastrointestinal tract and then be hydrolyzed *in vivo* to the parent drug **1a**. Syntheses of the *o*-carbomethoxyphenyl and *p*-nitrophenyl carbamate esters **4a,b** are outlined in Scheme I. Treatment of the mono-Boc-**1b** with *o*-carbomethoxyphenyl chloroformate,[3] followed by removal of the Boc-protecting group, gave **4a**. Alternatively, the appropriate

Scheme I

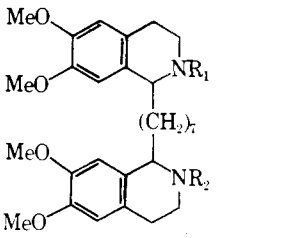


chloroformates were condensed with derivative **2**,[1] and the intermediates (3) were reduced by standard methods to 4a and **4b**.

The glycerol carbamate **5c** was also prepared, based on the rationale that it might be susceptible to *in vivo* hydrolysis to **1a**, glycerol, and CO_2. Treatment of **1b** with *N,N'*-carbonyldiimidazole[4] gave **5a**. Displacement of the

imidazole moiety by the anion of isopropylideneglycerol[5] afforded the protected derivative **5b**, which was then converted to **5c** by acid hydrolysis.

Derivatives Susceptible to Enzymatic and/or Hydrolytic Side-Chain Cleavage. Eckert, *et al.*,[6] have recently shown that mono-*n*-propylaminoacetylation of poorly soluble biologically active aromatic amines leads to more soluble derivatives. These compounds are then susceptible to enzymatic cleavage to the free amines by a carboxylesterase of swine liver microsomes. The potential for increased bioavailability in such a derivative of **1a** was apparent. Chloroacetylation of **1b** afforded **5d**, which upon condensation with *n*-propylamine and subsequent hydrolysis yielded the desired analog **5f**.

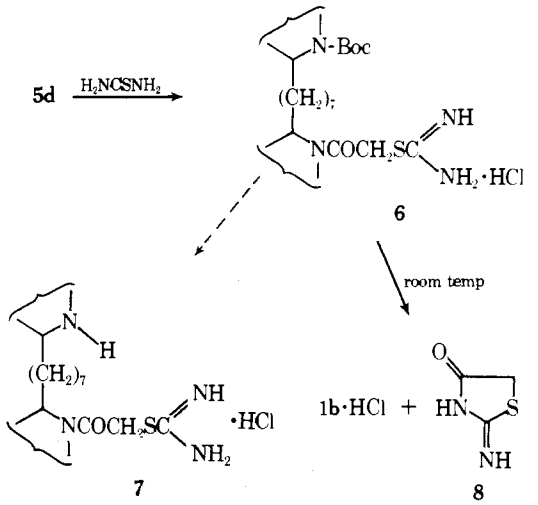


5a, R_1 = Boc; R_2 = CON(imidazole)
b, R_1 = Boc; R_2 = $COOCH_2$(dioxolane)
c, R_1 = H; R_2 = $COOCH_2CHOHCH_2OH$
d, R_1 = Boc; R_2 = $COCH_2Cl$
e, R_1 = Boc; R_2 = $COCH_2NHPr$
f, R_1 = H; R_2 = $COCH_2NHPr$
g, R_1 = Boc; R_2 = $COCH_2OEt$
h, R_1 = H; R_2 = $COCH_2OEt$
i, R_1 = H; R_2 = $(CH_2)_2OEt$
j, R_1 = Boc; R_2 = $(CH_2)_2COOEt$
k, R_1 = H; R_2 = $(CH_2)_2COO^-Na^+$
l, R_1 = H; R_2 = $(CH_2)_2SO_3H$
m, R_1 = Boc; R_2 = $(CH_2)_2CN$
n, R_1 = H; R_2 = $(CH_2)_2$(triazolium)
o, R_1 = Boc; R_2 = $SO_3^-NH(CH_3)_3$
p, R_1 = H; R_2 = $SO_3^-Na^+$
q, R_1 = Boc; R_2 = $COCHC_6H_5$(NH)CH_3 $CHCOOCH_3$
r, R_1 = H; R_2 = $COCHC_6H_5$(NH_2)
s, R_1 = H; R_2 = NO

Artini, *et al.*,[7] in a recent study of the analgesic and antiinflammatory activities of some 4-amino- and 4-amidobenzophenones, found that ethoxyacetylamino derivatives were efficiently metabolized to the parent amines in rats. Such a derivative (**5h**) of **1a** was prepared in the usual manner from **1b** *via* the intermediate **5g**. Reduction of **5h** to the ethoxyethyl derivative **5i** was carried out for activity comparison, since mono-*N*-ethyl derivatives synthesized previously had shown high intrinsic activity.[1]

The possibility of isolating a labile intermediate in the removal of chloroacetyl groups on amines by thiourea[8] prompted a study of this reaction in our series. The sequence (Scheme II) involved treatment of **5d** with thiourea to give the intermediate thioformamidine hydrochloride **6**. If **6** could be isolated, anhydrous acid treatment

Scheme II

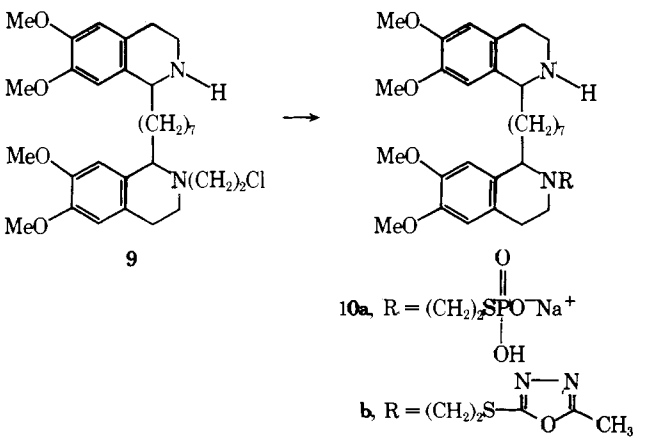


should effect Boc removal to give **7**, without loss of the thioformamidine function; **7** would then be susceptible to hydrolysis to the free amine as reported[8] and therefore would have the potential to release **1a** by hydrolytic cleavage *in vivo*. Unfortunately, the intermediate **6** displayed this cleavage behavior upon standing in CH_2Cl_2 solution at room temperature, being smoothly converted to **1b**·HCl and precipitating pseudothiohydantoin (**8**) from solution.

Derivatives with Anionic Side Chains. The potency of mono-*N*-ethyl derivatives [**1**, R = Et, $(CH_2)_2SH$, $(CH_2)_2OC_6H_5$] upon parenteral administration has been described previously.[1] Endeavoring to maintain this potency, and to increase oral absorption, a series of anionic groups was attached to the ethyl moiety.

The S-phosphorylated derivative **10a** of the thiol [**1**, R = $(CH_2)_2SH$] was a particularly attractive candidate, since the S–P bond of such compounds is known to be highly labile in biological systems,[9] hence providing the possibility of liberating the parent thiol *in vivo*. The monosodium salt of **10a** was synthesized by treating the β-chloroethyl derivative **9**[1] with sodium thiophosphate,[10] followed by the addition of 1 equiv of NaOH (see Scheme III).

Scheme III



The corresponding carboxylate derivative **5k** was obtained by Michael condensation of **1b** and ethyl acrylate to give **5j**, followed by hydrolysis and ion-exchange chromatography. Alkylation of **1b** with sodium 2-bromoethanesulfonate,[11] followed by acid hydrolysis, afforded the sulfonic acid analog **5l**. Michael condensation using acrylonitrile yielded nitrile **5m**, which could be treated with alu-

minum azide,[12] followed by hydrolysis, to give the tetrazolylethyl derivative **5n.**

The *N*-sulfonic acid sodium salt **5p** was synthesized in order to evaluate an analog having an anionic group attached directly to the nitrogen atom. It was prepared from **1b** and $SO_3N(CH_3)_3$ *via* the intermediate **5o.**

Miscellaneous Analogs. It is well known that an α-phenylglycine side chain in penicillins and cephalosporins is associated with a superior degree of oral absorption.[13] A bis(tetrahydroisoquinoline) of this type (**5r**) was prepared from **1b** *via* **5q**, using the method of Spencer, *et al.*[14]

The oxadiazole **10b** was prepared from **9** and the appropriate oxadiazolethiol (Scheme III), and the nitroso analog **5s** was obtained from **1b** *via* the method of Bumgardner, *et al.*[15]

Fibrinolytic Activities. The modified *in vivo-in vitro* dilute blood clot lysis assay, using male Long Evans rats, was used to evaluate the compounds (mixtures of isomers).[1] Comparison of activities after ip injection (Table I) again shows that *N*-Boc-N′-substituted intermediates (**5a,e,g**) have no fibrinolytic activity at the screening dose of 20 mg/kg.[1] Mono-*N*-ethyl derivatives bearing an anionic group (**5k,l,n** and **10a**) retain good ip activity, comparable to the parent reference standard drug **1a** (MED ≃ 2 mg/kg).

In oral screening at 100 mg/kg, no significant activity was seen with any of the analogs, with the possible exception of the thiophosphate **10a** (see Table I). Although inactive when administered in Tween–H_2O, PEG 400–H_2O, and DMAC–H_2O vehicles, **10a** consistently showed statistically significant fibrinolytic activity (60–65% lysis) *vs.* vehicle controls (30–35% lysis) when administered in 1:1 ethanol–water. The parent drug **1a** showed no significant oral activity in any of the vehicles mentioned at doses up to 250 mg/kg. Since a useful level of oral activity was not obtained in these derivatives, no attempts were made to assess the susceptibility of some of the side chains to hydrolytic and/or metabolic breakdown as discussed herein.

In conclusion, our studies on the bis(tetrahydroisoquinolines) have shown that structurally diverse N-monosubstituted derivatives, although maintaining high parenteral fibrinolytic activity in many cases, do not possess significantly altered absorption characteristics from the parent drug **1a.**

Experimental Section†

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(*o*-carbomethoxyphenoxycarbonyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (4a) Hydrochloride. Method A. According to the method of Verbiscar and Abood,[3] the "dihydro-tetrahydro" isoquinoline intermediate **2**·2HCl[1] (2.0 g, 0.0036 mol) was suspended in 10 ml of H_2O and placed under N_2 atmosphere in an ice-water bath, and a solution of Na_2CO_3 (0.768 g, 0.00725 mol) in 2 ml of H_2O was added with stirring. $CHCl_3$ (25 ml) was then added, followed by the dropwise addition over 5 min of a solution of *o*-carbomethoxyphenyl chloroformate (0.795 g, 0.0037 mol) in 5 ml of $CHCl_3$. The mixture was then stirred at room temperature for 2 hr and worked up by separating the layers and washing the $CHCl_3$ layer with water. Drying ($MgSO_4$) and solvent removal under reduced pressure gave a crude oil (2.37 g). Chromatography on a column of neutral alumina gave the purified intermediate **3a** (1.71 g, 71.6%) as a colorless oil upon elution with Et_2O + 1% EtOH. Dissolution in EtOAc–Et_2O and treatment with HCl(g) gave the amorphous hydrochloride salt after solvent removal. *Anal.* ($C_{38}H_{46}N_2O_8$·HCl) C, H, N.

The free amine **3a** (0.71 g, 0.0011 mol) was dissolved in 35 ml of reagent MeOH and cooled to 5–10°, and sodium borohydride (100 mg) was added with stirring. After stirring at room temperature for 2 hr, H_2O was added, the MeOH was stripped off under reduced pressure, and the product was extracted into EtOAc. The usual washing and drying procedures gave the product (0.628 g, 87%) as a light yellow gum. Column chromatography on neutral alumina gave purified **4a** (201 mg) upon elution with Et_2O + 1–5% EtOH. The HCl salt was prepared in the usual manner. The nmr spectrum ($CDCl_3$) showed two singlets for the methyl ester (δ 3.53, 3.76). Heating of the sample to 80° caused the peaks to coalesce to a singlet (δ 3.67), indicating the presence of rotational isomers at the amide linkage. *Anal.* ($C_{38}H_{48}N_2O_8$·HCl) C, H, N. Mass spectrum *m/e* 660 (M^+ of free base).

Method B. The mono-Boc intermediate **1b** (1.3 g, 0.00224 mol) was treated with *o*-carbomethoxyphenyl chloroformate (0.5 g, 0.0023 mol) as in method A, affording 1.47 g of a pale yellow oil. The oil was then dissolved in 30 ml of 97% formic acid and stirred at room temperature for 2.5 hr. The formic acid was stripped off under reduced pressure and the residue was dissolved in water and extracted with Et_2O to remove any neutral material. Basification of the aqueous phase with 5% NaOH solution and extraction of the product into Et_2O afforded crude **4a** (1.167 g) after drying ($MgSO_4$) and solvent removal. Column chromatography on neutral alumina gave pure **4a** (0.7 g, 47%) upon elution with Et_2O + 2% EtOH. The HCl salt was prepared in the usual manner and the resultant **4a**·HCl was identical (tlc, ir, and nmr) with material from method A.

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(*p*-nitrophenoxycarbonyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (4b) Hydrochloride. The intermediate dihydroisoquinoline **3b** was prepared from **2**·2HCl (5.26 g, 0.0095 mol) and *p*-nitrophenyl chloroformate (2.02 g, 0.01 mol) by method A, described for **4a**. Chromatography of the crude product on a column of neutral alumina afforded **3b** (2.9 g) upon elution with Et_2O. Treatment of **3b** (2.5 g) with sodium borohydride (1.7 g) in MeOH (120 ml), as described for **4a**, afforded 2.12 g (83.7%) of crude product. Column chromatography on neutral alumina gave a pure fraction of **4b** (1.05 g) upon elution with Et_2O + 1% EtOH. Treatment with HCl(g) in the usual manner gave **4b**·HCl. *Anal.* ($C_{36}H_{45}N_3O_8$·HCl) C, H, N.

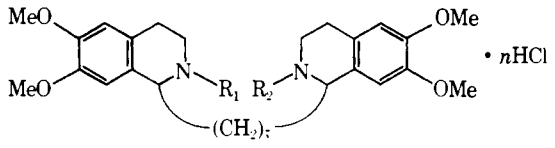
1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(2,3-dihydroxy-*n*-propyloxycarbonyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (5c) Hydrochloride. The mono-Boc-**1b** (7.0 g, 0.012 mol) and carbonyldiimidazole (1.95 g, 0.012 mol) were dissolved in 175 ml of dry THF and stirred at room temperature in an atmosphere of N_2 for 16 hr.[4] The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and extracted successively with cold dilute HCl, saturated $NaHCO_3$, and brine. Drying ($MgSO_4$) and solvent removal yielded a yellow foam (7.3 g). Chromatography on a column of neutral alumina provided purified **5a** (4.12 g, 50.7%) upon elution with Et_2O + 5% EtOH. *Anal.* ($C_{38}H_{52}N_4O_7$) C, H, N. Mass spectrum: *m/e* 676 (M^+).

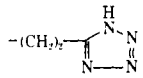
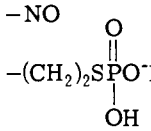
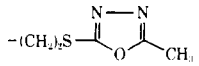
Sodium amide (0.156 g, 0.004 mol) was suspended in 100 ml of dry THF and cooled to 0°. A solution of isopropylideneglycerol[5] (0.528 g, 0.004 mol) in 5 ml of THF was then added with stirring. The mixture was then allowed to warm to room temperature over 15 min under a slight vacuum in order to remove the generated NH_3. A solution of the intermediate **5a** (2.6 g, 0.0038 mol) in 10 ml of THF was then added dropwise over 5 min. The mixture was placed under N_2 atmosphere and refluxed for 2.5 hr. Solvent removal under reduced pressure was followed by partitioning of the residue between CH_2Cl_2 and H_2O. The usual washing and drying of the organic layer afforded 2.8 g of crude oil. Column chromatography on neutral alumina (elution with Et_2O + 1% EtOH) gave **5b** (1.1 g).

A solution of **5b** (3.7 g, 0.0049 mol) in 200 ml of $CHCl_3$ was saturated with HCl(g) and stirred at room temperature for 6 hr. The solution was then shaken with excess 5% NaOH solution, followed by H_2O and brine. Drying ($MgSO_4$) and solvent removal gave crude **5c** as an orange oil (1.8 g, 61%). Chromatography on a column of CC-7 silica gel (elution with 2:1 Et_2O–EtOH) allowed the separation of a purified sample (0.6 g). Treatment with sodium borohydride in MeOH to reduce dihydroisoquinoline (from air ox-

†Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values (see also Table I). No melting point data are given since all of the compounds are noncrystalline. In general, compounds were purified by column chromatography and then converted to appropriate amorphous salts for characterization and biological evaluation. Merck alumina (neutral and basic aluminum oxide) and Mallinckrodt SilicAR (100–200 mesh) were used in column chromatography and Analtech, Inc., Uniplates (alumina GF and silica gel GF, 250 μ) were used in appropriate eluting solvents for tlc monitoring of compound purity. Ir and nmr spectral data for all compounds were consistent for the reported structures and were recorded on Beckman IR9 and Varian A-60 (Me_4Si as internal standard) recording spectrometers, respectively. Mass spectra were recorded at 70 eV on an LKB-9000 mass spectrometer.

Table I. *N*-Monosubstituted Bis(tetrahydroisoquinolines) and Intermediates



No.	R_1	R_2	*n*	Formula	Analyses[a]	MED, mg/kg[b] ip	MED, mg/kg[b] po
4a	H	$-COOC_6H_4$-*o*-$COOCH_3$	1	$C_{38}H_{48}N_2O_8 \cdot HCl$	C, H, N	5	>100
4b	H	$-COOC_6H_4$-*p*-NO_2	1	$C_{36}H_{45}N_3O_8 \cdot HCl$	C, H, N	10–20	>100
5a	Boc		0	$C_{38}H_{52}N_4O_7$	C, H, N	>20	>100
5c	H	$-COOCH_2CHOHCH_2OH$	1	$C_{33}H_{48}N_2O_8 \cdot HCl$	H; C, N[c,d]	5	>100
5e	Boc	$-COCH_2NH(CH_2)_2CH_3$	1	$C_{39}H_{59}N_3O_7 \cdot HCl$	C, H, N	>20	>100
5f	H	$-COCH_2NH(CH_2)_2CH_3$	2	$C_{34}H_{51}N_3O_5 \cdot 2HCl$	C, H, N	>20	>100
5g	Boc	$-COCH_2OCH_2CH_3$	0	$C_{38}H_{56}N_2O_8$	C, H, N	>20	>100
5h	H	$-COCH_2OCH_2CH_3$	1	$C_{33}H_{48}N_2O_6 \cdot HCl$	C, H, N	5–20	>100
5i	H	$-(CH_2)_2OCH_2CH_3$	2	$C_{33}H_{50}N_2O_5 \cdot 2HCl$	H, N; C[d,e]	5–20	>100
5k	H	$-(CH_2)_2COO^-Na^+$	0	$C_{32}H_{45}N_2NaO_6$	C, H, N	5	>100
5l	H	$-(CH_2)_2SO_3H$	2	$C_{31}H_{46}N_2O_7S \cdot 2HCl$	H, N; C[f]	5	>100
5n	H		2	$C_{32}H_{46}N_6O_4 \cdot 2HCl$	d	2–5	>100
5p	H	$-SO_3^-Na^+$	0	$C_{29}H_{41}NaN_2O_7S$	C, H, N, S[g]	5–20	>100
5r	H	$-COCH(NH_2)C_6H_5$	2	$C_{37}H_{49}N_3O_5 \cdot 2HCl$	C, H; N[h]	~2	>200
5s	H	$-NO$	1	$C_{29}H_{41}N_3O_5 \cdot HCl$	C, H, N	2–5	>100
10a	H		0	$C_{31}H_{46}N_2NaO_7PS$	C, H, N, P, Na	~2	~100
10b	H		2	$C_{34}H_{48}N_4O_5S \cdot 2HCl$	C, H, N	>20	>100

[a] See footnote †. [b] Dilute blood clot lysis assay (see ref 1). [c] C: calcd, 62.20; found, 61.75. N: calcd, 4.40; found, 3.96. [d] Mass spectral analysis (see Experimental Section). [e] C: calcd, 63.15; found, 63.60. [f] C: calcd, 56.10; found, 56.52. [g] See Experimental Section. [h] N: calcd, 6.10; found, 5.44.

idation),[1] followed by conversion to the HCl salt in the usual manner, afforded **5c**·HCl (0.74 g). *Anal.* ($C_{33}H_{48}N_2O_8 \cdot HCl$) C, H, N. Mass spectrum: *m/e* 601 ($M^{+\cdot}$).

1,1'-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2'-(*n*-propylaminoacetyl)-6',7'-dimethoxy-1',2',3',4'-tetrahydroisoquinoline (5f) Dihydrochloride. Triethylamine (1.32 g, 0.013 mol) was added with stirring to a solution of **1b** (6.0 g, 0.010 mol) in 250 ml of CH_2Cl_2. The mixture was placed under N_2 atmosphere and cooled to near 0° in an ice-H_2O bath, and a solution of chloroacetyl chloride (1.43 g, 0.013 mol) in 25 ml of CH_2Cl_2 was added dropwise over 15 min. After stirring at room temperature for 1 hr the mixture was poured into ice-H_2O and the layers were separated. The aqueous phase was extracted with a second portion of CH_2Cl_2 and the combined organics were washed successively with cold dilute HCl, bicarbonate solution, and H_2O. Drying ($MgSO_4$) and solvent removal gave **5d** (6.0 g) of sufficient purity for further elaboration.

A solution of **5d** (3.81 g, 0.0058 mol) in excess *n*-propylamine (25 ml) was refluxed in an atmosphere of N_2 for 4 hr. The excess amine was distilled off under reduced pressure and the residue was partitioned between Et_2O (two portions) and H_2O. The usual washing, drying, and solvent removal procedures afforded **5e** as an orange syrup (3.51 g, 89%). Column chromatography on neutral alumina provided purified **5e** (2.82 g) upon elution with Et_2O + 5% EtOH. The HCl salt was prepared in the usual manner. *Anal.* ($C_{39}H_{59}N_3O_7 \cdot HCl$) C, H, N.

The free amine **5e** (1.75 g, 0.0026 mol) was dissolved in 50 ml of 97% formic acid and stirred at room temperature under N_2 for 2 hr. The usual work-up provided **5f** (1.41 g, 94.8%). A purified sample (0.47 g) was obtained by column chromatography on neutral alumina (elution with Et_2O + 2% EtOH). The dihydrochloride of **5f** was prepared in the usual manner. *Anal.* ($C_{34}H_{51}N_3O_5 \cdot 2HCl$) C, H, N.

1,1'-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2'-ethoxyacetyl-6',7'-dimethoxy-1',2',3',4'-tetrahydroisoquinoline (5h) Hydrochloride. Triethylamine (1.11 g, 0.011 mol) was added to a solution of **1b** (5.96 g, 0.0102 mol) in CH_2Cl_2 (40 ml) and the stirred mixture was placed under N_2 and cooled to near 0° in an ice-H_2O bath. A solution of ethoxyacetyl chloride[16] (1.35 g, 0.011 mol) in CH_2Cl_2 (10 ml) was added dropwise over 20 min. Subsequent stirring at room temperature for 19 hr, solvent removal, and work-up in the usual manner yielded crude **5g** (6.36 g, 93%). Column chromatography (neutral alumina, elution with Et_2O + 1% EtOH) gave a pure sample. *Anal.* ($C_{38}H_{56}N_2O_8$) C, H, N.

Treatment of crude **5g** (5.28 g, 0.0079 mol) with 97% formic acid in the usual manner gave 5h (3.63 g, 82%) and column chromatography on neutral alumina gave purified material (1.74 g) upon elution with Et_2O + 2% EtOH. Tlc revealed the presence of some dihydroisoquinoline,[1] necessitating reduction with $NaBH_4$ in MeOH prior to conversion to the HCl salt (**5h**·HCl, 1.93 g) in the usual manner. *Anal.* ($C_{33}H_{48}N_2O_6 \cdot HCl$) C, H, N.

1,1'-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2'-ethoxyethyl-6',7'-dimethoxy-1',2',3',4'-tetrahydroisoquinoline (5i) Dihydrochloride. To a stirred ice-cooled solution of 1 *M* BH_3 in THF (5.0 ml, 0.005 mol) in dry THF (40 ml) under N_2 was added a solution of 5h (0.86 g, 0.0015 mol) in THF (40 ml) over 20 min. The mixture was then refluxed for 22 hr, cooled to room temperature, and then treated successively with 3 *N* HCl (4.0 ml) and H_2O (40 ml). The solution was briefly heated to reflux and the THF was then removed under reduced pressure. Basification (1 *N* NaOH), extraction with CH_2Cl_2, and the usual

isolation procedure gave **5i** (0.84 g, quantitative) as a pale yellow oil that appeared homogeneous on tlc. Treatment with HCl(g) in the usual manner afforded **5i**·2HCl (0.493 g). *Anal.* ($C_{33}H_{50}N_2O_5$·2HCl) C, H, N. Mass spectrum: *m/e* 555 (M^+).

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(β-carboxyethyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Sodium Salt (5k). A solution of ethyl acrylate (0.55 g, 0.0055 mol) in absolute EtOH (5 ml) was added dropwise with stirring under N_2 atmosphere to a solution of **1b** (2.77 g, 0.00475 mol) in absolute EtOH (75 ml). Triethylamine (5 drops) was added and the mixture was refluxed for 60 hr. Stripping of solvent and excess acrylate under reduced pressure, followed by column chromatography of the crude product on CC-7 silica gel, gave the ester **5j** (2.3 g, 70.8%) upon elution with Et_2O + 2% EtOH.

The ester **5j** (1.46 g, 0.00214 mol) was dissolved in 95% EtOH (60 ml), KOH pellets (0.33 g, 0.0059 mol) were added, and the mixture was stirred at room temperature for 3.5 hr. After solvent removal, the residue was dissolved in H_2O and extracted with Et_2O to remove any neutrals. The aqueous layer was acidified with concentrated HCl and then heated for 2 hr at 50°. The EtOH was removed under reduced pressure, brine was added to the remaining aqueous slurry, and the mixture was extracted with two portions of CH_2Cl_2. The usual isolation procedure yielded crude **5k**·2HCl (1.36 g) as a foam. Purification was effected *via* ion-exchange column chromatography on Dowex 50W-X1 resin (Na form).[17] A solution of **5k**·2HCl (0.668 g) in a minimum volume of pH 6.82 phosphate buffer was applied to the column and the purified sodium salt **5k** (0.359 g) was eventually eluted with pH 8.37 buffer (60%) + *n*-PrOH (40%). *Anal.* ($C_{32}H_{45}N_2O_6Na$) C, H, N.

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(β-sulfoethyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (5l) Dihydrochloride. A solution of 2-bromoethanesulfonic acid Na salt[11] (1.43 g, 0.0068 mol) in 30 ml of H_2O was added in one portion to a stirred mixture of **1b** (3.6 g, 0.00618 mol), triethylamine (0.69 g, 0.0068 mol), and KI (80 mg) in 75 ml of dioxane. The resultant mixture was placed under N_2 atmosphere and refluxed for 16 hr. The solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with brine, dried ($MgSO_4$), and stripped of solvent to give the intermediate Boc derivative as a light yellow foam (4.15 g). The foam (3.48 g, 0.00489 mol) was dissolved in 75 ml of $CHCl_3$, saturated with HCl(g), and stirred at room temperature for 4.5 hr. Stripping of solvent under reduced pressure provided a quantitative yield (3.2 g) of **5l**·2HCl *Anal.* ($C_{31}H_{46}N_2O_7S$·2HCl) C, H, N.

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-[β-(5-tetrazolyl)ethyl]-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (5n) Dihydrochloride. A mixture of **1b** (5.1 g, 0.0087 mol), TEA (0.2 g), and acrylonitrile (0.96 g, 0.018 mol) in absolute EtOH (200 ml) was stirred under N_2 and refluxed for 17 hr. Solvent removal under reduced pressure gave a light yellow oil which was purified by column chromatography on neutral alumina (elution with Et_2O + 0.5% EtOH) to give the nitrile **5m** (4.3 g, 78.2%).

The nitrile **5m** (1.76 g, 0.00276 mol) was dissolved in dry THF (30 ml), sodium azide (0.539 g, 0.0083 mol) and aluminum chloride (0.42 g, 0.00315 mol) were added, and the mixture was stirred at reflux for 41 hr. The bulk of the THF was distilled off under reduced pressure and the residue was dissolved in 10% NaOH solution and extracted with Et_2O to remove neutrals. The aqueous phase was then acidified with 1 *N* HCl, some insoluble inorganics were filtered off, and the filtrate was stripped to dryness under reduced pressure. The residue was treated with CH_2Cl_2, which dissolved the desired **5n**·2HCl (0.543 g), recovered as a yellow foam after solvent removal. Chromatographic purification attempts on columns of CC-7 silica or Dowex 50W-X1 resin failed to provide an analytical sample. The mass spectrum confirmed the identity of the product: *m/e* 579 (M^+ of free base).

1,1′-Heptamethylene-6,7-dimethoxy-2-sulfo-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Sodium Salt (5p). A mixture of the mono-Boc-**1b** (3.00 g, 0.005 mol) and sulfur trioxide–trimethylamine (0.72 g, 0.005 mol) in CH_2Cl_2 (50 ml) was stirred at 25° for 2 hr. The resultant solution of **5o** was stored at 4° for 66 hr and then was treated with HCl gas and stirred at 25° for 2.5 hr. The solvent was evaporated, EtOH was added, and the resultant solution was treated with aqueous 1 *N* NaOH (5.4 ml). The neutral solution was evaporated and the residue was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave a foam which was triturated under Et_2O to yield quantitatively **5p** as a friable solid. *Anal.* ($C_{29}H_{41}NaN_2O_7S$) C, H, N, S.

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(α-phenylglycyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (5r) Dihydrochloride. A solution of ethyl chloroformate (1.05 g, 0.00966 mol) and *N,N*-dimethylbenzylamine (6 drops, catalyst) in dry CH_2Cl_2 (150 ml) was placed under N_2 atmosphere and cooled to 0° in an ice–salt bath. D(−)-α-[(1-carbomethoxypropen-2-yl)amino]phenyl acetate[14] (2.62 g, 0.00966 mol) was added with stirring, producing a white precipitate. After 5–10 min a solution of **1b** (5.06 g, 0.00868 mol) in CH_2Cl_2 (100 ml) was added slowly, keeping the reaction temperature below 5°. After the addition was complete the mixture was refluxed for 16 hr, followed by filtration and removal of solvent to give crude **5q** (7.68 g). Treatment with 97% formic acid and then NaOH solution in the usual manner afforded crude **5r**, containing the monocarboethoxylated bisisoquinoline derivative as the main impurity (confirmed by mass spectrum, *m/e* 554). Chromatography on neutral alumina yielded purified **5r** (1.06 g) upon elution with Et_2O + 5% EtOH. Conversion to the dihydrochloride salt was carried out in the usual manner. *Anal.* ($C_{37}H_{49}N_3O_5$·2HCl) C, H, N.

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-nitroso-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (5s) Hydrochloride. According to the method of Bumgardner, *et al.*,[15] 3-nitro-9-nitrosocarbazole (Eastman, 4.0 g, 0.0166 mol) and **1b** (4.5 g, 0.00772 mol) were stirred in C_6H_6 under N_2 at reflux for 45 min. Cooling to 10–15°, removal of the solid 3-nitrocarbazole by filtration, and stripping of the filtrate under reduced pressure gave an orange froth. Chromatography on a column of CC-7 silica gel effected purification of the intermediate nitrosated Boc (3.04 g) upon elution with Et_2O. Treatment with 97% formic acid and subsequent conversion to the HCl salt in the usual manner afforded **5s**·HCl (1.42 g). *Anal.* ($C_{29}H_{41}N_3O_5$·HCl) C, H, N.

1,1′-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2′-(β-mercaptoethyl)-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline-*S*-sodium Hydrogen Phosphate (10a). The mono-β-chloroethyl derivative 9[1] (2.43 g, 0.0039 mol) was dissolved in DMF (30 ml) and H_2O (15 ml) and added to a solution of sodium thiophosphate (0.71 g, 0.0039 mol) in H_2O (5 ml) and DMF (2.5 ml). The mixture was stirred under N_2 atmosphere at room temperature for 10 min, followed by heating in an oil bath at 50° for 10 min. At this point 1 *N* NaOH solution (3.9 ml, 0.0039 mol) was added and stirring at 50° was continued for an additional 10 min. After cooling to room temperature the solution was decanted from a small quantity of gum with the aid of added H_2O and Et_2O. Extraction with two portions of Et_2O was followed by stripping of the aqueous DMF layer to dryness at 50° under reduced pressure. The residue was triturated with warm EtOH and the NaCl was removed by filtration. The filtrate was stripped and trituration of the residue with $CHCl_3$ gave a second crop of NaCl. Subsequent solvent removal from the filtrate gave **10a** as a foam (1.61 g, 64%). Trituration with Et_2O afforded the product as a light tan amorphous solid. *Anal.* ($C_{31}H_{46}N_2NaO_7PS$) C, H, N, P, Na.

1,1′-Heptamethylene-2-[2-(5-methyl-1,3,4-oxadiazol-2-yl)-mercaptoethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (10b) Dihydrochloride. A mixture of **9**·2HCl (2.90 g, 0.005 mol), 2-methyl-5-thio-1,3,4-oxadiazole (2.00 g, 0.02 mol), and K_2CO_3 (1.38 g, 0.01 mol) in DMF (50 ml) was stirred at 135° for 16 hr. The mixture was cooled and diluted with Et_2O–H_2O and the supernatant was decanted from the precipitated gum. The gum was dissolved in $CHCl_3$ and the solution was extracted three times with H_2O. The $CHCl_3$ was dried and then evaporated to leave a foam (2.7 g); chromatography on neutral alumina (elution with MeCN) gave pure **10b** (0.83 g, 13%); treated with 2 equiv of HCl in *n*-PrOH to yield the dihydrochloride salt. *Anal.* ($C_{34}H_{48}N_4O_5S$·2HCl) C, H, N.

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Cycloalkanones. 4. Antifertility Activity

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A number of mono- and disubstituted cycloalkanones were tested in female rodents for their antifertility activity. 2,8-Dibenzylcyclooctanone, 2,4-dibenzyl-3-pentanone, 2-(2-fluorobenzyl)-8-(α-ethoxy-2-fluorobenzyl)cyclooctanone, and 2,8-bis(2-methylbenzyl)cyclooctanone were found to inhibit pregnancy completely at 50 mg/kg. The MED_{100} for 2,8-dibenzylcyclooctanone in CF_1 mice was 28 mg/kg while the MED_{100} for Sprague–Dawley rats was <1 mg/kg. These compounds had no effect on male fertility.

For continual use of an oral contraceptive it is important that the agent be nontoxic, essentially nonestrogenic, nonteratogenic, and 100% effective in preventing pregnancy. Currently estrogens and progestrogens are being used which, because of their adverse effects, are not desirable for extended periods of time. Presented below is a series of substituted cycloalkanones which possess substantial antifertility activity in rodents but possess a different mode of action than estrogens.

Procedures and Methods

Chemical. Melting points were taken on a Mel-Temp apparatus and are corrected. Satisfactory elemental analyses were obtained (Atlantic Microlab) for all compounds and are indicated by element. The synthetic procedures for many of the substituted cycloalkanones listed in Table I have been reported previously.[1-3] However, further related compounds have now been synthesized which are described below and their biological activities are reported in Table I.

2,3:6,7-Dibenzosuberone (8) was used as received from Aldrich Chemical Co. after tlc showed no contamination.

7-Benzyl-2,3-benzosuberone (9) was prepared by sodium ethoxide catalyzed condensation of 8 g (0.05 mol) of 2,3-benzosuberone with 5.3 g (0.05 mol) of benzaldehyde using the method described previously.[3] The yield after hydrogenation and chromatography (silica–benzene) was 8 g (64%). The ylidene has a melting point of 81–82° and the reduced material is an oil. *Anal.* ($C_{18}H_{18}O$) C, H.

1-Methyl-2,8-dibenzylcyclooctanol (24). A 2.31 *M* solution (7 ml) of methyllithium in ether was added to 2.06 g (0.0061 mol) of 2,8-dibenzylcyclooctanone in 50 ml of ether under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 hr. Acetone was added slowly, followed by water, until no reaction was visible upon further addition. The mixture was extracted with three 20-ml portions of water and dried, and the ether was removed. The remaining oil was chromatographed on 60 g of 70–325 mesh silica gel [benzene–petroleum ether (bp 30–60°), 50:50] to give 1.9 g (97%) of solid, mp 53–55°. *Anal.* ($C_{23}H_{30}O$) C, H.

1-Methyl-2,8-dibenzylcyclooctene (25). 24 (6 g, 0.019 mol) was dissolved in 50 ml of glacial acetic acid and 1 ml of 45% BF_3·Et_2O was added. The solution was allowed to stand 30 hr at room temperature during which time an oil separated. The mixture was extracted four times with ligroine and the combined extracts were washed with aqueous sodium bicarbonate and then with water until neutral to pH paper. The organic layer was dried, solvent removed, and the oil chromatographed (silica gel, ligroine) to give 5.6 g (98%) of colorless oil. *Anal.* ($C_{23}H_{18}$) C, H.

2,8-Bis(*N*-morpholinomethyl)cyclooctanone Dihydrochloride (31). A mixture of 12.6 g (0.1 mol) of cyclooctanone, 6 g (0.2 mol) of paraformaldehyde, and 24.7 g (0.2 mol) of morpholine hydrochloride in 40 ml of glacial acetic acid was maintained at 95° while stirring for 2.5 hr. The solvent was removed under reduced pressure and 70 ml of acetone added to the residue which slowly dissolved. After 4 hr at room temperature the precipitate was filtered and recrystallized from ethanol to give 12.3 g (31%) of colorless crystals, mp 171–173° dec. *Anal.* ($C_{18}H_{34}Cl_2N_2O_3$) C, H.

2-Benzyl-8-(α-methoxybenzyl)cyclooctanone (32) was synthesized by hydrogenation of the product of the condensation of cyclooctanone with benzaldehyde in MeOH instead of the usual EtOH:[3] mp 107–109° (30% overall yield). *Anal.* ($C_{23}H_{29}O_2$) C, H.

2-(4-Methylbenzyl)-8-(α-methoxy-4-methylbenzyl)cyclooctanone (33) was prepared *via* our previously reported method[3] (ylidene: mp 149–151°; 27%): mp 95–97° (87%). *Anal.* ($C_{25}H_{32}O_2$) C, H.

2,8-Bis(4-phenylbenzyl)cyclooctanone (38) was prepared by our general method.[3] The ylidene had a melting point of 166–168° (20% yield) and the reduced compound had mp 121–123° (62%). *Anal.* ($C_{34}H_{30}O$) C, H.

2-(2-Fluorobenzyl)-8-(α-ethoxy-2-fluorobenzyl)cyclooctanone (43) was made by the general method to give an ylidene (mp 126–128°, 8%) and reduced compound, mp 63–65° (15% yield). *Anal.* ($C_{24}H_{26}F_2O_2$) C, H.

1-Benzoyl-7-(α-hydroxybenzyl)-8-oxabicyclo[5.1.1]nonan-9-one (53). Diepoxydibenzylcyclooctanone[3] (10 g, 0.03 mol) was dissolved in 100 ml of dry DMSO. BF_3·Et_2O (1 ml) was added and the solution stirred at 100° for 12 hr. The reaction was poured into 2 l. of H_2O and extracted with ether in a continuous extractor until the aqueous layer was clear. The ether layer was washed with water, dried, and flash-evaporated. The remaining oil was recrystallized from methanol. The yield was 3.4 g (32%), mp 181–183°. *Anal.* ($C_{22}H_{22}O_4$) C, H.

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