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Synthetic Fibrinolytic Agents. 1. *N*-Monoacyl, *N*-Monoalkyl, and Related Bis(tetrahydroisoquinolines)

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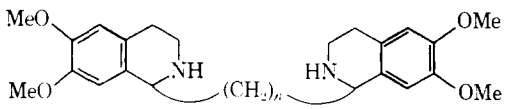
A number of N-monosubstituted bis(tetrahydroisoquinolines) of general structure **2** were synthesized in an attempt to discover fibrinolytic agents having biological absorption properties superior to the parent unsubstituted bis(tetrahydroisoquinoline) **1a**. Two synthetic routes were developed: the first involved selective initial blocking of one of the two nitrogen atoms to give the versatile mono-*tert*-butoxycarbonyl intermediate **3**; the second method was a synthesis wherein the intermediate **15a** allowed selective reaction at the tetrahydroisoquinoline nitrogen in some cases. Although a number of analogs had parenteral activity comparable to **1a** in the dilute blood clot lysis assay in rats, none possessed significant oral activity.

The awareness of the magnitude and scope of the problem of thrombosis has led to increasingly extensive evaluation of anticoagulant and fibrinolytic agents in the treatment of disorders ranging from pulmonary embolism and deep vein thrombosis to acute myocardial infarction.[1] Anticoagulants can lower the incidence of blood clot formation, but they have little effect on clots or thrombi that have already formed. Fibrinolytic agents, on the other hand, have the potential for dissolving blood clots. There is a need for fibrinolytic agents in the treatment of both acute thromboembolic episodes and in prophylactic long-term treatment to prevent recurrent thrombosis. Enzymes such as streptokinase (SK) and urokinase (UK) hold promise in the treatment of acute episodes[1] but necessarily have no oral activity. In addition, SK has pyrogenic and anaphylactic properties, and UK is very expensive to produce.

Synthetic agents offer the possibility of oral fibrinolytic activity, and a recent review of synthetic drug approaches to fibrinolysis has been provided by Schor.[2] Bis(tetrahydroisoquinolines) of type 1 have been known for a number of years[3] but only recently has their fibrinolytic activity upon parenteral or intravenous administration to animals and man been discovered.[2,4] The oral activity of these compounds, however, is very low, due to extremely poor absorption from the gastrointestinal tract. Substitution on both nitrogens of 1 results in a greatly reduced level of activity.[4a]

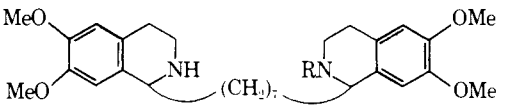
In an attempt to obtain agents having significant oral activity, a number of N-monosubstituted derivatives of the series member having the highest intrinsic activity



1

1a, $n = 7$

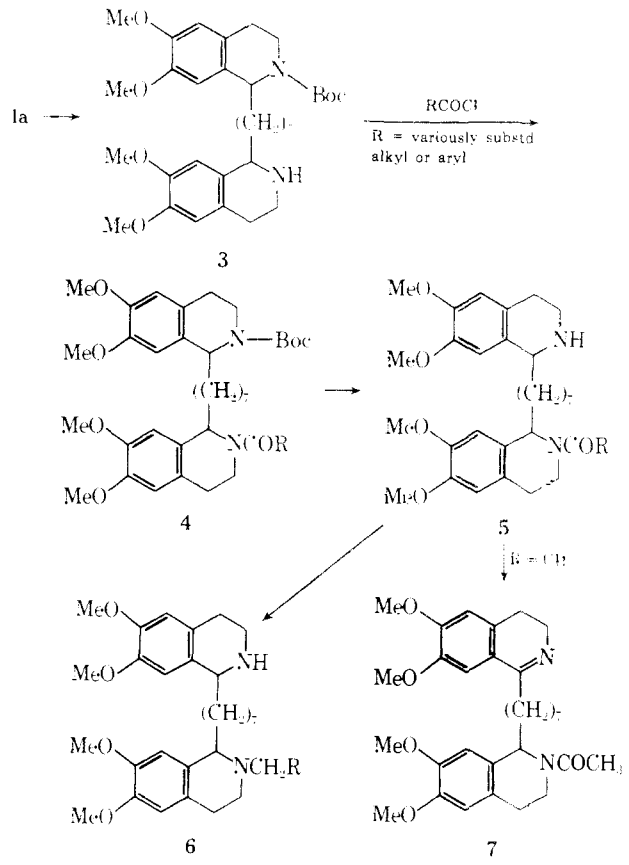
(**1a**)[4a] were synthesized. It is well known that a decrease in the basicity of a drug results in less ionization in the upper gastrointestinal tract and, hence, better absorption through the lipoid membranes of the gastric epithelium and intestinal mucosa.[5] It was hoped that the compounds described would be more efficiently absorbed, due to the neutralization of the basic character of the substituted nitrogen atom and/or to their increased lipid solubility. In order to be effective fibrinolytics after absorption, these agents would then have to be sufficiently active as intact species or be susceptible to hydrolytic or metabolic cleavage to the fully active parent species **1a**. This paper describes the synthesis and fibrinolytic evaluation of a variety of mono-*N*-acyl, *N*-alkyl, and *N*-sulfonyl analogs of general structure **2**. A subsequent paper[6] will discuss a number of related monosubstituted compounds whose side chains were more specifically designed for drug latentiation and/or increased oral absorption.

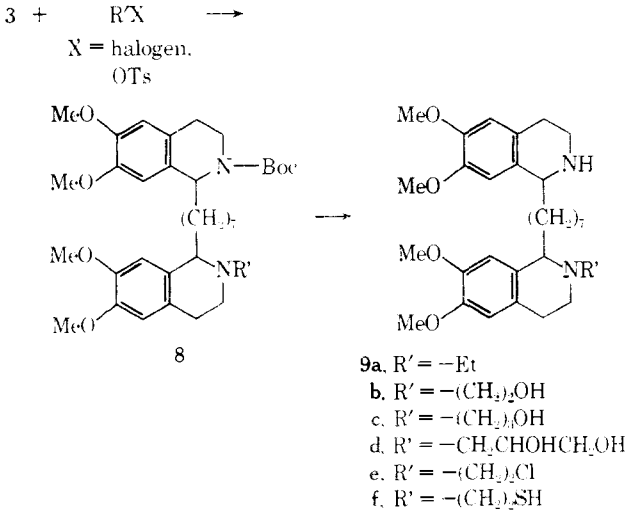


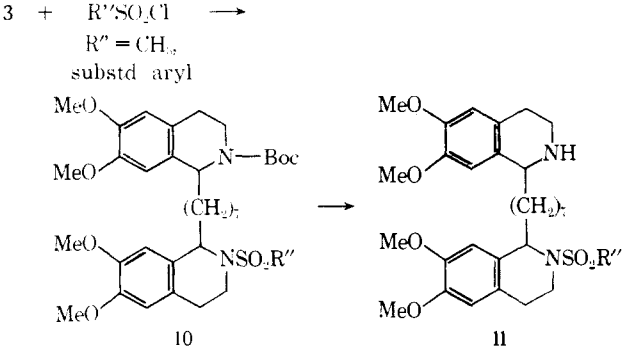
2. R = acyl, alkyl, sulfonyl moieties

Chemistry. Two approaches were taken in our efforts to prepare unsymmetrical compounds of general structure **2**. The first was to begin with the readily available compound **1a**[3,4] and effect substitution at only one of the nitrogen atoms with a suitable protecting group. Reaction at the unprotected nitrogen with the desired acylating or alkylating agents followed by removal of the protective group would then give the desired products of type **2**. This approach was successfully completed *via* the synthesis of the key mono-*tert*-butoxycarbonyl intermediate **3** as outlined in Scheme I. The synthesis of **3** involved treatment of a dilute solution of **1a** in dioxane–water with slightly more than 1 equiv of Boc azide[7] over a period of several

Scheme I







hours. Although noncrystalline, 3 was isolated in 40–45% yield, with separation from unchanged 1a and the bis Boc derivative being dependent upon appropriate pH adjustments during the work-up (*cf.* Experimental Section). Standard acylation, alkylation, and sulfonation methods were then used to prepare substituted intermediates of types 4, 8, and 10. Mild acid hydrolysis gave the final products (5, 9a, and 11), and reduced derivatives of type 6 were obtained using known methods. The alcohols **9b** and **9c** were obtained by acid hydrolysis of their tetrahydropyranyl precursors, and the diol **9d** was prepared by hydrolysis of its acetonide derivative. Thionyl chloride was used to convert **9b** to the chloride **9e** and subsequent treatment with sodium hydrosulfide afforded the thiol **9f**.

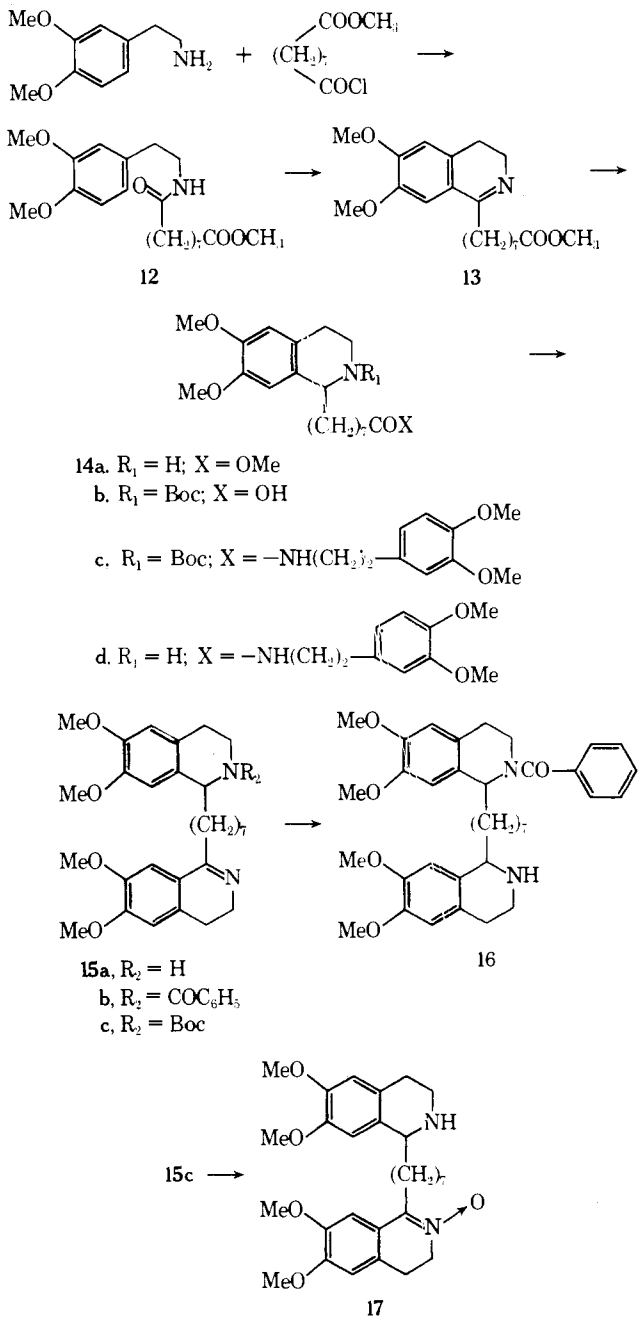
The second method was a total synthesis wherein each of the isoquinoline moieties was elaborated separately. The sequence for the mono-*N*-benzoyl derivative 16 is outlined in Scheme II. Homoveratrylamine and the acid chloride of azelaic acid monomethyl ester were condensed to give the amide 12, which was then cyclized to 13 with phosphorus oxychloride; subsequent reduction gave the tetrahydroisoquinoline **14a**. Protection of the nitrogen atom with the Boc group, followed by alkaline hydrolysis gave the acid **14b**. Subsequent coupling with homoveratrylamine *via* the mixed anhydride technique afforded the amide **14c**. Acid hydrolysis, followed by polyphosphoric ester cyclization, gave the unsubstituted "dihydro-tetrahydro" derivative **15a**. Benzoylation yielded 15b, which was reduced with sodium borohydride to the final product 16. Acylation of 15a with aliphatic acid chlorides gave complex mixtures of products. The mono-*N*-oxide 17 could be obtained from 15a *via* the Boc derivative 15c and subsequent oxidation with *m*-chloroperbenzoic acid.

All of the products of type 2 were susceptible to air oxidation in the unsubstituted ring, giving 3,4-dihydroisoquinoline derivatives. In the case of the monoacetyl derivative (5, R = CH_3; 30 in Table II) treatment with mercuric acetate resulted in efficient conversion to the dihydroisoquinoline 7 (Scheme I). These oxidized derivatives were easily detected by their highly fluorescent nature under long-wave uv light (tlc) and could readily be converted back to tetrahydroisoquinolines upon treatment with sodium borohydride.

None of the products of type 2 are crystalline solids. It will be recognized that the starting material 1a has two identical asymmetric centers and, hence, exists in meso and *dl* forms. Early in the work we used pure *meso*-1a in the synthesis of 3 but found that the product was also noncrystalline. Since *meso*- and *dl*-1a would presumably have equal potency as fibrinolytic agents,[4a] the mixture of isomers was used in all subsequent preparations. No attempts were made to separate product isomers. Most of the intermediates and products could be purified by column chromatography. For characterization and screening purposes, hydrochloride salts of the majority of the purified products were prepared and were found to be manageable amorphous solids.

Spectral data were often definitive in the characterization of the compounds described. The ir spectra of the oxidized monosubstituted derivatives such as 7 clearly show the C=N absorption at about 1570 cm^{-1}. In addition, the nmr spectra of compounds such as 7 differentiate between the aromatic protons of the tetrahydroisoquinoline moiety (broad singlet, δ 6.6) and those of the dihydroisoquinoline moiety (two singlets, δ 6.7, 7.0). Mass spectral data were valuable in confirming the structures of a number of compounds. Molecular ions of the N-monosubstituted derivatives are well defined and in some cases are accompanied by a prominent M − 2 peak, indicative of the ease of for-

Scheme II



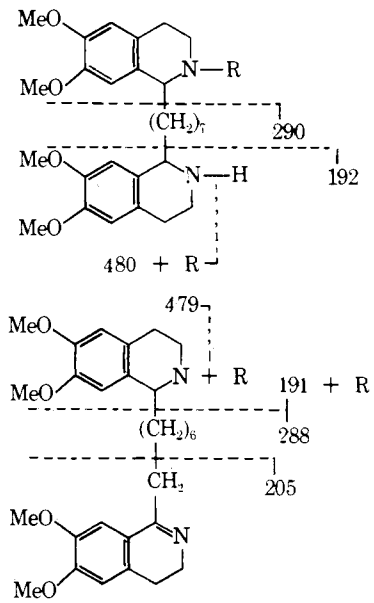
mation of the dihydroisoquinoline in the unsubstituted moiety. Some of the common fragments are indicated in Chart I.

Fibrinolytic Evaluation. A modification of the mixed *in vivo–in vitro* dilute blood clot lysis assay developed by Fearnley, *et al.*,[8] and Billimoria, *et al.*,[9] was employed to measure fibrinolytic activity. Male Long Evans rats weighing about 250 g were fasted overnight. The test compounds were dissolved in either water, 50% propylene glycol, or 50% PEG 400 and injected intraperitoneally into the animals. Each group contained five rats and control animals received vehicle alone. Later (45 min), blood was withdrawn from the lightly anesthetized rats *via* the abdominal aorta and immediately diluted (1:10) with cold, citrated phosphate buffer. Aliquots of the diluted blood were clotted with thrombin and incubated for 3 hr at 37°. The clot and supernatant were separated and digested with 0.1 *N* NaOH, and the concentration of alkaline hematin was determined spectrophotometrically (540 mμ). The per cent clot lysis was calculated by dividing the hematin in the clot by the sum of the hematin in the clot and supernatant and multiplying by 100. Generally, compounds that induced a response which was at least 15% greater than the control had statistically significant activity. The lowest dose that produced such activity was the MED. The screening dose was 20 mg/kg.

Reference agents employed were serotonin (MED ≃ 5 mg/kg) and the dihydrochloride salts of the bis(tetrahydroisoquinolines) 1a (MED ≃ 2 mg/kg) and 1 (n = 4, MED ≃ 5 mg/kg). Comparison of the activity of 1 (n = 4) with literature values indicates that our assay is less sensitive than that of Fliedner, *et al.* (ED_{50} = 0.3–0.4 mg/kg),[4a] but somewhat more sensitive than that of Markwardt, *et al.* (MED ≃ 10 mg/kg).[4d] Data are recorded in Tables I–III.

Structure–Activity Relationships. It is apparent that one of the isoquinoline moieties must have an unsubstituted nitrogen and be in the "tetrahydro" form in order to maintain a high level of fibrinolytic activity. The *N*-Boc-*N'*-substituted intermediates 18–29 (Table I) show little or no activity at the screening dose. In the active monosubstituted derivatives **3**, **16**, and **30**, oxidation of the unsubstituted ring to the 3,4-dihydroisoquinoline (**15c**, **15b**, and **7**, respectively) substantially reduces activity. The unsubstituted "dihydro-tetrahydro" analog **15a** has activity comparable to **1a**, but conversion to the *N*-oxide (**17**) results in decreased potency.

Chart I

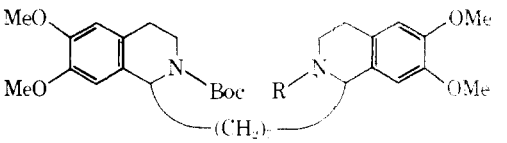


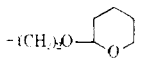
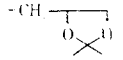
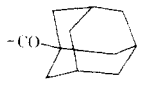
No consistent pattern emerges in comparing variously substituted monoamides except that the most potent members of this group (**30** and **41**) are aliphatic amides.

N-Monoalkyl derivatives with a variety of substituent groups have generally good activity. In some cases (**9a**, **35**, and **38**) the reduced compounds show similar or increased potency in comparison with their *N*-monoacyl analogs **30**, **34**, and **37**, while in other cases (**42**, **44**, and **47**) the activity is inferior to the corresponding monoacyl compounds **41**, **43**, and **46**. The monosulfonamides **50–54** also show a high level of fibrinolytic activity.

Thus, a number of N-monosubstituted derivatives have activity (ip) comparable to the unsubstituted reference standard **1a**; however, none of the compounds showed significant oral activity in the dilute blood clot lysis assay when administered to rats at 100 mg/kg.

Table I. *N-tert*-Butyloxycarbonyl-*N'*-substituted Bis(tetrahydroisoquinolines)



No.	R	Method	Yield,[a] %	Formula	Analyses[b]	MED, mg/kg[c]
18	$-COC_6H_4$-*p*-OCF_3	B	80.7	$C_{42}H_{53}F_3N_2O_8$	C, H, N	>20
19	$-COEt$	B	93.7	$C_{37}H_{54}N_2O_7$	C, H, N	>20
20	$-COC_6H_3$-3,5-$(NO_2)_2$	B	95.8	$C_{41}H_{52}N_4O_{11}$	C, H, N	>20
21	$-COCH_2OC_6H_5$	B	53.7	$C_{42}H_{56}N_2O_8$	C, H, N	>20
22	$-COC_6H_{11}$	B	55.0	$C_{41}H_{60}N_2O_7$	C, H, N	>20
23	$-CO(CH_2)_5CH_3$	B	53.5	$C_{41}H_{62}N_2O_7$	C, H, N	~20
24		D	69.0	$C_{41}H_{62}N_2O_8$	C, H, N	>20
25		E	21.0	$C_{40}H_{60}N_2O_8$	H, N; C[d]	>20
26	$-Et \cdot HCl$	D	65	$C_{36}H_{54}N_2O_6 \cdot HCl$	C, H, N	~20
27		B	52.7	$C_{44}H_{64}N_2O_7$	C, H, N	>20
28	$-COCH_2CO_2Et$	B	61.5	$C_{39}H_{58}N_2O_9$	C, H, N	>20
29	$-COC_6H_4$-*o*-CO_2CH_3	B	73.1	$C_{43}H_{56}N_2O_9$	C, H, N	>20

[a] After purification by column chromatography. [b] See footnote †. [c] Dilute blood clot lysis assay (see Fibrinolytic Evaluation). [d] C: calcd, 68.93; found, 68.49.

Experimental Section†

1,1'-Heptamethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2'-(*tert*-butoxycarbonyl)-6',7'-dimethoxy-1',2',3',4'-tetrahydroisoquinoline (3). To a stirred solution of **1a**[4a] (180.0 g, 0.373 mol) and TEA (41.5 g, 0.41 mol) in 3.7 l. of dioxane and 3.2 l. of H_2O, maintained at 50° under an N_2 atmosphere, was added dropwise a solution of *tert*-butoxycarbonyl azide (Aldrich, 58.7 g, 0.41 mol) in 500 ml of dioxane over 3 hr. After an additional 3 hr at 50° the bulk of the solvents were removed under reduced pressure at approximately 50°. The aqueous suspension was extracted with three portions of Et_2O. [*Note:* the aqueous phase contained all of the unreacted diamine **1a** which could be recovered (~25%) by basification to pH >8 with dilute NaOH solution and extraction with Et_2O in the usual manner.] The Et_2O extracts were extracted with three portions of ice-cold 1 *N* HCl solution. The combined aqueous solution was back extracted with Et_2O and the combined Et_2O extracts could be worked up in the usual manner to yield 69 g of the bis-Boc derivative. The HCl extracts were immediately chilled with crushed ice and basified with 5% NaOH solution. Extraction with three portions of CH_2Cl_2, washing with H_2O and brine, drying (Na_2SO_4), and solvent evaporation afforded 102.3 g of crude **3** as a dark amber glass. The dihydroisoquinoline contaminant was converted to **3** by $NaBH_4$ (6.6 g) in MeOH or THF at room temperature in the usual manner. The resultant amber glass (94.4 g, 43.5%) was sufficiently pure for further elaboration and was stored under an N_2 atmosphere. The material could be further purified by column chromatography on neutral alumina, **3** being eluted with 3% EtOH in Et_2O. The mass spectrum was consistent for the structure: *m/e* 582 (M^+), 581, 580, 292, 206, 205, 192.

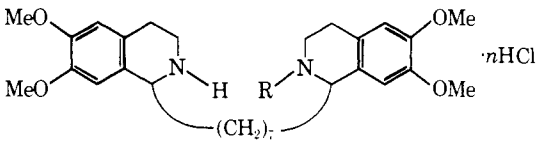
Method A. 1,1'-Heptamethylene-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6',7'-dimethoxy-1',2',3',4'-tetrahydroisoquinoline Hydrochloride (30). A solution of **3** (2.75 g, 0.0047 mol) and TEA (0.51 g, 0.005 mol) in CH_2Cl_2 (50 ml) was placed under a dry N_2 atmosphere and cooled to near 0° in an ice-H_2O bath. Acetyl chloride (0.4 ml, ~0.005 mol) was added dropwise with stirring over 1 min and stirring in the cold was continued for 10 min, followed by stirring at room temperature for 1 hr. The mixture was then poured into ice-H_2O, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organics were successively washed with dilute HCl, dilute $NaHCO_3$, and H_2O. Drying ($MgSO_4$) and solvent removal yielded 2.71 g of the acylated mono-Boc intermediate as a yellow syrup. This intermediate (2.3 g, 0.0037 mol) was dissolved in 50 ml of 98% HCOOH and stirred at room temperature for 2 hr under an N_2 atmosphere. Stripping of the formic acid under vacuum afforded the formate salt of the product which was then dissolved in H_2O and basified with 5% NaOH solution. The oily amine was extracted into CH_2Cl_2 and treated in the usual manner to give 1.8 g of crude **30** free base. Purification was achieved by chromatography on neutral alumina, pure product (1.2 g, 62.2%) being eluted with 3% EtOH in Et_2O. Spectral data (ir, nmr, and mass spectrum) were consistent and the HCl salt (**30**) was prepared using HCl(g) in Et_2O-EtOAc. *Anal.* ($C_{31}H_{44}N_2O_5 \cdot HCl$) C, H, N.

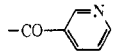
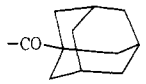
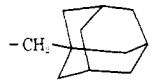
Compound **39** was prepared in a similar manner, using the acid chloride of succinic acid monomethyl ester (Aldrich). The product was purified by chromatography on CC-7 silica using 10% EtOH in Et_2O for elution (see Table II).

Method B. 1,1'-Heptamethylene-2-(*p*-trifluoromethoxybenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2'-(*tert*-butoxycarbonyl)-6',7'-dimethoxy-1',2',3',4'-tetrahydroisoquinoline (18). To a stirred solution of **3** (3.06 g, 0.0053 mol) and TEA (0.585 g, 0.0058 mol) in 25 ml of CH_2Cl_2 at ~5° and under an atmosphere of dry N_2 was added a solution of *p*-trifluoromethoxybenzoyl chloride (1.3 g, 0.0058 mol) in 15 ml of CH_2Cl_2. The mixture was stirred at ~5° in an ice bath for 1 hr and then at room temperature for 2 hr. It was then poured into ice-H_2O, the layers were separated, and the aqueous phase was extracted with a second portion of CH_2Cl_2. The combined extracts were washed with dilute HCl (cold), saturated $NaHCO_3$ solution, and saturated NaCl solution, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product (4.0 g) was chromatographed on a column of neutral alumina, purified **18** being eluted

†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 aslo Tables I and II). Melting points were obtained in a Mel-Temp block and are uncorrected. 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. Merck alumina (neutral aluminum oxide, unless otherwise indicated) and Mallinckrodt CC-7 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.

Table II. *N*-Monosubstituted Bis(tetrahydroisoquinolines)



No.	R	*n*	Method	Yield,[a] %	Formula	Analyses[b]	MED, mg/kg[c]
3	$-CO_2C(CH_3)_3$	0		43.5	$C_{34}H_{50}N_2O_6$	*d*	~5
9a	-Et	2	C	75.3	$C_{31}H_{46}N_2O_4 \cdot 2HCl$	C, H, N	2–5
			D	91.3			
9b	$-(CH_2)_2OH$	2	D	90.0	$C_{31}H_{46}N_2O_5 \cdot 2HCl$	C, H, N, Cl	5–20
9c	$-(CH_2)_3OH$	2	D	33.1	$C_{32}H_{48}N_2O_5 \cdot 2HCl$	C, H, N	~5
9d	$-CH_2CHOHCH_2OH$	2	E	89.0	$C_{32}H_{48}N_2O_6 \cdot 2HCl$	H, N; C[d,e]	2–5
9f	$-(CH_2)_2SH$	2	F	25.0	$C_{31}H_{46}N_2O_4S \cdot 2HCl$	H, N, S; C[f]	2–5
16	$-COC_6H_5$	1	K	72.7	$C_{36}H_{46}N_2O_5 \cdot HCl$	*d*	~20
30	$-COCH_3$	1	A	62.2	$C_{31}H_{44}N_2O_5 \cdot HCl$	C, H, N	2–5
31	$-CO_2Et$	1	G	36.8	$C_{32}H_{46}N_2O_6 \cdot HCl$	C, H, N	>20
32		2	G	90.2	$C_{35}H_{45}N_3O_5 \cdot 2HCl$	C, H, N	>20
33	-COEt	1	B	90	$C_{33}H_{46}N_2O_5 \cdot HCl$	C, H, N	~20
34	$-COC_6H_4$-*p*-OCF_3	1	B	76.9	$C_{37}H_{45}F_3N_2O_6 \cdot HCl$	C, H, N	~10
35	$-CH_2C_6H_4$-*p*-OCF_3	2	C	55.2	$C_{37}H_{47}F_3N_2O_5 \cdot 2HCl$	C, H, N	~5
36	$-COC_6H_3$-3,5-$(NO_2)_2$	1	B	69.4	$C_{36}H_{44}N_4O_9 \cdot HCl$	C, H, N	5–20
37	$-COC_6H_{11}$	1	B	69.1	$C_{36}H_{52}N_2O_5 \cdot HCl$	C, H, N	>20
38	$-CH_2C_6H_{11}$	2	C	73.7	$C_{36}H_{54}N_2O_4 \cdot 2HCl$	C, H, N	5–20
39	$-CO(CH_2)_2CO_2CH_3$	1	A	67.1	$C_{34}H_{48}N_2O_7 \cdot HCl$	C, H, N	>20
40	$-(CH_2)_4OH$	2	C	Quant	$C_{33}H_{50}N_2O_5 \cdot 2HCl$	C, H; N[g]	>20
41	$-CO(CH_2)_5CH_3$	1	B	43.7	$C_{36}H_{54}N_2O_5 \cdot HCl$	C, H, N	~2
42	$-(CH_2)_6CH_3$	2	C	62.7	$C_{36}H_{56}N_2O_4 \cdot 2HCl$	H, N; C[h]	~5
43	-CHO	1	H	17.0	$C_{30}H_{42}N_2O_5 \cdot HCl$	C, H, N	~5
44	$-CH_3$	2	C	30.4	$C_{30}H_{44}N_2O_4 \cdot 2HCl$	C, N; H[i]	~20
45	$-COCH_2CO_2Et$	1	B	46.2	$C_{34}H_{48}N_2O_7 \cdot HCl$	C, H, N	~5
46		1	B	40	$C_{40}H_{56}N_2O_5 \cdot HCl$	N; C, H[j]	~5
47		2	C	44.2	$C_{40}H_{58}N_2O_4 \cdot 2HCl$	*d*	~20
48	$-(CH_2)_2OC_6H_5$	2	C	68.3	$C_{37}H_{50}N_2O_5 \cdot 2HCl$	N; C, H[d,k]	2–5
49	$-COC_6H_4$-*o*-CO_2CH_3	1	B	76.9	$C_{38}H_{48}N_2O_7 \cdot HCl$	C, H, N	5–20
50	$-SO_2C_6H_4$-*p*-CH_3	1	J	19.9	$C_{36}H_{48}N_2O_6S \cdot HCl$	H, N, S; C[l]	5–20
51	$-SO_2CH_3$	1	J	37.5	$C_{30}H_{44}N_2O_6S \cdot HCl$	H, N; C[m]	~10
52	$-SO_2C_6H_4$-*p*-Cl	1	J	36.4	$C_{35}H_{45}ClN_2O_6S \cdot HCl$	C, H, N	~5
53	$-SO_2C_6H_4$-*p*-OMe	1	J	51.3	$C_{36}H_{48}N_2O_7S \cdot HCl$	C, H, N	2–5
54	$-SO_2C_6H_4$-*o*-NO_2	1	J	67.7	$C_{35}H_{44}N_2O_6S \cdot HCl$	C, H, N	~5

[a] Free amine, after column chromatography. [b] See footnote †. [c] Dilute blood clot lysis assay (see Fibrinolytic Evaluation). [d] Mass spectral analysis, see Experimental Section. [e] C: calcd, 61.04; found, 60.04. [f] C: calcd, 60.47; found, 60.96. [g] N: calcd, 4.46; found, 4.03. [h] C: calcd, 66.14; found, 66.69. [i] H: calcd, 8.14; found, 7.70. [j] C: calcd, 70.51; found, 69.70. H: calcd, 8.43; found, 7.91. [k] C: calcd, 65.77; found, 66.24; H: calcd, 7.76; found, 7.21. [l] C: calcd, 64.22; found, 64.65. [m] C: calcd, 60.34; found, 59.91.

with 1% EtOH in Et_2O. Removal of solvent and drying under vacuum gave **18** (3.6 g, 80.7%) as a glassy noncrystalline solid. Spectra (ir and nmr) were consistent with the structure. *Anal.* ($C_{42}H_{53}F_3N_2O_8$) C, H, N.

Compounds prepared analogously (chromatography absorbent and eluting solvent in parentheses) were **19, 20, 23** (neutral alumina, 1% EtOH in Et_2O); **21, 22, 27** (neutral alumina, 0.5% EtOH in Et_2O); **28, 29** (CC-7 silica, Et_2O).

1,1′-Heptamethylene-2-(*p*-trifluoromethoxybenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Hydrochloride (34). A solution of **18** free base (2.91 g, 0.0038 mol) in 50 ml of 98% HCOOH was stirred at room temperature under N_2 atmosphere for 2 hr and then worked up as described for **30** (method A). The crude product (2.4 g) was chromatographed on a column of neutral alumina to give **34** free base (1.9 g, 76.9%) upon elution with 1% EtOH in Et_2O. Treatment with HCl(g) in the usual manner gave **34** as an amorphous solid. *Anal.* ($C_{37}H_{45}F_3N_2O_6 \cdot HCl$) C, H, N.

Compounds prepared in a similar manner (chromatography absorbent and eluting solvent in parentheses) were **33, 37** (neutral alumina, 2% EtOH in Et_2O); **36** (neutral alumina, 3% EtOH in Et_2O); **41** (neutral alumina, 4% EtOH in Et_2O); **45** (CC-7 silica, 8:1 Et_2O–EtOH); **46** (neutral alumina, 1% EtOH in Et_2O); **49** (CC-7 silica, 25% MeOH in Et_2O) (see Table II).

Method C. 1,1′-Heptamethylene-2-cyclohexylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Dihydrochloride (38). A 1 *M* BH_3 solution in THF (4.6 ml, 0.004 mol) and 20 ml of dry THF was mixed under anhydrous conditions. The stirred solution was cooled to ~5° and a solution of **37** free base (0.97 g, 0.0016 mol) in

Table III. Fibrinolytic Activity of Miscellaneous Compounds

No.	MED, mg/kg[a]	No.	MED, mg/kg[a]
7[b]	>20	**15a**	2–5
13	>20	**15b**	>20
14a	~20	**15c**	~20
14d	>20	**17**	~20

[a] See Fibrinolytic Evaluation. [b] Oxalate salt.

20 ml of dry THF was added over 10 min. The mixture was refluxed for 2.5 hr and cooled and 2 ml of 3 *N* HCl was added, followed by 20 ml of H_2O. After briefly heating to reflux, an additional 5 ml of 3 *N* HCl was added, and the mixture was cooled and basified with 1 *N* NaOH. Extraction with CH_2Cl_2, washing (H_2O, brine), drying ($MgSO_4$), and solvent removal gave 0.94 g of crude product. Chromatography on neutral alumina yielded essentially pure **38** free base (0.7 g, 73.7%) upon elution with 2% EtOH in Et_2O. The dihydrochloride salt **38** was prepared in the usual manner. *Anal.* ($C_{36}H_{54}N_2O_4$·2HCl) C, H, N. Other compounds prepared from their monoamides in a similar manner (chromatography absorbent and eluting solvent in parentheses) were **9a** (neutral alumina, Et_2O); **35** (neutral alumina, 5% EtOH in Et_2O); **42** (neutral alumina, 1% EtOH in Et_2O); **44** (neutral alumina, 0.4% EtOH in Et_2O) (see Table II); **47** (neutral alumina, 1% EtOH in Et_2O), mass spectrum *m/e* 630 (M^+), 629, 628, 340, 206, 205, 192; **48** (neutral alumina, 25% EtOH in Et_2O), mass spectrum *m/e* 602 (M^+), 601, 600, 312, 206, 205, 192.

The 4-hydroxybutyl derivative **40** was prepared from **39** free base using 5 molar equiv of BH_3 in THF (see Table II).

Method D. 1,1′-Heptamethylene-2-(2-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (9b) Dihydrochloride. A mixture of 3 (4.57 g, 0.0078 mol), 2-(2-bromoethoxy)tetrahydropyran[10] (1.92 g, 0.0092 mol), K_2CO_3 (1.08 g, 0.0078 mol), and KI (0.49 g, 0.0029 mol) in MeCN (110 ml) was stirred at reflux for 12 hr. Work-up in the usual manner gave 6.52 g of gum. Chromatography on alumina (elution with 90:10 Et_2O–MeCN) gave **24** as a noncrystalline glass (4.20 g, 69%). *Anal.* ($C_{41}H_{62}N_2O_8$) C, H, N.

A solution of **24** (2.5 g, 0.0035 mol) in EtOH (270 ml) and aqueous 3 *N* HCl (30 ml) was heated under reflux for 75 min. The solvents were removed and the residue was partitioned between aqueous NaOH and Et_2O. Evaporation of the dried Et_2O solution yielded **9b** (1.67 g, 90%). Treatment in *n*-PrOH with 2 equiv of 1 *N* HCl, followed by evaporation and trituration of the residue under Et_2O, gave the dihydrochloride salt. *Anal.* ($C_{31}H_{46}N_2O_5$·2HCl) C, H, N, Cl.

Intermediate **26** was prepared in a similar manner to **24**, using EtI as alkylating agent (see Table I), and was converted to **9a** as described above for **9b**. The hydroxypropyl derivative **9c** was also prepared as described above, using 2-(3-chloropropyloxy)tetrahydropyran[9] as the alkylating agent.

Method E. 1,1′-Heptamethylene-2-(2,3-dihydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoinoline (9d) Dihydrochloride. A mixture of 3 (4.40 g, 0.0075 mol), 2,2-dimethoxy-1,3-dioxolane-4-methanol *p*-toluenesulfonate[11] (2.28 g, 0.0008 mol), K_2CO_3 (1.04 g, 0.0075 mol), and KI (0.50 g, 0.003 mol) in hexamethylphosphorictriamide (40 ml) was stirred at 110° for 36 hr. The solvent was removed at 0.1 mm and the residue was dissolved in Et_2O. The solution was washed with H_2O (six times), then dried, and evaporated. The product (after treatment with $NaBH_4$ in MeOH) was purified by chromatography on alumina; elution with Et_2O yielded **25** (1.12 g, 21%). *Anal.* ($C_{40}H_{60}N_2O_8$) H, N; C: calcd, 68.93; found, 68.49. Mass spectrum: *m/e* 696 (M^+), 595, 495, 206, 205, 192.

Treatment of **25** as described in method D for **24** yielded **9d** (0.78 g, 89%). The dihydrochloride salt was prepared in the usual manner. *Anal.* ($C_{32}H_{48}N_2O_6$·2HCl) H, N; C: calcd, 61.04; found, 60.04. Mass spectrum: *m/e* 556 (M^+), 555, 266, 206, 205, 192.

Method F. 1,1′-Heptamethylene-2-(2-mercaptoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (9f) Dihydrochloride. To a stirred solution of **9b** (3.1 g, 0.0052 mol) in $CHCl_3$ (EtOH free, 25 ml) was added a solution of $SOCl_2$ (0.93 g, 0.0078 mol) in $CHCl_3$ (EtOH free, 10 ml) over 30 min at room temperature. After refluxing for 1 hr the mixture was stripped of solvent and excess reagent with the aid of added $CHCl_3$. Evaporation at 0.01 mm afforded crude **9e** (3.1 g, nearly quantitative) as a tan froth. Spectra (ir and nmr) were consistent with structure. The dihydrochloride was prepared in the usual manner. A solution of $NaSH·xH_2O$ (Fisher, 3.80 g) in H_2O (5 ml) was added to a solution at 10° of **9e**·2HCl (2.56 g, 0.0042 mol) in DMF (25 ml). The mixture was stirred under N_2 at 50° for 1 hr. The DMF was removed at 4 mm and the residue was taken up in H_2O and extracted with Et_2O. Evaporation of the dried Et_2O solution left 1.58 g; chromatography on alumina gave a fraction (eluted with 95:5 Et_2O–EtOH) containing pure **9f** (0.55 g, 25%). Treatment in *n*-PrOH with 2 equiv of 1 *N* HCl gave, after work-up, the dihydrochloride salt. *Anal.* ($C_{31}H_{46}N_2O_4S$·2HCl) H, N, S; C: calcd, 60.47; found, 60.96.

Method G. 1,1′-Heptamethylene-2-carboethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Hydrochloride (31) and 1,1′-heptamethylene-2-(3-nicotinoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Dihydrochloride (32). A solution of nicotinic acid (0.431 g, 0.0035 mol) and TEA (0.354 g, 0.0035 mol) in 50 ml of CH_2Cl_2 was cooled to −10° under an atmosphere of dry N_2. Ethyl chloroformate (0.38 g, 0.0035 mol) was added and the mixture stirred at −10° for 1 hr. A solution of 3 (2.04 g, 0.0035 mol) in 50 ml of CH_2Cl_2 was then added over 0.5 hr, allowing the temperature of the reaction mixture to rise to ~10°. Further stirring at 10–15° for 15 min was followed by washing of the mixture with 2% Na_2CO_3 solution, H_2O, and brine. Drying (Na_2SO_4) and solvent removal afforded 2.3 g of crude products. Chromatography on an alumina column gave two main fractions, A (0.71 g, eluted with Et_2O) and B (0.94 g, eluted with 99:1 Et_2O–EtOH).

Fraction A was treated with 98% HCOOH in the standard manner (see method A) and chromatographed on an alumina column to give, upon elution with CH_3CN, 31 free base (0.22 g, 36.8%). The HCl salt (31) was prepared in the standard manner. *Anal.* ($C_{32}H_{46}N_2O_6$·HCl) C, H, N.

Fraction B, treated as above for A, but without chromatography, afforded 32 free base (0.72 g, 90.2%). The 2HCl (32) was prepared in the usual manner. *Anal.* ($C_{35}H_{45}N_3O_5$·2HCl) C, H, N.

Method H. 1,1′-Heptamethylene-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Hydrochloride (43). The mono-Boc 3 (3.22 g, 0.0055 mol) was added to formic-acetic anhydride[12] (50 ml) under N_2 atmosphere and stirred at 35° for 17 hr. The yellow solution was poured into ice-H_2O-CH_2Cl_2 and basified by the addition of solid Na_2CO_3 to the stirred mixture. Treatment of the organic layer in the usual manner yielded a crude product that was chromatographed on an alumina column to give 0.43 g of the intermediate *N*-Boc-*N*′-CHO derivative. Treatment of the intermediate with 98% HCOOH as described previously cleanly gave 43 free base (0.33 g, 17% from 3) and the HCl salt (43) was prepared in the standard manner. *Anal.* ($C_{30}H_{42}N_2O_5$·HCl) C, H, N.

Method J. 1,1′-Heptamethylene-2-(*p*-methoxybenzenesulfonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline Hydrochloride (53). A mixture of 3 (4.0 g, 0.0068 mol) and anhydrous Na_2CO_3 (0.95 g, 0.0089 mol) in 75 ml of $CHCl_3$ under N_2 atmosphere was cooled to 0° and *p*-methoxybenzenesulfonyl chloride (Aldrich, 1.5 g, 0.0071 mol) was added with stirring. The cooling bath was removed and the mixture was stirred at room temperature for 20 hr. Successive washing with H_2O, 3 *N* HCl, 5% Na_2CO_3 solution, H_2O, and brine, followed by drying (Na_2SO_4) and removal of $CHCl_3$ under reduced pressure, afforded, after chromatography on alumina (elution with 0.5% EtOH in Et_2O), 3.8 g of intermediate Boc. Treatment with 98% HCOOH in the usual manner yielded 53 free base (2.3 g, 51.3% from 3) after chromatography on alumina (elution with 0.5% EtOH in Et_2O). *Anal.* [HCl salt (53)] ($C_{36}H_{48}N_2O_7S$·HCl) C, H, N.

Using the appropriate sulfonyl chlorides and similar conditions, the following analogs were prepared (chromatography absorbent and elution solvent in parentheses): 50 (alumina, 95:5 Et_2O–EtOH); 51 (alumina, 98:2 Et_2O–EtOH); **52** (alumina, 0.2% EtOH in Et_2O); 54 (alumina, 0.2% EtOH in Et_2O) (see Table II).

Method K. 7-Carbomethoxy-*N*-β-(3,4-dimethoxyphenethyl)-octanamide (12). A solution of azelaic acid monomethyl ester[13] (4.04 g, 0.02 mol) and $SOCl_2$ (30 ml) in 100 ml of CH_2Cl_2 was refluxed for 3 hr. After removal of solvent and excess $SOCl_2$ under reduced pressure, the acid chloride was added with stirring under N_2 to a solution of homoveratrylamine (3.98 g, 0.022 mol) and TEA (2.02 g, 0.02 mol) in 30 ml of C_6H_6. The mixture was refluxed for 2 hr, cooled, and washed with H_2O, 5% HCl, H_2O, 5% K_2CO_3 and brine. Drying (Na_2SO_4), solvent removal, and tritu-

ration of the residue with Et_2O-Skellysolve B afforded crystalline product. Recrystallization from EtOAc-Skellysolve B gave pure **12** (5.7 g, 78%), mp 56–58°. *Anal.* ($C_{20}H_{31}NO_5$) C, H, N.

Methyl 8-[1-(6,7-Dimethoxy-3,4-dihydroisoquinolyl)]octanoate (13) Hydrochloride. To a stirred suspension of **12** (32.0 g, 0.087 mol) in 350 ml of toluene was added 150 ml of $POCl_3$ and the mixture was refluxed for 2 hr. The cooled mixture was evaporated under high vacuum to remove solvent and reagent and H_2O was added to the residue. Cooling in an ice bath was followed by basification (concentrated NH_4OH) and extraction of the product into Et_2O. Standard washing and drying procedures yielded an oil which was dissolved in Et_2O and treated with HCl(g). Evaporation of the Et_2O, trituration of the residue with warm EtOAc, and recrystallization of the resultant solid from CH_3CN-Et_2O gave pure crystalline **13**·HCl (29.4 g, 88%), mp 129–131°. *Anal.* ($C_{20}H_{29}NO_4$·HCl) C, H, N.

Methyl 8-[1-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-octanoate (14a) Hydrochloride. To a solution of **13**·HCl (2.0 g, 0.0052 mol) in 50 ml of MeOH was added $NaBH_4$ (0.2 g, 0.0052 mol) and the mixture was stirred at room temperature for 4 hr. Solvent removal, addition of H_2O to the residue, and standard work-up with Et_2O afforded an oil. The HCl salt was prepared in Et_2O in the usual manner and recrystallization of the resultant solid from CH_3CN-Et_2O gave **14a**·HCl (1.74 g, 86.5%), mp 129–131°. A second recrystallization from MeOH-Et_2O gave analytical material, mp 132–133°. *Anal.* ($C_{20}H_{31}NO_4$·HCl) C, H, N.

8-[1-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]-*N*-(3,4-dimethoxyphenethyl)octanoamide (14d) Hydrochloride. To a stirred solution of **14a** (3.6 g, 0.0104 mol) and TEA (1.2 g, 0.012 mol) in 50 ml of aqueous dioxane was added Boc azide (1.6 g, 0.011 mol) and the mixture was heated at 50–55° for 17 hr. Cooling, addition of 200 ml of H_2O, and standard Et_2O work-up gave a quantitative yield of the Boc derivative as an oil. The oil (4.7 g) was slurried in 50 ml of H_2O, 10 ml of 5 *N* NaOH solution was added, and the mixture was stirred at room temperature for 22 hr. Cooling in an ice bath, addition of 10 ml of 5 *N* HCl, and Et_2O work-up yielded the acid **14b** (3.85 g) as an oil. **14b** and TEA (0.89 g, 0.088 mol) were dissolved in 40 ml of CH_2Cl_2 and cooled to −10°, and isobutyl chloroformate (1.21 g, 0.0088 mol) was added with stirring followed by the dropwise addition over 5 min of a solution of homoveratrylamine (1.61 g, 0.0088 mol) in 10 ml of CH_2Cl_2. The mixture was then stirred at room temperature for 2 hr and washed with H_2O, 5% $NaHCO_3$, 5% HCl, H_2O, and brine, followed by drying and solvent evaporation, to give **14c** (3.3 g) as an oil. A mixture of **14c** (3.3 g, 0.0055 mol) and 70 ml of 50% HCOOH was heated at 55° for 3 hr. Evaporation of reagent, addition of H_2O, basification with concentrated NH_4OH, and work-up in CH_2Cl_2 gave crude **14d**, which was then converted to crystalline **14d**·HCl in Et_2O (2.14 g, 72.8%): mp 159–164°. Recrystallization from CH_3CN-Et_2O gave pure product, mp 168–170°. *Anal.* ($C_{29}H_{42}N_2O_5$·HCl) C, H, N.

1-[1-(6,7-Dimethoxy-3,4-dihydroisoquinolyl)]-7-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolyl)]heptane (15a) Dihydrochloride. $CHCl_3$ (150 ml) was added to P_2O_5 (75 g), followed by 75 ml of anhydrous Et_2O, and the sitrred mixture was heated at 70° for 24 hr.[14] To the solution of PPE was added a solution of **14d** (1.85 g, 0.0037 mol) in 20 ml of $CHCl_3$ and stirring at 70° was continued for 2 hr. Evaporation of solvent, addition of H_2O to the residue, basification with concentrated NH_4OH, and extraction into EtOAc yielded, after standard washing and drying procedures, **15a** as a crude oil. Treatment with HCl(g) in EtOAc-Et_2O and recrystallization of the resultant solid from EtOH-Et_2O gave **15a**·2HCl monohydrate (1.67 g, 79.3%), mp 210–212°. Further recrystallization from EtOH-Et_2O gave material with mp 213–215°: ir λ_{max} (KBr) 1561 cm^{-1} (C=N); nmr δ ($CDCl_3$) 6.93, 7.01 (1 H singlets, "tetrahydro" aromatics), 7.32, 7.47 (1 H singlets, "dihydro" aromatics). *Anal.* ($C_{29}H_{40}N_2O_4$·2HCl·H_2O) C, H, N.

1,1′-Heptamethylene-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline (16) Hydrochloride. To a solution of **15a** (1.89 g, 0.0039 mol) and TEA (0.4 g, 0.0039 mol) in 30 ml of C_6H_6 was added dropwise a solution of benzoyl chloride (0.55 g, 0.0039 mol) in 10 ml of C_6H_6. After stirring at room temperature for 4 hr and standard work-up, the crude product was chromatographed on a column of alumina, **15b** being eluted with 1% EtOH in Et_2O. Treatment with HCl(g) in Et_2O gave **15b**·HCl (1.8 g, 73.8%) as a noncrystalline solid. Spectral data (ir and nmr) were consistent for the structure. **15b** (1.1 g, 0.0019 mol) was dissolved in 20 ml of MeOH and $NaBH_4$ (0.144 g, 0.0038 mol) was added and the mixture was stirred at 25° for 2 hr. Standard work-up and chromatography of the crude product on alumina (elution with 0.2% EtOH in Et_2O) afforded **16** (0.8 g, 72.7%). The HCl salt was prepared in the usual manner. The mass spectrum was consistent for the structure: *m/e* 587 (M^+ of free amine), 586, 585, 479, 296, 205, 192.

1,1′-Heptamethylene-2-(*tert*-butoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-3′,4′-dihydroisoquinoline (15c) Hydrochloride. To a stirred mixture of **15a**·2HCl (11.43 g, 0.02 mol) and TEA (6.17 g, 0.061 mol) in 250 ml of 50% aqueous dioxane under an argon atmosphere was added, dropwise over 20 min, a solution of Boc azide (3.0 g, 0.021 mol) in 25 ml of 50% aqueous dioxane. After stirring at 55° for 4 hr, H_2O was added and the product was extracted into Et_2O. After standard treatment, the Et_2O extracts yielded crude **15c** (11.65 g). Chromatography on alumina, eluting with Et_2O, gave pure **15c** (5.51 g, 47.5%). A sample was converted to the HCl salt hemihydrate: mp 95–96° dec. *Anal.* ($C_{34}H_{48}N_2O_6$·HCl·0.5H_2O) C, H, N.

1,1′-Heptamethylene-6,7-dimethoxy-3,4-dihydroisoquinoline-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinoline 2-Oxide (17) Dihydrochloride. A solution of **15c** (2.0 g, 0.0035 mol) in 20 ml of CH_2Cl_2 was cooled to 0° and a solution of *m*-chloroperbenzoic acid (0.87 g, 0.0042 mol) in 15 ml of CH_2Cl_2 was added dropwise with stirring over 5 min. Stirring was continued at 0° for 1.5 hr and then at room temperature for 1 hr. Washing with 5% $NaHCO_3$ and brine, drying (Na_2SO_4), and solvent removal yielded an oil. Hydrolysis in 20 ml of 98% HCOOH in the standard manner (see method A) gave crude **17**, which was converted to **17**·2HCl (1.59 g, 81%) in the usual manner: mp 115–116° dec. *Anal.* ($C_{29}H_{40}N_2O_5$·2HCl) C, H, N, Cl.

1,1′-Heptamethylene-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-6′,7′-dimethoxy-3′,4′-dihydroisoquinoline (7). To a solution of **30** (0.89 g, 0.0017 mol) in 28 ml of H_2O and 4 ml of HOAc was added $Hg(OAc)_2$[15] (4.0 g, 0.012 mol) and the mixture was refluxed for 2 hr. After cooling, the precipitated HgOAc was filtered off and washed with aqueous EtOH. The filtrate was warmed to 40–45°, treated with H_2S(g) for 10 min, acidified with 2 *N* HCl, and treated with H_2S for a further 20 min. Digestion at ~50° for a further 15 min was followed by filtration through Supercel with the aid of hot acidified aqueous EtOH to remove the black salts. The EtOH was removed by evaporation and the aqueous solution was basified with 5% NaOH and extracted with EtOAc. These extracts yielded crude **7** (0.71 g) which was then purified by column chromatography on neutral alumina, **7** (0.496 g, 55.8%) being eluted with 1% EtOH in Et_2O: ir λ_{max} (KBr) 1570 cm^{-1} (C=N); nmr δ ($CDCl_3$), 6.6 (broad 2 H singlet, "tetrahydro" aromatics), 6.7, 7.0 (1 H singlets, "dihydro" aromatics). *Anal.* ($C_{31}H_{42}N_2O_5$) C, H, N.

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

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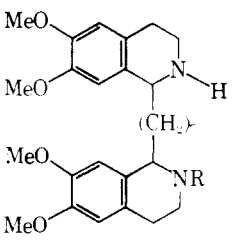
Certain N-monosubstituted analogs (1) of the bis(tetrahydroisoquinoline) 1a were specifically designed and synthesized in an attempt to enhance the oral absorption characteristics of this class of fibrinolytic agents. A number of latentiated derivatives were prepared, wherein the N-substituents were 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.

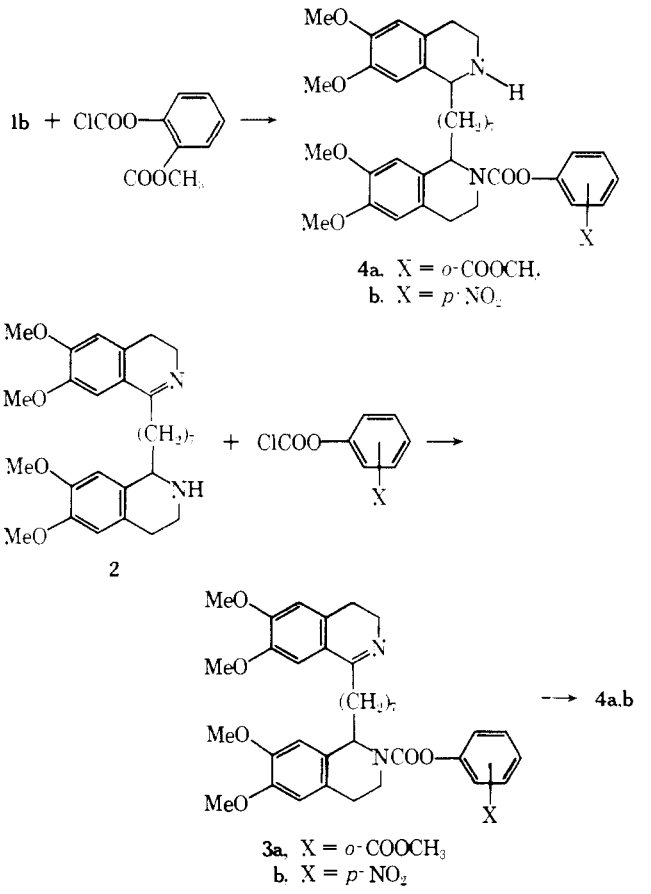
A preceding paper[1] described the rationale for synthesizing monosubstituted bis(tetrahydroisoquinolines) of general structure 1 as potential orally effective fibrinolytic agents. Two general syntheses were developed, and a series of mono-*N*-acyl, *N*-alkyl, and *N*-sulfonyl analogs was prepared, primarily 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