Synthesis and Structure–Activity Relationships of Fibrinolytic Bis(tetrahydroisoquinolines)[1]

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The area of fibrinolysis–thrombolysis represents a vast potential for readily available, synthetic medicinal agents. The promising results obtained in animal clot lysis experiments with *meso*-1,1′-tetramethylenebis(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline) dilactate (bisobrin lactate) prompted the preparation of a series of related compounds. The 3-step synthetic approach involved condensation of 2 moles of a phenethylamine with 1 mole of a dibasic acid to yield a bis(amide) III. Dehydrative cyclization of the latter to a bis(dihydroisoquinoline) IV, followed by $NaBH_4$ reduction, provided the desired compounds V in generally good overall yields. Structural variations include nature of the ring N atoms, aromatic substitution pattern, and chain length. The effect of these variables on fibrinolytic activity as measured in the rat (ip) is discussed.

The urgent need to develop effective agents for the treatment of thromboembolic disease states is gradually showing promise of fulfillment. The protein agents, streptokinase and urokinase, pointed the way toward the possibility of practical therapy, although their drawbacks, such as antigenicity and availability, respectively, are by now well recognized.[2] Readily available, synthetic medicinals represent, therefore, an as yet untapped potential for both acute and prophylactic use in antithrombotic therapy.

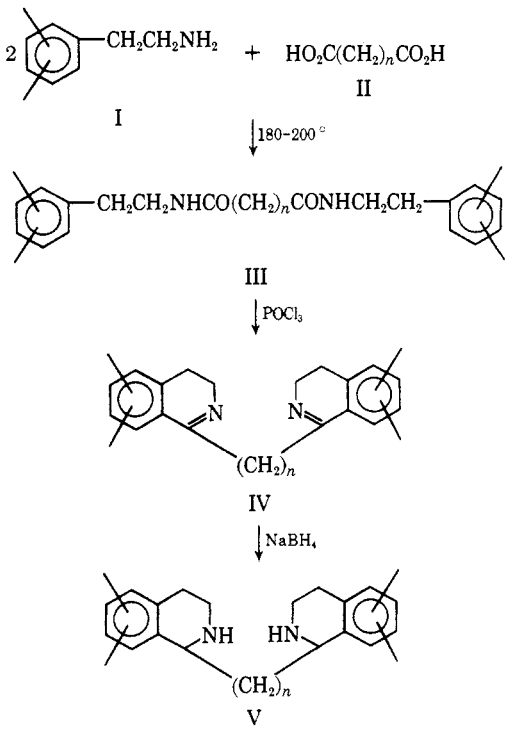
Enhancement of the body's natural fibrinolytic system to effect dissolution of a thrombus has been considered to be a sound approach to thrombolytic therapy.[2] Several classes of compounds, for example, epinephrine and related sympathomimetic amines, nicotinic acid, and sulfonylureas, have been shown to produce increased blood fibrinolytic activity in both human and animal clot lysis experiments.[3] All of the synthetic fibrinolytics examined, however, were found to be deficient in some respect, such as minimal potency, short-lived effect, tolerance, and other side effects, with the result that none of these agents have been committed to detailed clinical trial.

With their effectiveness in thrombolytic therapy yet to be proved, the search for superior fibrinolytic agents continues and was given impetus by the discovery by Schor and coworkers of the fibrinolytic action of bisobrin lactate.[4,5] Further encouragement is provided by the recent report on the ability of bisobrin lactate to lyse experimental thrombi *in vivo* in dogs.[6] The present paper describes some of the chemistry and structure–activity relationships of this interesting class of compounds.

Chemistry.—Bis(tetrahydroisoquinolines) V[7] with 2 secondary N atoms have been studied to a certain extent in connection with the search for new amebicides,[8–11] muscle relaxants,[12] and bronchodilators.[13] As part of a program of systematic molecular modification a number of new compounds of this type were prepared and some of the older compounds were reinvestigated and, for reasons described below, recharacterized.

The synthetic route (Scheme I) involved a standard

SCHEME I



sequence of reactions in which 2 moles of a phenethylamine I and 1 mole of a dibasic acid II were condensed to yield a bis(amide) III. Subsequent Bischler–Napieralski cyclization to a bis(3,4-dihydroisoquinoline)

(1) Presented in part before the Division of Medicinal Chemistry, Joint Chemical Institute of Canada–American Chemical Society Conference, Toronto, Canada, May 24, 1970.

(2) J. M. Schor, Ed., "Chemical Control of Fibrinolysis-Thrombolysis," Wiley, New York, N. Y., 1970.

(3) G. R. Fearnley, "Fibrinolysis," The Williams and Wilkins Co., Baltimore, Md., 1965, p 83.

(4) J. M. Schor, V. Steinberger, E. Tutko, S. Aboulafia, and I. J. Pachter, 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 31, 1968, N 24.

(5) Bisobrin lactate is the nonproprietary name adopted by the USAN Council for *meso*-1,1′-tetramethylenebis(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline) dilactate. The corresponding dihydrochloride salt is **20**, Table III.

(6) C. H. Shellenberger and A. A. Rubin, 54th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 12, 1970, No. 2263.

(7) Roman numerals refer to Scheme I and arabic numerals refer to compd in the tables.

(8) R. Child and F. L. Pyman, *J. Chem. Soc.*, 2010 (1929).

(9) G. Hahn and H. F. Gudjons, *Ber.*, **71B**, 2183 (1938).

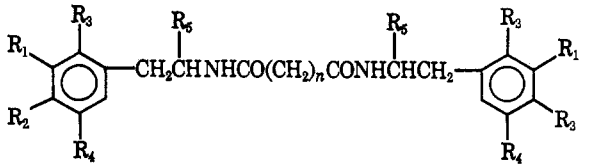
(10) M. R. Amin, W. H. Linnell, and L. K. Sharp, *J. Pharm. Pharmacol.*, **9**, 588 (1957).

(11) O. E. Fancher, S. Hayao, and G. Nichols, *J. Amer. Chem. Soc.*, **80**, 1451 (1958).

(12) H. Plieninger, L. Horn, and A. Lutz, *Arch. Pharm. (Weinheim)*, **286**, 285 (1953).

(13) P. N. Craig and F. P. Nabenhauer, U. S. Patent 2,659,728 (1953).

TABLE I[a]



No.	n	R_1	R_2	R_3	R_4	R_5	Yield, %[b]	Recrystn solvent	Mp, °C[c]	Formula[d]
1	4	MeO	H	H	H	H	85	MeOH	152–153	$C_{24}H_{32}N_2O_4$
2	4	MeO	$PhCH_2O$	H	H	H	92	AcOH	197–198	$C_{38}H_{44}N_2O_6$
3	4	MeO	H	MeO	H	H	76	MeOH	138–139	$C_{26}H_{36}N_2O_6$
4	4	MeO	MeO	H	MeO	H	78	MeOH	174–175	$C_{28}H_{40}N_2O_8$
5	7	MeO	H	H	H	H	82	MeOH	124–125	$C_{27}H_{38}N_2O_4$
6	7	MeO	$PhCH_2O$	H	H	H	75	MeOH	147–153	$C_{41}H_{50}N_2O_6$
7	7	MeO	MeO	H	H	Me	49	MeOH–Et_2O	94–99	$C_{31}H_{46}N_2O_6$[e]

[a] For the synthesis of intermediates which are not described, see R. Child and F. L. Pyman, *J. Chem. Soc.*, 2010 (1929), and G. Hahn and H. F. Gudjons, *Ber.*, **71B**, 2183 (1938). [b] One recrystallization. [c] Anal. sample. [d] Satisfactory anal. were obtained for C, H, and N. [e] O. E. Fancher, S. Hayao, and G. Nichols, *J. Amer. Chem. Soc.*, **80**, 1451 (1958), mp 98–102°.

IV, followed by reduction to the corresponding bis(1,2,-3,4-tetrahydroisoquinoline) V all proceeded in moderate to good yield.

The majority of bis(tetrahydroisoquinolines) (Table III) which were prepared contain one or more alkoxy groups on the aromatic portion of the molecule. The activating effect of such substituents on the Bischler–Napieralski reaction, particularly when para to the site of ring closure, has been noted frequently.[14] In the present case, all the alkoxy-substituted bis(amides) (Table I) underwent facile cyclization, with $POCl_3$, either neat or in refluxing toluene, the reagent of choice. By contrast, it has been reported that the unsubstituted phenethylamides of the dibasic acids from malonic through sebacic failed to cyclize under a variety of conditions.[8] We have reexamined the cyclization of two members of this series, the bis(amides) derived from adipic and suberic acids, in hot polyphosphoric acid and obtained the desired bis(dihydroisoquinolines), **10** and **15**, respectively, in reasonable yields.

Reduction of the bis(dihydroisoquinolines) IV to the tetrahydro derivatives V was effected with excess $NaBH_4$—a reagent commonly used for similar reductions in the mono series. Most of the previous work[8–13] on bis(tetrahydroisoquinolines) antedates this method of reduction which for our purposes gave uniformly good yields in both small- and large-scale preparations.

Two tertiary amines, **40** and **41**, were prepared by standard procedures for assay of their fibrinolytic activity and are included in Table III.

The bis(tetrahydroisoquinolines) (Table III) have at least two centers of asymmetry which are identical and which give rise to meso, D, and L forms. Compound **39** with two different pairs of identical asymmetric centers presents an even more complex isomeric picture. In two cases, **20** and **21**, and **35** and **36**, the crude mixture of isomeric dihydrochlorides resulting from reduction of the corresponding bisdihydroisoquinolines was separated by fractional crystallization into the meso and DL racemic modifications. For the remaining cases, the crude mixture of isomers was treated as a single entity and purified by recrystallization from suitable solvents. This sometimes entailed considerable loss of product as each crop of crystals was enriched to a variable extent in the less soluble isomer. Yields reported in Table III (one recrystallization) are, therefore, deceptively low. Crude yields of the mixed isomers were generally above 70%. As expected, the melting points of the crude (not reported) and recrystallized dihydrochloride salts frequently showed wide separation.

All of the compounds in Tables I–III were characterized by ir spectra. New compounds gave satisfactory microanalytical data while the melting points of known bis(amides) and bis(dihydroisoquinolines) were compared with literature values and the compounds were reanalyzed when serious discrepancies were found.

Comparative melting point data were found to be an unreliable index of identity in the case of known bis(tetrahydroisoquinoline)·2HCl salts both because of the problem of isomeric composition as well as their tendency to form species contg variable amounts of water of hydration. In addition, some of the known compd are reported in the patent literature without mp or anal. data. All of the compd in Table III were, therefore, recharacterized by elemental anal.

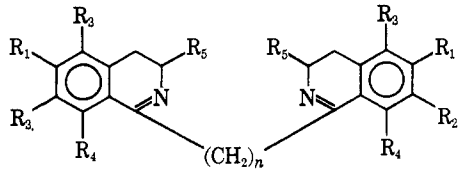
Biological Evaluation.—The general method for measurement of fibrinolytic activity involved a modified, mixed *in vivo–in vitro* assay based on Fearnley's dilute blood clot lysis method.[15,16] The compd to be tested was dissolved or suspended in saline or 1% aq CM-cellulose and injected ip into the rat. After 0.75 hr blood was withdrawn, citrated, dild with phosphate buffer, and clotted with thrombin. After incubation for 4 hr at 37°, the remaining clot and supernatant were sepd and each was digested with 0.1 *N* NaOH to convert the hemoglobin to alkaline hematin. The concn of the latter was detd spectrophotometrically (540 mμ) and the per cent clot lysis was calcd by dividing the hematin in the filtrate by the sum of hematin in clot and filtrate and multiplying by 100. The ED_{50} (mg/kg) represents that dose which causes 50% of the clot to lyse in a standard period of time (4 hr). A minimum of 3 rats was used for each ip dose. Base line fibrinolytic activity was detd by injection of vehicle in place of compound. Serotonin was used as the lab standard for synthetic agents and had an ED_{50} of 1 mg/kg. Details of the present assay procedure have been published.[2]

(14) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1961).

(15) G. R. Fearnley, G. V. Balmforth, and E. Fearnley, *Clin. Sci.*, **16**, 645 (1957).

(16) J. D. Billimoria, J. Drysdale, D. C. O. Jones, and N. F. Maclagan, *Lancet*, **2**, 471 (1959).

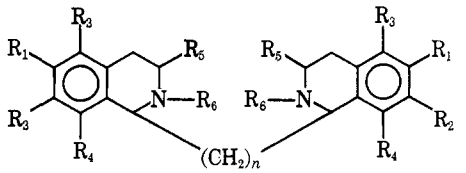
TABLE II[a]



No.	n	R_1	R_2	R_3	R_4	R_5	Method[b]	Yield, %[c]	Recrystn solvent	Mp, °C[d]	Formula[e]	ED_{50},[h] mg/kg
8	7	MeO	MeO	H	H	H	A, 5	50	Cyclohexane	104–105[f]	$C_{29}H_{38}N_2O_4$	
9	10	MeO	MeO	H	H	H	A, 18	68	*i*-PrOH	117–118	$C_{32}H_{44}N_2O_4$	>50
10	4	H	H	H	H	H	C	47	Me_2CO	101–102	$C_{22}H_{24}N_2$	>50
11	4	MeO	H	H	H	H	B, 0.5	40	Cyclohexane	107–108	$C_{24}H_{28}N_2O_2$	
12	4	MeO	$PhCH_2O$	H	H	H	B, 1	65	EtOH	165–166	$C_{38}H_{40}N_2O_4$	
13	4	MeO	H	MeO	H	H	B, 0.25	38	C_6H_6–hexane	185–187	$C_{26}H_{32}N_2O_4$	
14	4	MeO	MeO	H	MeO	H	B, 0.5	59	Cyclohexane	127–129	$C_{28}H_{36}N_2O_6$	>50
15	6	H	H	H	H	H	C	52	Me_2CO	90–92	$C_{24}H_{28}N_2$	>50
16	7	MeO	H	H	H	H	B, 1	61	Hexane	66–67	$C_{27}H_{34}N_2O_2$	>50
17	7	MeO	$PhCH_2O$	H	H	H	B, 2	61	Me_2CO–Et_2O	107–108	$C_{41}H_{46}N_2O_4$	
18	7	MeO	MeO	H	H	Me	A, 3	74		Oil	$C_{43}H_{48}N_8O_{18}$[g]	

[a] For the synthesis of intermediates which are not described, see footnote *a*, Table I and M. R. Amin, W. H. Linnell, and L. K. Sharp, *J. Pharm. Pharmacol.*, **9**, 588 (1957). [b] Capital letters refer to the procedure, numbers refer to the hours of reflux; see Experimental Section. [c] One recrystn. [d] Anal. sample. [e] Satisfactory anal. were obtained for C, H, and N. [f] Second ref, footnote *a*, Table I, mp 140°. [g] Dipicrate, mp 191–193° dec ($MeOCH_2CH_2OH$). [h] The bis(dihydroisoquinoline) precursors of **20** (**21**), **22**, and **29** also had an $ED_{50} > 50$ mg/kg.

TABLE III[a]



No.[a]	n	R_1	R_2	R_3	R_4	R_5	R_6	Yield, %[b]	Recrystn solvent	Mp, °C[c]	Formula[d]	ED_{50}, mg/kg
19	3	MeO	MeO	H	H	H	H	24	MeOH	262–263	$C_{25}H_{36}Cl_2N_2O_4 \cdot H_2O$[e]	6
20	4	MeO	MeO	H	H	H	H	30	H_2O	260–261 dec	$C_{26}H_{38}Cl_2N_2O_4$[f]	0.3
21	4	MeO	MeO	H	H	H	H	19	H_2O–EtOH	269–270 dec	$C_{26}H_{38}Cl_2N_2O_4$[g]	0.4
22	6	MeO	MeO	H	H	H	H	38	MeOH	264–265 dec	$C_{28}H_{42}Cl_2N_2O_4 \cdot H_2O$[h]	0.2
23	7	MeO	MeO	H	H	H	H	74	95% EtOH	207–210	$C_{29}H_{44}Cl_2N_2O_4 \cdot 0.5H_2O$[i]	0.05
24	8	MeO	MeO	H	H	H	H	43	H_2O–EtOH	258–259 dec	$C_{30}H_{46}Cl_2N_2O_4$[j]	0.09
25	10	MeO	MeO	H	H	H	H	46	95% EtOH	233–234	$C_{32}H_{50}Cl_2N_2O_4$	0.7
26	4	H	H	H	H	H	H	32	H_2O	344–346 dec	$C_{22}H_{30}Cl_2N_2$[k]	5
27	4	MeO	H	H	H	H	H	89	MeOH–Et_2O	272–273 dec	$C_{24}H_{34}Cl_2N_2O_2$	2
28	4	HO	H	H	H	H	H	62	H_2O	294–296 dec	$C_{22}H_{30}Br_2N_2O_2$	3
29	4	O-CH_2-O		H	H	H	H	45	$MeOCH_2CH_2OH$	195–197	$C_{24}H_{28}N_2O_4$	18
30	4	MeO	HO	H	H	H	H	55	H_2O–Me_2CO	262–263 dec	$C_{24}H_{34}Cl_2N_2O_4 \cdot H_2O$[l]	1
31	4	HO	HO	H	H	H	H	61	H_2O	258–260 dec	$C_{22}H_{30}Br_2N_2O_4$	4
32	4	MeO	$PhCH_2O$	H	H	H	H	85	EtOH–Et_2O	252–254	$C_{38}H_{46}Cl_2N_2O_4$	3
33	4	MeO	H	MeO	H	H	H	78	95% EtOH	229–230 dec	$C_{26}H_{38}Cl_2N_2O_4 \cdot 2.5H_2O$	5
34	4	MeO	MeO	H	MeO	H	H	54	MeOH–Et_2O	243–245	$C_{28}H_{42}Cl_2N_2O_6$	0.8
35	6	H	H	H	H	H	H	33	MeOH–EtOAc	291–294 dec	$C_{24}H_{34}Cl_2N_2$	5
36	6	H	H	H	H	H	H	28	EtOH	246–248	$C_{24}H_{34}Cl_2N_2$	5
37	7	MeO	H	H	H	H	H	76	95% EtOH	259–260 dec	$C_{27}H_{40}Cl_2N_2O_2$	6
38	7	MeO	$PhCH_2O$	H	H	H	H	41	H_2O–EtOH	240–241	$C_{41}H_{52}Cl_2N_2O_4 \cdot 2H_2O$	1.5
39	7	MeO	MeO	H	H	Me	H	61	95% EtOH	263–265	$C_{31}H_{46}Cl_2N_2O_4$[m]	15–25
40	4	MeO	MeO	H	H	H	Me	67	95% EtOH	251–253	$C_{28}H_{42}Cl_2N_2O_4$	20
41	4	MeO	MeO	H	H	H	$PhCH_2$	45	EtOH–Et_2O	249–252	$C_{40}H_{50}Cl_2N_2O_4 \cdot 0.5H_2O$	12

[a] All compd are in the form of dihydrochloride salts, except **28** and **31** (dihydrobromide salts), and **29** (free base). [b] One recrystallization. [c] Anal. sample. [d] Unless indicated, satisfactory anal. were obtained for C, H, and N. [e] Footnote *a*, Table II, last ref, mp 265–268° dec. [f] P. N. Craig and F. P. Nabenhauer, U. S. Patent 2,659,728 (1953), mp 258–260°. [g] Mp 262–264°.[f] [h] Footnote *a*, Table I, second ref, mp 254°. [i] Mp 225–227° dec.[h] [j] Mp 248°.[h] [k] C: calcd 67.16; found 66.74. [l] H: calcd 7.21; found 7.66. [m] Footnote *e*, Table I, mp 255–256.5°.

Structure–Activity Relationships.—Among the more obvious gross structural requirements for substantial fibrinolytic activity was the secondary nature of the ring N atoms. Both the imine linkage of the dihydroisoquinoline precursors and the tertiary amine character of N-alkylated derivatives (**40** and **41**) caused a greatly diminished effect. Me groups at the 3 position of the rings (**39**) flanking the secondary N were also seriously deactivating, possibly reflecting steric hindrance to interaction between the amino function and a biological substrate.

The influence of distance separating the 2 tetrahydroisoquinoline nuclei was examined in **19–25** wherein the substitution pattern of the aromatic rings was maintained constant. Activity reached a maximum at seven methylene groups (**23**), and declined as the chain was either lengthened or shortened. Dramatic differences in activity among members of this series were ob-

served only in the case of the trimethylene compound **19** which was about 100 times less active than **23**. The variation of activity with chain length was largely masked in compounds **26** and **35**, **27** and **37**, and **32** and **38**. The aromatic substitution patterns involved in these cases, however, produced generally less active compounds.

Activity was affected by the number, type, and position of substituents on the aromatic rings. For a constant chain length of 4 CH_2 groups, the following order of decreasing activity was observed: 6,7-$(MeO)_2$ > 6,7,8-$(MeO)_3$ ≅ 6-MeO, 7-HO > 6-MeO > 6-HO ≅ 6-MeO, 7-$PhCH_2O$ > 6,7-$(HO)_2$ > unsubstituted ≅ 5,6-$(MeO)_2$ > 6,7-CH_2O_2. The superiority of the 6,7-dimethoxy substitution pattern was also borne out in the smaller number of examples with chain lengths of 6 and 7 CH_2 groups.

The meso and DL racemic forms were purposely isolated in two cases (**20–21** and **35–36**) to assess the effect of molecular configuration on fibrinolytic activity. In each case no significant difference in activity between isomers was observed.

Experimental Section

Unless otherwise stated, the yields, mp, recrystn solvents, and elemental anal. for all compd are given in Tables I–III. Melting points were detd with a Thomas-Hoover capillary app and are uncorrected. Ir spectra (Nujol mulls) were measured on a Perkin-Elmer infracord 137 spectrometer. Absorption bands were as expected. Elemental anal. were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Where anal. are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theoretical values. The phenethylamines used as starting materials were obtained, where possible, from commercial sources or synthesized according to known, standard literature procedures. EtOH refers to a commercial 2B grade of abs EtOH.

Amides (Table I). General Procedure.—The phenethylamine (2.0–2.1 moles) and dibasic acid (1.0 mole) were placed in an oil bath preheated to 195° and the mixt was heated at 180–200° for 3–4 hr under a slow stream of N_2. High melting amides solidified during the course of the reaction in which case the temp was raised just above the mp to complete the reaction. After cooling, the residue was recryst.

3,4-Dihydroisoquinolines (Table II). Procedure A.—A suspension of x g of amide and $3x$ ml of $POCl_3$ contained in a flask fitted with a reflux condenser and $CaCl_2$ drying tube was warmed gently and carefully on the steam bath with frequent manual swirling. About the time complete soln occurred (5–15 min), an exothermic reaction ensued (**CAUTION.**—very vigorous in large scale prepn) which was moderated by cooling in an ice bath. On further stirring at room temp (*ca.* 30 min) to allow heat evolution to abate, a cryst ppt formed in a few cases. The reaction was completed by refluxing (see Table II). After cooling, cryst ppt were filtered and washed thoroughly with C_6H_6 and a little MeOH. Otherwise, the resulting soln was evapd *in vacuo* to remove excess $POCl_3$. In either case the residue was then dissolved in H_2O, with warming if necessary, and the clear soln was made strongly basic with 20% NaOH. The mixt was extd with $CHCl_3$, and the combined ext were washed with H_2O and dried (Na_2SO_4). Evapn *in vacuo* gave the crude solid products which were isolated and recryst.

Procedure B.—A suspension of x g of amide, $3x$ ml of $POCl_3$, and $10x$ ml of dry $PhCH_3$ was refluxed for various periods of time (Table II). Initially, clear soln were obtd, followed, in most cases, by the sepn of yellow cryst ppt or oils which subsequently solidified on cooling. After cooling, the solid was filtered and washed thoroughly with C_6H_6 and a little Me_2CO or MeOH. In two cases, **13** and **16**, the oils which sepd failed to solidify. To insure their complete sepn an equal vol of hexane was added and after standing several hours the solvents were decanted. The complex (solid or oil) was then dissolved in H_2O and worked-up as described in procedure A.

Procedure C.—Typically, 35.2 g (0.100 mole) of *N,N'*-diphenethylhexanediamide[8] and 175 g of polyphosphoric acid were placed in an oil bath preheated to 200° and the mixt was heated with magnetic stirring at 190–195° for 1.5 hr. After cooling to 100°, the mixt was poured onto 400 g of cracked ice and the resulting dark brown soln was washed with $CHCl_3$ (3 × 100 ml). The aq layer was made strongly basic with 10% NaOH and extd thoroughly with C_6H_6, and the combined ext were washed with H_2O and concd to 150 ml on the steam bath. The resulting soln was placed on a column of neutral Al_2O_3 (Activity 1, 300 g) and eluted with C_6H_6. The eluates were evapd to dryness *in vacuo* and the combined residues were recrystd (charcoal).

1,2,3,4-Tetrahydroisoquinolines (Table III). General Procedure.—The dihydroisoquinoline (0.1 mole) was dissolved in 500–1000 ml of EtOH (with steam bath heating to 50–60° max if necessary) and the stirred soln was treated in portions with $NaBH_4$ (0.4 mole) over the course of *ca.* 15 min. Each addn of $NaBH_4$ was accompanied by moderate heat evolution and foaming. The mixt was stirred at room temp for 0.5 hr and then refluxed for 2–3 hr. After evapg most of the EtOH *in vacuo*, the residue was treated with H_2O to dissolve inorg material and the org phase was extd with $CHCl_3$ or C_6H_6. The combined ext were washed with H_2O, dried (Na_2SO_4), and evapd *in vacuo*. The resulting free base (oil or solid) was dissolved in EtOH (100–200 ml) and treated with a soln of 12 g of anhyd HCl in 50–100 ml of EtOH. In most cases heavy ppt formed which, after cooling, were filtered, washed with EtOH, and dried. If no ppt formed or if the amount of solid appeared slight, anhyd Et_2O was added to complete pptn. The crude yields of the mixed, isomeric dihydrochloride salts varied between 75 and 95%. Purification was effected by recrystn from suitable solvents, frequently with considerable loss due to the differing soly of the component isomers.

Compd 28 and 31.—A suspension of 5.0 g (0.011 mole) of **27** and 42 ml of 48% aq HBr was refluxed for 26 hr. At no time did complete soln occur. After cooling, filtering, and washing with EtOH, 5.2 g (92%) of crude **28**, mp 294–296° dec, was obtained. Similarly, a suspension of 5.0 g (0.011 mole) of the free base derived from **20** and 25 g of 48% aq HBr was refluxed for 3 hr. Initially, complete soln occurred followed by sepn of a cryst ppt. After cooling, the solid was filtered, washed (a little ice-cold H_2O), and dried, 5.6 g (90%) of crude **31**, mp 258–260° dec.

Compd 30.—A mixt of 9.99 g (0.015 mole) of **32**, 200 ml of H_2O–EtOH (1:1), 2.5 ml of concd HCl, and 2.0 g of 10% Pd/C was shaken in a Parr app overnight at 50° and 50 psig.[2] After filtering and washing the catalyst (H_2O), the filtrates were evapd *in vacuo* almost to dryness and the residue was triturated (EtOH–Et_2O, 1:2). The solid was filtered, washed (Et_2O), and dried, to yield 6.7 g (92%) of crude product, mp 259–261° dec.

Compd 40.—The free base derived from **20** was reductively methylated with aq HCHO and $NaBH_4$ according to the method of Kubota.[17] The product (free base) was converted directly to its dihydrochloride salt **40** in the usual manner.

Compd 41.—The intermediate, 1,1'-tetramethylenebis(2-benzyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide), was prepd by adding 6.84 g (0.040 mole) of $PhCH_2Br$ to a warm soln of 4.36 g (0.010 mole) of 1,1'-tetramethylenebis(3,4-dihydro-6,7-dimethoxyisoquinoline)[9] in 44 ml of $PhCH_2OH$ and heating the mixt on the steam bath for 3 hr. The hot soln was treated with EtOAC to the cloud point and cooled. The solid was filtered, washed (EtOAc), and recrystd (EtOH), to yield 6.2 g (80%) of the quaternary salt, mp 212–213° dec. *Anal.* ($C_{40}H_{46}N_2O_4 \cdot 2H_2O$) C, H; N: calcd, 3.44; found, 3.87.

The quaternary salt was reduced to **41** with $NaBH_4$ as described by the general procedure for 1,2,3,4-tetrahydroisoquinolines.

(17) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).