Hydroxyguanidines. A New Class of Antihypertensive Agents

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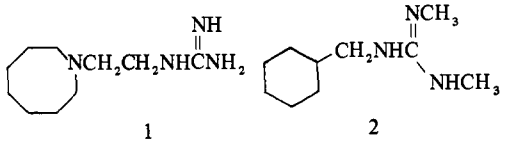
A series of 3,4-dihydro-2(1*H*)-isoquinolinecarboxamidoximes has been prepared and assayed for antihypertensive activity in rats and dogs. The compounds, which are prepared by the interaction of 3,4-dihydro-2(1*H*)-isoquinolinecarbonitriles and hydroxylamine, are $>10^3$ times less basic than their carboxamidine analogs. A central component of action was implicated by cross-circulation experiments in dogs, and two compounds, 1-methyl-3,4-dihydroisoquinolinecarboxamidoxime (**73**) and (1*R*,3*S*)-3,4-dihydro-2(1*H*)-isoquinolinecarboxamidoxime (**80**), were selected for further evaluation.

The introduction of guanethidine **1** as an orally effective agent for reducing sympathetic tone[1,2] introduced an era of synthesis, still in progress, that has produced thousands of guanidine compounds.[3] Included in this diverse group of substances are the benzylguanidines such as bethanidine **2**[4] and the cyclized benzylguanidines such as debrisoquin **3**.[5]



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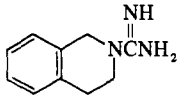


3

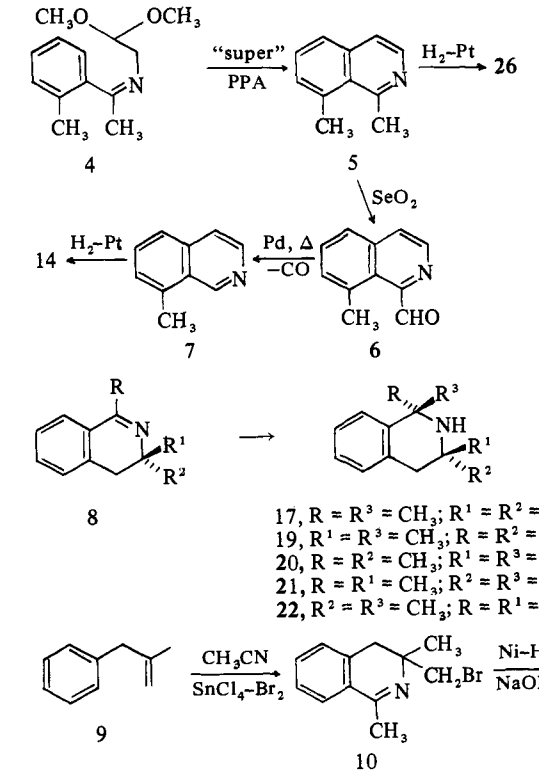
The above guanidines are all very strong bases and are completely ionized in serum. As a result of this ionization, the blood-brain barrier prevents the compounds from entering the CNS and their modes of action are restricted to the peripheral tissues. (For a discussion of the mechanism of action of these and related guanidines, see ref 6.) As part of a major program directed toward the "centralization" of pharmacodynamic agents, we were interested in devising means by which the blood-brain barrier might be surmounted. Using materials of known physiological action as models, we hoped, by subtle structural alteration, to arrive at compounds with new or improved central components of action.

Our approach to the centralization of hypotensive guanidine functions was to reduce the basicity (and thus the degree of serum ionization) in such a way as to still allow maximum manipulation of functional substitution. One solution to the preparation of "less basic" guanidines proved to be the introduction of an *N*-hydroxyl group to give hydroxyguanidines.†

Chemistry. The first synthesis of hydroxyguanidine was accomplished by the interaction of H_2NCN and $NH_2OH \cdot HCl$.[9] Alkylated hydroxyguanidines were later prepared through substituted cyanamides[10] and thiourea derivatives.[11,12] The cyanamide-NH_2OH sequence appeared to be the most versatile and we selected the tetrahydroisoquinoline nucleus as an appropriate model.

Many of the required tetrahydroisoquinolines were known and were available by way of the Bischler-Napieralski (method A),[13] Pictet-Spengler (method B),[14] and Pomeranz-Fritsch (method C)[15] reactions. Several known 3,4-dihydroisoquinolines were converted to new tetrahydro derivatives by catalytic hydrogenation over platinum. Most of the remaining new compounds were prepared by method A in which the use of a "super" polyphosphoric acid (see Experimental Section) provided simplified work-ups and improved yields with formamides. Some special sequences are described in Scheme I. We were unable to reproduce the yield of 8-methylisoquinoline reported by Pomeranz[16] and so an alternative route was examined. The use of acetophenones in the Pomeranz-Fritsch reaction has been generally unsatisfactory;[15] however, when **4** (prepared from *o*-methylacetophenone and aminoacetaldehyde dimethyl acetal) was heated briefly with "super" polyphosphoric acid, a usable 30% yield of 1,8-dimethylisoquinoline (**5**) was realized. (For other examples of the use of PPA in the Pomeranz-Fritsch reaction, see ref 17 and 18.) Oxidation of **5** with SeO_2 proceeded selectively (for a similar selective oxidation, see ref 19) to give the aldehyde **6** which was smoothly decarbonylated

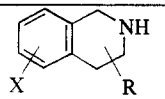
Scheme I



17, R = R³ = CH₃; R¹ = R² = H
19, R¹ = R³ = CH₃; R = R² = H
20, R = R² = CH₃; R¹ = R³ = H
21, R = R¹ = CH₃; R² = R³ = H
22, R² = R³ = CH₃; R = R¹ = H

†The pK_a values for the parent compounds, guanidine and hydroxyguanidine, are 13.6[7] and *ca.* 8.1,[8] respectively.

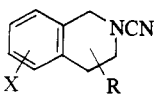
Table I. 1,2,3,4-Tetrahydroisoquinolines



Compd	R	X	Mp,[a] or bp (mm), °C	Crystn solvent[c]	Method
11	H	5-CH_3	212–213	A	A
12	H	6-CH_3	198–200	A, C	A
13	H	7-CH_3	230–231	B	A
14	H	8-CH_3	222–224	B	
15	H	5-NHAc	150–153[b]	E, C	
16	3-C_2H_5	H	213–214	A	A
17	1,1-$(CH_3)_2$	H	125–126 (23)		
18	4,4-$(CH_3)_2$	H	182–183	A, C	A
19	(1*R*,3*S*)-$(CH_3)_2$	H	125–130 (23)		A
20	(1*S*,3*R*)-$(CH_3)_2$	H	299–300	A, C	A
21	(1*S*,3*S*)-$(CH_3)_2$	H	125–130 (23)		A
22	(1*R*,3*R*)-$(CH_3)_2$	H	125–130 (23)		A
23	1-CH_3	5-CH_3	54–58 (0.04)		A
24	1-CH_3	6-CH_3	52–54 (0.02)		A
25	1-CH_3	7-CH_3	144–146 (23)		A
26	1-CH_3	8-CH_3	158–160	D	C
27	1-CH_3	7-OCH_3	101–102 (0.5)		C
28	3-CH_3	5-CH_3	241–243	A, C	A
29	1,3,3-$(CH_3)_3$	H	102–103 (9)		
30	1,4,4-$(CH_3)_3$	H	136–138 (23)		A

[a] HCl salt. [b] Free base. [c] A, EtOH; B, *i*-PrOH; C, Et_2O; D, Me_2CO; E, CH_2Cl_2.

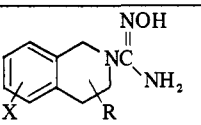
Table II. 3,4-Dihydro-2(1*H*)-isoquinolinecarbonitriles



Compd	R	X	Mp, °C[a]	% yield[b]	Crystn solvents[e]
31	H	H	42.5–43.5	100	C
32	H	5-CH_3	55–57	80	C, J
33	H	6-CH_3		77	
34	H	7-CH_3	75–75.5	99	I
35	H	8-CH_3		100	
36	H	5-OH	140–142	96	F
37	H	5-NHAc	192–193	64	H
38	H	6,7-$(OCH_3)_2$		30	
39	H	6,7-$(OCH_2Ph)_2$	101–103	64	A, C
40	1-CH_3	H		99	
41	3-CH_3	H		97	
42	1-C_2H_5	H		94	
43	3-C_2H_5	H		94	
44	1,1-$(CH_3)_2$	H		67	
45	3,3-$(CH_3)_2$	H		65	
46	4,4-$(CH_3)_2$	H		88	
47	(1*R*,3*S*)-$(CH_3)_2$	H	39–41	99	C, K
48	(1*S*,3*R*)-$(CH_3)_2$	H		87	
49	(1*S*,3*S*)-$(CH_3)_2$	H	*c*	94	C, K
50	(1*R*,3*R*)-$(CH_3)_2$	H	*d*	100	C
51	1-CH_3	5-CH_3	67–68	83	C, J
52	1-CH_3	6-CH_3		95	
53	1-CH_3	7-CH_3		97	
54	1-CH_3	8-CH_3	72.5–74	98	C, J
55	1-CH_3	6-OCH_3		91	
56	1-CH_3	7-OCH_3		88	
57	1-CH_3	6-OH	95–97	86	G
58	3-CH_3	5-CH_3	77–78	76	C, J
59	1,3,3-$(CH_3)_3$	H		73	
60	1,4,4-$(CH_3)_3$	H		100	
61	1-CH_3	6,7-$(OCH_3)_2$		98	
62	1-CH_3	6,7-$(OCH_2Ph)_2$	76–77	88	F, J
63	3-CH_3	6,7-$(OCH_3)_2$	97–101	88	C, J

[a] Of analytical sample; C, H, and N analyses within 0.4% of theory. [b] Crude. [c] Polymorphic, mp 57–59 and 67–68°. [d] Polymorphic, mp 59–60 and 67.5–68°. [e] A, EtOH; B, *i*-PrOH; C, Et_2O; D, Me_2CO; E, CH_2Cl_2; F, $CHCl_3$; G, PhH; H, MeCN; I, *i*-PrOAc; J, hexane; K, pentane.

Table III. 3,4-Dihydro-2 (1*H*)-isoquinolinecarboxamidoximes



Compd	R	X	Mp, °C	% yield	Crystn solvent[h]	AED_{50}, mg/kg po	Type[a] rat
1						19	R
3						>100	R
64	H	H	144-145[c]	50	B	40[b]	R
65	H	5-CH_3	142-144	44	D, C	>50	S
66	H	6-CH_3	152-154[d]	35	A, C	>20	S
67	H	7-CH_3	141-145	42	I	>50	S
68	H	8-CH_3	145-149	31	I	>50	S
69	H	5-OH	212-213 dec[d]	71	A, B	40	R
70	H	5-NHAc	164-166	54	H	>50	R
71	H	6,7-$(OCH_3)_2$	148-151 dec	21	H	>50	R
72	H	6,7-$(OH)_2$	198-200 dec[d]	64[e]	A, C	40	S
73	1-CH_3	H	170-172	72	B	28	R
74	3-CH_3	H	120-122	58	B	>50	R
75	1-C_2H_5	H	183-184 dec[d]	40	A, C	>50	S
76	3-C_2H_5	H	135-142[d]	33	A, G	40	S
77	1,1-$(CH_3)_2$	H	161-162	44	A, J	>50	R
78	3,3-$(CH_3)_2$	H	122-123	38	I, J	>50	R
79	4,4-$(CH_3)_2$	H	117-119	41	F, J	>50	R
80[f]	(1*R*, 3*S*)-$(CH_3)_2$	H	157-159	29	I	15	R
81[f]	(1*S*, 3*R*)-$(CH_3)_2$	H	157-159	44	F, J	>50	R
82[f]	(1*S*,3*S*)-$(CH_3)_2$	H	138-140	44	G	>50	R
83[f]	(1*S*,3*R*)-$(CH_3)_2$	H	136-138	30	C	>50	S
84	1-CH_3	5-CH_3	193-194[d]	64	A, C	>50	R
85	1-CH_3	6-CH_3	156-158	50	H, J	50	R
86	1-CH_3	7-CH_3	151-154	50	G	>50	R
87	1-CH_3	8-CH_3	210-213[d]	64	B, H	20	S
88	1-CH_3	6-OCH_3	135-137	24	A	30	R
89	1-CH_3	7-OCH_3	136-139	44	H	>50	R
90	1-CH_3	6-OH	179-181	18	B	40	R
91	3-CH_3	5-CH_3	118-120	47	F, J	>50	S
92	1,3,3-$(CH_3)_3$	H	161-163	30	F, J	40	R
93	1,4,4-$(CH_3)_3$	H	134-135	62	E, J	>50	R
94	1-CH_3	6,7-$(OCH_3)_2$	149-150	54	G	>50	R
95	1-CH_3	6,7-$(OH)_2$	195-197[d]	50[g]	A, C	>50	R
96	3-CH_3	6,7-$(OCH_3)_2$	178-181 dec[d]	44	A, L	>50	R

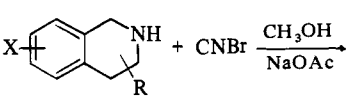
[a] R = renal hypertensive; S = spontaneous hypertensive (see text). [b] sc. [c] *p*-TsOH salt. [d] HCl salt. [e] Overall from **39**, first with NH_2OH, then H_2/Pd-C. [f] $[\alpha]^{25}D$ (1% in $CHCl_3$): 80, −18.8°; 81, +18.1°; (1% in MeOH) 82, −100.6°; 83, +101.4°. [g] Overall from **62**, first with NH_2OH, then H_2/Pd-C. [h] A, EtOH; B, *i*-PrOH; C, Et_2O; D, Me_2CO; E, CH_2Cl_2; F, $CHCl_3$; G, PhH; H, MeCN; I, *i*-PrOAc; J, hexane; K, pentane; L, dioxane.

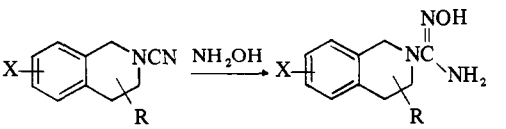
over Pd at elevated temperatures.[20] The overall conversion of **5** → **7** was 75%. Catalytic hydrogenation of (*S*)- and (*R*)-3,4-dihydro-1,3-dimethylisoquinoline produced mixtures containing 85-90%‡ of **19** and **20**, respectively. (See also ref 21 and 22.) Addition of CH_3Li to (*S*)- and (*R*)-3,4-dihydro-3-methylisoquinoline proceeded smoothly to give mixtures containing 85-90%‡ of **21** and **22**, respectively.[21,22] When CH_3MgBr was used in place of CH_3Li, no product was obtained. The structures of **19-22** were assigned on the assumption that new bond formation would proceed mainly on the less-hindered side of the molecule. The addition of CH_3Li failed with 3,4-dihydro-1-methylisoquinoline but the addition of CH_3MgBr proceeded without complication on the benzyl quaternary iodide. Removal of the *N*-benzyl group by catalytic hydrogenolysis gave **17** in good yield. Compound **29** was prepared by simultaneous hydrogenation-hydrogenolysis of **10**.[23] The new tetrahydroisoquinolines are tabulated in Table I.

All of the cynamides (Table II) were prepared by treating the amines in CH_3OH with an excess of CNBr, using NaOAc as a base. The neutral product was freed of any remaining starting material by an acid wash and the crude cyanamides were usually used without further purification. In the cases where the product was a solid, an aliquot was recrystallized from an appropriate solvent and submitted for analysis. Mass, ir, and nmr spectra of all of the cyanamides were consistent with the proposed structures.

The final 3,4-dihydro-2(1*H*)-isoquinolinecarboxamidoximes (Table III) were prepared by treating the cyanamides with hydroxylamine (Scheme II).

Scheme II





Although hydroxylamine is reported to react as an ambident nucleophile with cyanamides,[24] only the products of nitrogen attack were observed in this series. This was confirmed by the ready conversion of the products to the cor-

‡ By glc analysis of the *N*-acetyl derivatives.

responding guanidines by catalytic hydrogenolysis of the N-O bond. The hydroxyguanidines had characteristic absorption bands in the ir near 3590 (OH) and 3490, 3390 cm^{-1} (NH) with a broad band usually centered at 3270-3260 cm^{-1} (hydrogen bonding).[24]

In the case of compounds **80-83**, the cis and trans isomers were readily distinguishable by virtue of the characteristic positions of the C-CH_3 resonances in the nmr. Thus **80** (cis) showed resonances at 115 and 142 Hz (J = 6.62 Hz for both) while **82** (trans) showed resonances at 85 and 130 Hz (J = 6.25 Hz for both). The limit of detection of one isomer mixed with another was *ca.* 1%.

As anticipated, the products in Table III were $>10^3$ times less basic than debrisoquin **3** ($pK_a' > 11.4$), having pK_a' values in the range 7.6-8.4 (all in 50% MeOH).

Pharmacology. Compounds included in Table III were evaluated for antihypertensive activity in either of two hypertensive rat models, renal hypertension produced by latex bag encapsulation of both kidneys[25] (RHR) or the use of the Aoki strain of rat[26,27] (SHR) which has a genetically based spontaneous hypertension. Each compound was administered orally in 1% gum tragacanth solution or suspension to three rats at each dose level tested. Systolic blood pressures were determined prior to drug administration and 2, 6, and 24 hr post-medication. Measurements of systolic blood pressures were made in the unanesthetized animals utilizing the photoelectric tensometer method of Kersten, *et al.*[28] The highest dose tested was 50 mg/kg. The end point sought was that of reduction of systolic blood pressure to a normotensive level (130 mm). When activity was noted at the 50 mg/kg dose, at least two additional lower doses were administered to additional groups of three rats each based on a dose interval of 2 or 2.5. The approximate effective dose (AED_{50}) was obtained by the Wright method[29] for each compound which showed activity, the AED_{50} being that dose at which 50% of the animals treated responded with reductions of systolic blood pressure to a value of 130 mm or lower. The AED_{50} values are presented in Table III.

While 11 compounds showed activity in the rat screens, further testing in hypertensive dogs eliminated all but two, **73** and **80**, both of which produced excellent blood pressure control on chronic oral administration at daily doses as low as 0.3-1.25 mg/kg.

Further studies were performed to determine whether **73** and **80** in comparison with the guanidines, guanethidine and debrisoquin, would lower blood pressure *via* a direct central nervous system effect. These studies, in dogs, involved the use of a modification of the open-chest cross-circulation procedure of Swiss and Maison.[30] In this procedure the vascular circulation of the head of one animal is isolated from its systemic circulation, the head being supplied with blood from a donor animal *via* left vertebral arteries and two carotids. Drug injection was made into the left vertebral vessel. When either **73** or **80** was injected in a dose range of 0.4-0.8 mg/kg (based upon the whole body weight of the animal) marked (>20%) and sustained reductions in systemic blood pressures occurred. Neither guanethidine nor debrisoquin produced centrally induced systemic blood pressure reductions when tested at a similar dose range. These data tend to support the premise that the reduced basicity and consequent increase in nonionized species of both **73** and **80** at physiologic pH's in comparison with guanethidine or debroisquin has resulted in an altered physiological distribution.

Experimental Section §

Tetrahydroisoquinolines. Method A. The following is typical of an improved procedure with formamides using "super" PPA.

1,2,3,4-Tetrahydro-7-methylisoquinoline (13). A mixture of 50 g (0.37 mol) of (*p*-tolyl)ethylamine and 50 ml of 98% HCOOH was slowly heated to 200° in an oil bath. Water and excess HCOOH were allowed to distill off over 1 hr. "Super" PPA was prepared by heating and stirring a mixture of 65 g of P_2O_5 and 325 g of commercial PPA (MCB) at 170-180° for 1 hr. The mixture was cooled to 150° and the cooled crude formamide was added in a thin stream. The addition was accompanied by frothing and a 10° temperature rise. The mixture was stirred at 160-170° for 1.5 hr and was then cooled slightly and poured into 500 ml of H_2O.# Ice was added to keep the temperature below 80° during the addition and finally to cool the mixture to 25° at the end. A single Et_2O extract was discarded and the solution was stirred in a Dry Ice-Me_2CO bath while a saturated aqueous solution of KOH was added to a pH of *ca.* 9. The temperature must be kept <30° during the addition to prevent excessive frothing. The product was extracted with Et_2O from which it was recovered by stripping the solvent. The yield of crude solid, mp 40-45°, was 50 g (93% over all). The HCl salt had mp 179-181° (*i*-PrOH-Et_2O) (reported[31] mp 178-179°).

The standard procedure for the synthesis of 1-alkyltetrahydroisoquinolines is illustrated by the following.

1,2,3,4-Tetrahydro-1,6-dimethylisoquinoline (24). *N*-(*p*-Tolylethyl)acetamide was prepared from 31.2 g (0.23 mol) of the amine and excess Ac_2O. The crude solid amide was dissolved in 100 ml of $POCl_3$ and 80 g of P_2O_5 was added. The mixture was refluxed (oil bath) for 1.5 hr and was then cooled and poured over ice. The mixture was stirred 0.5 hr to hydrolize excess $POCl_3$ and neutral material was extracted with Et_2O. The aqueous portion was cooled while excess 35% NaOH was added to pH >10. Extraction of the mixture with Et_2O and evaporation of the dried ($MgSO_4$) solution left 33.6 g of dark, crude 3,4-dihydro-1,6-dimethylisoquinoline. This was hydrogenated at 3 atm in EtOH over 0.8 g of PtO_2. Removal of the solvent and distillation of the residue gave 23.4 g [63.3% overall from (*p*-tolyl)ethylamine] of colorless oil, 144-146° (23 mm), $n^{25}D$ 1.5475.

Method C. 1,2,3,4-Tetrahydro-1,8-dimethylisoquinoline (26). A solution of 50 g (0.37 mol) of *o*-methylacetophenone, 50 g (0.37 mol) of aminoacetaldehyde dicthyl acetal, and 0.5 g of *p*-TsOH · H_2O in 300 ml of PhMe was refluxed under a water trap for 24 hr. The solvent was stripped to leave 91 g of crude imine as a dark oil. PPA (1.4 kg) was stirred and heated to 110° (oil bath) and 70 g (0.28 mol) of the above imine was added dropwise over 10 min. The mixture was stirred at 120-130° for 20 min and was then poured onto ice. Two Et_2O extracts of the quenched solution were discarded and the aqueous solution was made basic by the addition of 50% KOH. The product, recovered by Et_2O extraction, was distilled [bp 131-133° (12 mm)] and 5 was obtained as a crystalline mass, 15 g (34%), mp 44-50° (C, H, N). The HCl salt (C, H, N) sublimed and showed no liquid phase to 290° (sealed tube). Catalytic hydrogenation of the salt in a Parr apparatus over PtO_2 and crystallization from Me_2CO gave **26** in 83% yield.

Miscellaneous Methods. 1,2,3,4-Tetrahydro-8-methylisoquinoline (14). A solution of 10.1 g (0.064 mol) of 1,8-dimethylisoquinoline (above) in 50 ml of dioxane was stirred in an 80° oil bath while a solution of 7.1 g (0.065 g-atom) of SeO_2 in 7 ml of H_2O and 50 ml of dioxane was dripped in over 2 hr. The bath temperature was raised to 120-130° and the mixture was refluxed (internal T, 91°) for 2 hr. Charcoal was added to the cooled mixture and the solids were filtered off and washed with dioxane. The filtrate was diluted with an equal volume of PhH, and $MgSO_4$ and

§Boiling points and melting points are uncorrected. Ir spectra were determined using a Perkin-Elmer Model 257 grating spectrophotometer. Nmr spectra were taken on a Varian Associates HA-100 spectrometer and chemical shifts are reported in hertz relative to Me_4Si as internal standard. Mass spectra were obtained on a Jeolco JMS-OISC high-resolution double-focusing mass spectrometer. All gas chromatographic (glc) analyses were performed on a Hewlett-Packard research chromatograph, Model 5751 B, equipped with glass columns packed with 3% OV-17 on 100-200 mesh Gas-Chrom Q. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Instranal Laboratories, Inc., Rensselaer, N. Y. Analytical results for C, H, and N for all new compounds cited in Tables I and III and for intermediates indicated by elemental symbols were within 0.4% of the theoretical values.

#The use of H_2O instead of ice permits a rapid quenching of the reaction mixture.

charcoal were added. After standing for 0.5 hr, the mixture was filtered and the filtrate was concentrated to 10.1 g (92% crude yield) of brown oil which solidified on standing. Glc analysis at 160° showed one peak; rt = 4.8 min; ir (film) 1710 cm^{-1} (–CHO); mass spectrum M^+ 171 (calcd for 6, 171). The crude aldehyde was mixed with 1 g of 10% Pd/C and 60 ml of dowtherm A and the mixture was heated under N_2 at 150–190° for 0.5 hr to remove the last traces of Se. The mixture was filtered and a fresh 1-g portion of 10% Pd/C was added. The mixture was heated under N_2 at 180–190° for 1 hr at the end of which time no more CO was being evolved. The catalyst was removed by filtration and was washed with PhMe. The filtrate was diluted with Et_2O and extracted with 4 × 100 ml of 3 *N* HCl. The acid extracts were made basic with 50% KOH and the product was extracted into Et_2O which was dried ($MgSO_4$) and charcoaled. Evaporation of the solvent left 6.9 g (82% yield) of light brown oil, picrate (C, H, N) mp 204–206° (reported[16] mp 204–205°). Hydrogenation of 7 in a Parr apparatus using EtOH as solvent and Pt as catalyst resulted in a smooth uptake of 2 equiv of H_2 (4 hr) and the production of an equal weight of 1,2,3,4-tetrahydro-8-methylisoquinoline. The HCl salt **14** was crystallized from *i*-PrOH, mp 222–224°.

(1*R*,3*S*)-1,2,3,4-Tetrahydro-1,3-dimethylisoquinoline (19). A solution of 15.9 g (0.1 mol) of (*S*)-3,4-dihydro-1,3-dimethylisoquinoline[21,22] (from (*S*)-*N*-acetylamphetamine) in 100 ml of glacial HOAc was hydrogenated at ambient temperature in a Parr apparatus over 0.5 g of PtO_2. After 5 hr the catalyst was filtered and the filtrate was stripped. The free base was liberated with KOH, isolated by extraction, and distilled, bp 125–130° (23 mm), $n^{25}D$ 1.5384. The yield was 12.0 g (74%). A glc analysis of acetylated amine (OV-17, 160°) showed components with retention times of 7.9 min (trans) and 10.5 min (cis) in the ratio of 1:9.

Similarly, starting with (*R*)-*N*-acetylamphetamine, there was prepared a 67% yield of (1*S*,3*R*)-1,2,3,4-tetrahydro-1,3-dimethylisoquinoline (**20**), bp 100–102° (8 mm). A glc analysis of acetylated amine as above indicated components with retention times of 8.2 and 10.5 min (trans and cis, respectively) in the ratio 1:19.

(1*S*,3*S*)-1,2,3,4-Tetrahydro-1,3-dimethylisoquinoline (21). A solution of 37.8 g (0.26 mol) of (*S*)-3,4-dihydro-3-methylisoquinoline (prepared according to method A) in 100 ml of Et_2O was added dropwise to a stirred, cooled (–20°) solution of 0.6 mol of MeLi in 500 ml of Et_2O. After the addition (1 hr), the mixture was stirred and cooled for 0.5 hr longer and was then quenched by the cautious addition of H_2O. Separation of the phases and evaporation of the dried organic solution left 37.1 g (88% crude yield) of brown oil. A glc analysis of acetylated product as above indicated that both trans (87%) and cis (13%) isomers were formed.

A similar ratio of trans:cis isomers was obtained beginning with (*R*)-3,4-dihydro-3-methylisoquinoline.

1,2,3,4-Tetrahydro-1,1-dimethylisoquinoline (17). A solution of 54.5 g (0.38 mol) of 3,4-dihydro-1-methylisoquinoline and 84 g (0.38 mol) of benzyl iodide in 300 ml of MeCN was refluxed for 6 hr and then concentrated to a red oil. Crystallization from MeCN–Et_2O gave 60 g (44% yield) of yellow quaternary salt, mp 185–187° (C, H, N). A suspension of 59 g (0.162 mol) of this quaternary in 550 ml of Et_2O was stirred while 218 ml of a 3 *M* solution of MeMgBr (0.65 mol) was added at a rate sufficient to maintain a gentle reflux. After an additional heating period of 4 hr, the mixture was quenched with saturated aqueous NH_4Cl. The solids were filtered off and the filtrate was concentrated to give 31 g (80% crude yield) of 2-benzyl-1,2,3,4-tetrahydro-1,1-dimethylisoquinoline as a yellow oil. Catalytic hydrogenolysis at ambient temperature in 100 ml of glacial HOAc using 3 g of 10% Pd/C in a Parr apparatus was complete in 17 hr. The catalyst was removed by filtration, the solution was concentrated to low volume, and the residue was diluted with Et_2O and excess 10% NaOH. Separation of the phases and concentration of the organic solution left an oil which was distilled. The product 17 was obtained as a colorless oil, bp 125–126° (23 mm), in 71% yield.

1,2,3,4-Tetrahydro-1,3,3-trimethylisoquinoline (29). A mixture of 3-bromomethyl-3,4-dihydro-1,3-dimethylisoquinoline (**10**),[23] 40 ml of 3 *N* NaOH, 8 g of Raney Ni, and 95% EtOH to a volume of 200 ml was shaken at ambient temperature in a Parr apparatus under 3 atm of pressure of H_2 until no further uptake was evident (96 hr). The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The crude amine was isolated by extraction with Et_2O. By vacuum distillation **29** was obtained as a colorless oil, 18.1 g (53% yield), bp 102–103° (9 mm).

3,4-Dihydro-1-methyl-2(1*H*)-isoquinolinecarbonitrile (40). A solution of 73 g (0.686 mol) of CNBr in 250 ml of MeOH was added dropwise with stirring to a cooled mixture of 92.0 g (0.625 mol) of 1,2,3,4-tetrahydro-1-methylisoquinoline, 103 g (1.75 mol) of anhydrous NaOAc, and 1.1 l. of MeOH. The reaction was stirred 2.5 hr at 5° and at ambient temperature 2–3 hr. The mixture was concentrated under vacuum and the residue was treated with 300 ml of H_2O and extracted three times with Et_2O. The organic extracts were washed with 2 *N* HCl and brine. The solution was dried over K_2CO_3 and the solvent was removed under vacuum to leave 106 g (99% crude yield) of light oil which was used directly in the next step.

3,4-Dihydro-1-methyl-2(1*H*)-isoquinolinecarboxamidoxime (73). To a solution of 74.5 g (1.07 mol) of $NH_2OH \cdot HCl$ and 106 g (0.617 mol) of the above nitrile in 530 ml of DMF was added 215 g (2.02 g-atom) of Na_2CO_3 over a period of 10 min. The mixture was heated for 1.25 hr over a steam bath, then cooled to 50°, and filtered. The inorganic salts were washed with a small amount of DMF and the combined filtrate and washings were concentrated to *ca.* 400 ml under vacuum. This was added slowly with scratching and stirring to 1 l. of iced H_2O. The product crystallized and was filtered off and washed thoroughly with H_2O. After drying overnight at 60° under vacuum, the crude product weighed 111 g and had mp 154–162°. The material was charcoaled and recrystallized from 1.5 l. of absolute EtOH to give 90 g (72%) of pure product *in* two crops mp 170–172°.

(1*R*,3*S*)-3,4-Dihydro-1,3-dimethyl-2(1*H*)-isoquinolinecarboxamidoxime (80). A mixture of 115 g (0.617 mol) of crude cyanamide **47**, 141 g (2.4 g-atoms) of $NH_2OH \cdot HCl$, and 382 g (3.6 g-atoms) of Na_2CO_3 in 1 l. of DMF was stirred at ambient temperature for 68 hr. Another 43 g of $NH_2OH \cdot HCl$, 86 g of Na_2CO_3, and 200 ml of DMF were added and stirring was continued for an additional 48 hr. The mixture was filtered and the filtrate was concentrated to a low volume under reduced pressure. A first crop (48 g) was collected by shaking the concentrate with H_2O and Et_2O. The Et_2O layer was extracted with 1 *N* HCl from which a second crop (11 g) was obtained by treatment with K_2CO_3 and extraction with $CHCl_3$. From the Et_2O phase was recovered 61 g of **47**. Based on recovered starting material, the crude yield of **80** was 93%. This could be recrystallized from $CHCl_3$ or *i*-PrOAc with 66–75% recovery.

Similarly, starting with crude **48**, **49**, and **50**, pure **81**, **82**, and **83**, respectively, were prepared. An nmr analysis showed each compound to be free of its geometric isomer.

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Diacetoxypiperidinium Analogs of Acetylcholine†

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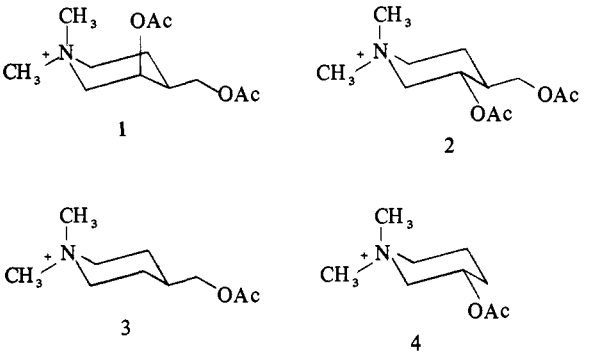
The syntheses of *cis*- and *trans*-*N,N*-dimethyl-4-acetoxymethyl-3-acetoxypiperidinium iodides (1 and 2), *N,N*-dimethyl-4-acetoxymethylpiperidinium iodide (3), and *N,N*-dimethyl-3-acetoxypiperidinium iodide (4) are described. Muscarinic action, 1/100 that of acetylcholine, was found in 1 and 4. Compounds 2 and 4 were relatively good substrates for acetylcholinesterase; compared to acetylcholine respective rates of hydrolysis of 55 and 71% were observed. Analysis of the models leads to the conclusion that the optimal torsional angle, the N–C–C–O portion of the molecule, is synclinal for agonist binding and antiperiplanar for esterase binding.

Many conformational studies have attempted to correlate acetylcholine (ACh) structure with the various biological activities. Most of these efforts have been focused on the optimal torsional angle of the N–C_α–C_β–O portion of ACh and the relationship to both muscarinic action and substrate activity for acetylcholinesterase (AChE). Approaches used to verify if this torsional angle defines the biological action have included the relative biological effects of conformational ACh analogs[1-23] (see ref 24 for a report on the muscarinic and esterase activities of **4**), X-ray crystallography of ACh analogs, and quantum mechanical calculations of preferred conformations of ACh.[25-30]

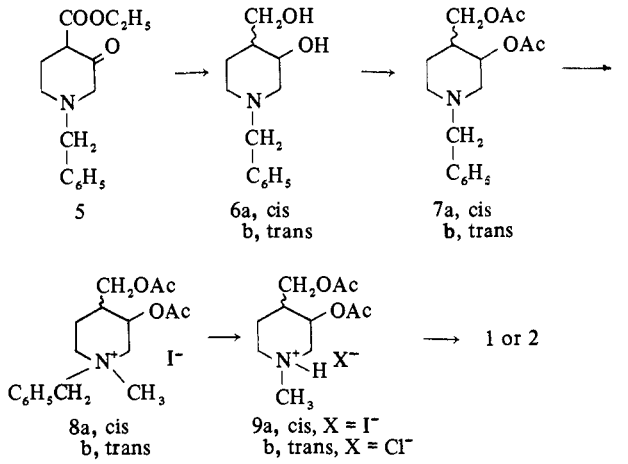
Recent conclusions defining the torsional angle with respective ACh activities are not consistent. While there is a great deal of support for muscarinic reception of the synclinal ACh structure ($\Phi \sim 60$), there is strong evidence for the antiperiplanar ($\Phi \sim 180$). Similarly, ACh as a substrate for AChE is proposed by the majority of investigators to adopt the 150° torsional angle; however, some studies suggest that the fully extended 180° angle is optimal.

In the course of our work some compounds became available that are useful models for examining the torsional angle of the N-C-C-O fragment analogous to ACh. *cis*- and *trans*-dimethyldiacetoxypiperidinium salts **1** and **2**, while not approaching the rigidity of perhydroquinoline or decalin models, have preferred conformers that can be assigned on the basis of the energy of steric interaction arising in the 3 and 4 substituents. The monoacetoxypiperidinium salts **3** and **4** were synthesized as control models to examine the biological response of the respective acetoxy groups individually.

Sodium borohydride reduction of **5** gave a 4:1 mixture of the diols **6a** and **6b** which were separated on alumina.



Acetylation of **6a** and **6b** gave the respective diacetates **7a** and **7b**. The nmr evidence for the assignment of structure (Table I) is based on the position and half width of



the methine porton at C_3. The trans compounds **6b** and **7b** with the C_3H axial show a higher field absorption than the equatorial C_3H (**6a**, **7a**) and a half width of about 20

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